1 Introduction to Solid Dispersions
2 Introduction to Hot-Melt Extrusion for Pharmaceuticals
3 Process Variables of Twin-Screw Extruders
4 Injection Molding Combined with Hot-Melt Extrusion
5 Extruder Granulation Processes
6 Spray Drying as a Solid Solution Preparation Technique
7 Analytical Investigations of Solid Dispersions
8 Downstream Processing with Hot-Melt Extrusion
9 General Notes on BASF Pharma Polymers
10 Physico-Chemical Characteristics – Processability
11 Extrusion Experiments
12 Injection Molding Experiments
13 Melt Granulation Experiments
14 Spray Drying Experiments
15 In-Vitro/In-Vivo Characteristics of HME Formulations
16 Manufacture of Final Dosage Forms
17 Flow Chart: From Screening to a Final Pharmaceutical Formulation
18 Practical Recommendations for Extrusion and Cleaning Procedure of the Extruder
19 Regulatory Aspects
20 Literature References
21 Alphabetical Index
## Contents

1. **Introduction to Solid Dispersions**  
2. **Introduction to Hot-Melt Extrusion for Pharmaceuticals**  
3. **Process Variables of Twin-Screw Extruders**  
4. **Injection Molding Combined with Hot-Melt Extrusion**  
5. **Extruder Granulation Processes**  
6. **Spray Drying as a Solid Solution Preparation Technique**  
7. **Analytical Investigations of Solid Dispersions**  
   7.1 **Analytical Methods**  
   7.1.1 X-Ray Diffraction  
   7.1.2 Differential Scanning Calorimetry  
   7.1.3 Microscopy  
   7.1.3.1 Light Microscope  
   7.1.3.2 Scanning Electron Microscopy  
   7.1.4 Atomic Force Microscopy  
   7.1.5 Solid-State Nuclear Magnetic Resonance  
   7.1.6 In-Vitro Release Characteristics  
8. **Downstream Processing with Hot-Melt Extrusion**  
9. **General Notes on BASF Pharma Polymers**  
   9.1 Kollidon® VA 64/VA 64 Fine  
   9.2 Soluplus®  
   9.3 Kollidon® 12 PF, Kollidon® 17 PF, Kollidon® 30 and Kollidon® 90 F  
   9.4 Kollidon® SR  
   9.5 Kollicoat® MAE 100P  
   9.6 Kollicoat® IR and Kollicoat® Protect  
   9.7 Kolliphor® P 407, Kolliphor® P 407 micro (Poloxamer 407) and Kolliphor® P 188, Kolliphor® P 188 micro (Poloxamer 188)  
   9.8 Kolliphor® RH 40  
   9.9 Polyethylene Glycols  
   9.10 Kolliphor® TPGS
10  Physico-Chemical Characteristics – Processability

10.1 Glass Transition and Melting Temperatures

10.1.1 DSC Analysis of Polymers and Plasticizers/Solubilizers
10.1.2 DSC Analysis of Polymer-Plasticizer Mixtures
10.1.3 DSC Analysis of Polymer Mixtures

10.2 Melt Viscosity

10.2.1 Melt Viscosity of Polymers
10.2.2 Influence of Plasticizers on Melt Viscosity

10.3 Decomposition by TGA

10.3.1 TGA of Polymers
10.3.2 TGA of Plasticizers
10.3.3 TGA of Active Pharmaceutical Ingredients

10.4 Specific Heat Capacity of Polymers

10.5 API Solubility Enhancement of Polymers

10.6 Calculation of Solubility Parameters of Polymers, Plasticizers and APIs

11  Extrusion Experiments

11.1 Extrusion of Polymers

11.1.1 Extrusion Temperature Range of Polymers
11.1.2 Appearance and Pelletizing Characteristics of Extrudates
11.1.3 Dissolution Characteristics of Polymer Extrudates
11.1.4 Decomposition of Polymers During Extrusion
11.1.4.1 Kollidon® VA 64 during Extrusion
11.1.4.2 Soluplus® during Extrusion

11.2 Extrusion of Polymer-Plasticizer Combinations

11.2.1 Extrusion Temperature Range of Polymer-Plasticizer Combinations
11.2.2 Appearance and Pelletizing Characteristics of Polymer-Plasticizer Extrudates
11.2.3 Miscibility of Polymer-Plasticizer Combinations

11.3 Extrusion of Polymer Mixtures

11.3.1 Extrusion Temperature Range of Polymer Mixtures
11.3.2 Appearance and Pelletizing Characteristics of Extrudates of Polymer Mixtures

11.4 Solubilization Capacity of Active Ingredients in Polymers for Hot-Melt Extrusion

11.4.1 Film Casting
11.4.2 Extrusion
11.4.3 Results and Comparison

12  Injection Molding Experiments
Acknowledgements

This extrusion compendium would not have been possible without the support of many people. First of all, we would like to convey our thanks to Nils Rottmann for initiating the project "Hot-Melt Extrusion with BASF Pharma Polymers".

We would like to thank Dr. Sameer Nalawade for providing his knowledge on the topic of injection molding.

Similarly, thanks to our colleagues of the R&D Pharma Ingredient Group for their valuable contributions, in particular the members of the Extrusion Team, Benjamin Strunk and Ronny Hoffmann.

Our special thanks go to James Brawley, Dr. Bettina Goldscheid, Dr. Angelika Maschke, Dr. Dejan Djuric, Dr. Thorsten Schmeller, Dr. Hendrik Hardung, Timo Münch, Sonja Kaiser, Ulf Matussek and Monika Haberecht for their support, proof-reading and constructive discussions.

A special acknowledgement is due to Prof. Dr. Jörg Breitkreutz (Institute for Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany) for his support and for providing the computer program SPWin (version 2.1) for the calculation of the solubility parameters.

Finally, we wish to thank all other persons who were involved in the compilation of this extrusion compendium.
1 Introduction to Solid Dispersions

The pharmaceutical industry is facing the challenge of having more and more poorly soluble drug molecules that have to be developed into dosage forms so that high and reliable drug absorption can be guaranteed on being administered to patients.

Different approaches are possible to overcome solubility issues. Solid dispersions are systems where one component is dispersed in a carrier (usually polymeric and often amorphous) and where the whole system appears to be in a solid state.

<table>
<thead>
<tr>
<th>Chemical modification</th>
<th>Physical modification</th>
<th>Carrier / Delivery systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pro-drugs</td>
<td>• Salts</td>
<td>• Co-solvents</td>
</tr>
<tr>
<td></td>
<td>• Crystal engineering (polymorphs/co-crystals)</td>
<td>• Polymeric systems</td>
</tr>
<tr>
<td></td>
<td>• Amorphous systems</td>
<td>• Cyclodextrins</td>
</tr>
<tr>
<td></td>
<td>• Particle size reduction (micronization, nanocrystals)</td>
<td>• Micelles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• (Micro) Emulsions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SMEDDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liposomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Micro-/Nanoparticles</td>
</tr>
</tbody>
</table>

This figure provides an overview of commonly used ways to improve the solubility and hence the bioavailability of drug molecules. Usually the drug company will seek a way to modify the molecule in a way that it becomes more soluble. This can be a suitable salt; it can be also a pro-drug that is metabolized in-vivo into the final drug molecule. If this fails, the challenge facing drug formulators is to identify a suitable method for enhancing the drug molecule’s bioavailability. Before selecting an approach to this, the solubility problem needs to be defined. Butler et al. [2] therefore modified the biopharmaceutical classification system (BCS) to cope with this situation. Class II drugs are now subdivided into class IIa, where the dissolution rate is the challenge, and class IIb, where the apparent solubility of the drug molecule is low.
IUPAC has defined solubilization of a drug molecule as a process by which an agent increases the solubility or the rate of dissolution of a solid or liquid solute [3].

The apparent solubility (saturation solubility) is a drug-specific constant which is solvent- and temperature-dependent. Above the saturation limit, precipitation and recrystallization of the drug occurs. Surfactants and other solubilizing molecules such as Soluplus® are used to enhance the apparent solubility and hence to maintain the drug dissolved in a supersaturated state. Soluplus®, a polymeric solubilizer, enhances the apparent solubility by the formation of micellar structures and non-covalent interaction with the drug molecule.

In the case of a limited dissolution rate, decreasing the particle size of the drug crystals can improve solubility. By downsizing the particle size, the surface will increase; this usually improves the wettability and hence dissolution kinetics. Downsizing particles leads to a molecularly dispersed system. This can be a liquid or solid solution. It is mathematically described by the Noyes-Whitney-equation,

\[
\frac{dW}{dt} = \frac{DA (c_s - c)}{L}
\]

where \( \frac{dW}{dt} \) is the dissolution rate, \( D = \) diffusion coefficient, \( A = \) surface area of the solid, \( c_s = \) concentration in the diffusion layer (saturation concentration), \( c = \) concentration in the dissolution medium and \( L = \) thickness of the diffusion layer.
The more the particle size is reduced, the lower the thermodynamic stability becomes. To leave the crystalline state, energy is required. Transforming the drug into an amorphous state means bringing it to a higher energy state; to achieve this, the lattice energy must be overcome. However, only the crystalline structure is in the thermodynamically favored energy state. If the drug is in an amorphous state, stability (both chemical and physical) is often limited. Amorphous drug molecules often tend to re-crystallize since this is the favored energy state. Amorphous solid dispersions can be stabilized if the "freezing effect" is sufficient due to a high glass transition temperature of the system or, better, by interaction such as hydrogen bonding formation between the dispersed drug and the (often polymeric and amorphous) carrier.
Since solid dispersions usually capture the drug molecule in very small particle sizes, they often lead to an improvement in bioavailability. Newman et al. [4] reviewed scientific papers from the past 10–15 years in the field of solid dispersions. They found that in about 80 % of all cases, amorphous solid dispersions led to improved bioavailability. In 10 % of the cases no improvement was found and in approx. another 10 % amorphous solid dispersions resulted in reduced bioavailability.

**What are solid dispersions?**

Janssens et al. [5] provide a good overall definition of solid dispersions:

"Formulation of poorly soluble compounds as solid dispersions might lead to particle size reduction, improved wetting, reduced agglomeration, changes in the physical state of the drug and possibly dispersion on a molecular level, according to the physical state of the solid dispersion. The physical state of the solid dispersion will depend on the physicochemical properties of the carrier and the drug, the drug-carrier interactions and the preparation method."

This definition indicates that there are several types of solid dispersions:

<table>
<thead>
<tr>
<th>Type of solid dispersion</th>
<th>Matrix</th>
<th>Drug</th>
<th>Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Eutectics</td>
<td>C</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>II Amorphous precipitates in crystalline matrix</td>
<td>C</td>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>III Solid solutions</td>
<td>C</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Continuous vs. discontinuous</td>
<td>C</td>
<td>M</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Substitutional vs. interstitial</td>
<td>C</td>
<td>M</td>
<td>1 or 2</td>
</tr>
<tr>
<td>IV Glass suspension</td>
<td>A</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>V Glass suspension</td>
<td>A</td>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>VI Glass solution</td>
<td>A</td>
<td>M</td>
<td>1</td>
</tr>
</tbody>
</table>

Type IV is classified as a crystalline glass suspension, type V as an amorphous glass suspension whereas type VI is usually referred to as a solid glassy solution. To obtain a solid glassy solution, a certain degree of miscibility, i.e. a certain degree of solubility of one component in the other is required. This means that the drug can dissolve in the polymer up to a certain degree.
The latter three types of solid dispersions are prominent nowadays when preparation methods such as hot-melt extrusion or spray drying are involved. The next figure illustrates their composition. Type IV (on the left) is achieved if the drug is dispersed as crystals in the amorphous polymer phase. This is a two-phase system. In a thermogram obtained by differential scanning calorimetry (DSC), the melting of the drug and the original glass transition phase of the polymer would be detected. This type of solid dispersion is very stable since the drug remains in its favored crystalline state. Type V (center) means that the drug is transformed into an amorphous state but is not molecularly dispersed in the polymer matrix. This in turn means that there are amorphous drug clusters incorporated in the polymer. In this case, a DSC thermogram will show two glass transition temperatures (Tg): one Tg will result from amorphous polymer, the other Tg will result from amorphous drug. If the glass transition temperature ranges of drug and polymer overlap too much, it might be difficult to discriminate by DSC whether it is a type V or a type VI solid dispersion. In the case of type VI (on the right), the solid dispersion of the drug is molecularly dispersed in the polymer phase. This results in a single-phase system showing only one glass transition temperature. Type V solid dispersions are usually meta-stable. This means that, in the case of a too large amorphous drug cluster, nuclei formation and hence nuclei growth resulting in fast recrystallization is likely to occur. If the cluster of the amorphous drug is small enough that it does not contain a sufficient number of drug molecules to recrystallize, then the amorphous glass suspension (type V solid dispersion) stability can be kinetically controlled by immobilizing the drug in a super-saturated state in the highly viscous polymer; this can be ensured via a high glass transition temperature of the polymer. Since water acts as a plasticizer and lowers the glass transition temperature, moisture absorption needs to be avoided in the case of type V solid dispersions in order to maintain sufficient stability. To achieve type VI solid dispersions, the molecular dispersed drug should be immobilized by interaction with the polymer. This interaction can be via hydrogen bonding. Polymers such as Soluplus® and Kollidon® VA 64, due to their amide structure, provide the drug molecule with hydrogen bond acceptors; they thus act as suitable carriers for a broad variety of drug molecules in achieving type VI solid dispersions which are thermodynamically stabilized since their compositions are similar to those of liquid solutions. An important aspect of having a solid glassy solution is that the total interaction forces between drug and polymer are stronger than the self-association forces among the drug molecules themselves.
The glass transition temperature of the solid glassy solution can be predicted using the equation compiled by Gordon-Taylor [7] or the simplified form by Fox [8].

\[ T_g = \frac{w_a T_a + w_b T_b}{w_a + k w_b} \]  \hspace{1cm} \text{Equation 1-1}

Equation 1-1 comprises: \( T_g \) – Glass transition temperature of blend; \( T_a, T_b \) – Glass transition temperatures of components a and b; \( w_a, w_b \) – weight fractions and \( k \) – constant.

The Fox-equation is:

\[ \frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \]  \hspace{1cm} \text{Equation 1-2}

The common and proven technologies for the manufacture of amorphous solid dispersions with their advantages and disadvantages are shown below.
In this book, hot-melt extrusion will be discussed with its advantages and disadvantages in the following chapters. It is a process for preparing solid dispersions. Co-rotating twin-screw extruders are used in the pharmaceutical industry to prepare solid dispersions.

The parameters of relevance for the stability of solid glassy solutions and for the stabilization of the drug after release to a super-saturated aqueous phase are displayed below.

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hot-melt extrusion</td>
<td>- Solvent-free</td>
<td>- Temperature</td>
</tr>
<tr>
<td></td>
<td>- Fast + continuous process</td>
<td>- Downstream processing</td>
</tr>
<tr>
<td></td>
<td>- Low cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Small footprint</td>
<td></td>
</tr>
<tr>
<td>• Spray drying</td>
<td>- Fast process</td>
<td>- Solvent residues (temperature)</td>
</tr>
<tr>
<td></td>
<td>- Flexible particle sizes</td>
<td>- Cost</td>
</tr>
<tr>
<td>• Freeze drying</td>
<td>- Mild conditions</td>
<td>- Solvent residues - Cost</td>
</tr>
<tr>
<td>• Supercritical fluid drying</td>
<td>- Mild conditions</td>
<td>- CO₂ has limited solubility - Cost</td>
</tr>
</tbody>
</table>
There are two major challenges: the first is to develop a solid dispersion which remains unchanged over the substance shelf-life. A totally unchanging solid dispersion is practically impossible to achieve. This is because amorphous polymers experience an "aging" process after being processed by hot-melt extrusion or spray drying where the polymer chains were fully flexible during processing but where, after processing, the polymer is stored below its glass transition temperature range. The "aging" depends on different parameters; cold flow is one of several. However, the cooling rate of the extruded melt may have an impact because it determines how relaxed the melt is when it reaches a point below its glass transition. The spray drying process is analogous where the solvent evaporation rate can be seen to be similar to the cooling rate in HME. Another challenge in developing a solid dispersion is that the drug, after being released from the protecting polymer matrix, does not precipitate when released at a super-saturated concentration level. The capability to maintain the drug dissolved in a super-saturated state is strongly dependent on the polymer characteristics. Soluplus® was developed with its amphiphilic structure as a polymeric surfactant and can maintain many drug molecules in a super-saturated state. In practice it is often not necessary to avoid precipitation fully. The precipitation rate must not be higher than the absorption rate for the drug molecules.
How does the hot-melt extrusion process generate solid dispersions?

As can be seen in Figure 1-4, the crystal lattice energy has to be overcome to transform the drug into its amorphous form. Additionally, the drug and the polymer need to be blended and subsequently co-dispersed. This is what the extruder does by applying shear stress to the drug and to the polymer. It generates energy by friction in order to overcome the crystal lattice energy and to soften the polymer. On the extruder screws the material is mixed and dispersed at the same time. The basic extrusion process is shown in the figure below. The API (crystalline) and amorphous polymers are fed into the extruder, conveyed, exposed to shear inside the extruder and subsequently the melt is pressed out under a certain pressure. The melt is then collected for further processing.

Figure 1-8  ▪ Hot-melt extrusion is an efficient processing method for obtaining solid dispersions
Hot-melt extrusion (HME) is a recognized process for the manufacturing of solid dispersions and innovative new dosage forms. It 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 high glass transition temperatures (such as polyvinylpyrrolidones) to pharmaceuticals [9]. Later, Soliqs, the drug delivery business unit of Abbott GmbH & Co KG, commercialized the technology and subsequently launched several drugs [10]. A number of research groups have demonstrated that the HME process is a viable technique for the preparation of pharmaceutical drug delivery systems, including granules [11, 12], pellets [13, 14], sustained release tablets [15, 16, 17, 18, 19], transdermal and transmucosal drug delivery systems [20, 21, 22, 23, 24, 25, 26, 27, 28] and implants [29, 30, 31, 32]. HME is thus an attractive alternative to traditional processing methods [33]. Examples for solving pharmaceutical challenges via HME are given in the table below.

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution by HME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (low/unreliable) bioavailability due to inadequate API solubility</td>
<td>Use of hot-melt extrusion to prepare solid solution/dispersions or SEDDS (enhanced dissolution)</td>
</tr>
<tr>
<td>Poor API stability during processing caused by hydrolysis</td>
<td>Use of hot-melt extrusion as alternative to wet agglomeration (no hydrolytic stress)</td>
</tr>
<tr>
<td>Unreliable sustained release action</td>
<td>Use of hot-melt extrusion to prepare sustained release dosage forms (single/multiple units)</td>
</tr>
<tr>
<td>Poor stability or tolerability of API in the stomach</td>
<td>Use of hot-melt extrusion to prepare enteric dosage forms (single/multiple units)</td>
</tr>
<tr>
<td>Poor taste of the API</td>
<td>Use of hot-melt extrusion to prepare taste-masked dosage forms</td>
</tr>
<tr>
<td>Manufacturing of films</td>
<td>Use of hot-melt extrusion to prepare oral strips or dermal patches in a solvent-free process</td>
</tr>
</tbody>
</table>

Hot-melt extrusion is currently generating more and more interest as the percentage of poorly soluble new chemical entities in drug development is constantly increasing. For such molecules, hot-melt extrusion offers an opportunity to make them orally bioavailable [34]. Additional benefits are the creation of a reliable drug release profile and a robust manufacturing process which can be run in practically any pharmaceutical factory. 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 tableting,
hot-melt extrusion is still an emerging technology and its potential has not yet been fully explored. The technology itself can be defined as a process where a material which melts or softens under elevated temperatures and pressures 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. BASF offers a range of approved polymers with different structures and properties for use in hot-melt extrusion.

The 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 and hence the contact surface, which must meet regulatory requirements. The contact parts of the extruders used in pharmaceuticals must not be reactive nor may they release components into the product. The extruder equipment is specially configured to fulfill all cleaning and validation standards applicable to the pharmaceutical industry.

The utilization of extruders in the pharmaceutical industry cannot be seen as a niche application; this is clearly shown in the figure below demonstrating four fields of versatility of the technology. Not all of the benefits have been actively adopted to date.

In principle, an extruder consists of barrels enclosing single or twin screws which transport and subsequently force the melt through a die, 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 pharmaceuticals [35]. The hot-melt extrusion process comprises the steps melting, mixing and shaping.

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 by circulation in a helical path by means of transverse flow, drag flow, pressure flow and leakages [33]. 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 barrels, the attached die dictates the shape of the extrudates.

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

Rauwendaal [36] further recommends measuring and monitoring at least the following parameters in an extrusion process with standard instrumentation:
- Melt pressure
- Melt temperature
- Torque or power consumption
- Barrel and die temperatures
- Screw speed
- Energy transfer in each temperature zone (heating and cooling)
- Ambient temperature
- Relative humidity
- Temperature of feed stock entering the extruder
- Moisture level of feed stock entering the extruder
- Vacuum level at venting port (when applicable)

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 [33].

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 [33]:
- Easier material feeding
- High kneading potential
- High dispersing capacities
- Less tendency to overheat
  (important for sensitive APIs)
- Shorter and constant residence times

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 [37, 38].

![Basic nomenclature of a screw element](image)

D₁ is the inner diameter and D₀ the outer diameter of the screw. The D₀/D₁ ratio is very important and indicates the available free volume of the extruder. The length of the extruder barrel and subsequently the length of the screws is given as a multiple of the outer screw diameter. This means an extruder with a functional length of 40 L/D has a screw length 40-times the outer screw diameter. For scale-up purposes, it is important to keep the functional length and the D₀/D₁ ratio constant.

The configuration of the screws can be varied by number and arrangement of conveying and kneading elements [34].
Conveying elements

Profiles with open chambers:
- In the feeding sections
- For melt exchange
- For degassing (venting)

Profiles with closed chambers:
- For high pressure build-up
- In front of kneading elements

Kneading elements

Kneading elements are used to introduce shear energy to the extruded materials.

The elements are arranged in different offset angles (30°, 60° and 90°) used for:
- Plasticizing
- Mixing
- Dispersing

Figure 2-5  Screw elements, their application and effects on the extrusion process

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 forwarding (30° and 60°) and neutral (90°) to reversing (30° reverse) character. Neutral elements (90°) push material neither forwards nor backwards. Irrespective of the reverse-flighted element, ability for mixing and shearing...
of the material increases the higher the advance angle. Reverse-flight kneading blocks have a retaining character and are usually utilized when substantial mechanical stress has to be exerted onto the material [12].

For each section, the most relevant influencing parameters are given in the next figure [39]. Start on the left side (solid feeding) with the extrusion process flow chart for better readability.

![Figure 2-6](image)

**Figure 2-6** Relevant parameters influencing the performance of the different screw sections [39] (drawn screws courtesy of Coperion, Germany)
Below, the major tasks of the different sections inside a twin-screw extruder are described:

**Solid feeding:**
- Conveying and compression of solids
- Removal of air

**Melting and plastification:**
- Softening of polymer
- Pre-dispersion of components such as the drug

**Melt conveying zone:**
- Conveying melt

**Distributive mixing zone:**
- Distribution of solids or fluids in the (polymer) melt

**Dispersive mixing zone:**
- Breaking down solids, polymer particles and droplets

**Devolatization zone:**
- Removal of water, residual monomers and solvents

**Pressure build-up zone:**
- Build-up of pressure for discharge (extrusion)

**Distributive versus dispersive mixing**

As displayed in the following figures, some mixing elements have a stronger distributive mixing effect while others have a more dispersive effect. Both types of mixing are required in the preparation process for a solid dispersion. The distributive mixing process ensures that the active pharmaceutical ingredient (API) is homogeneously distributed throughout the whole polymer matrix. The distributive screw element leads to a state of homogeneity whereas the dispersive mixing elements apply more shear stress and have less conveying capability and therefore break down any agglomerates. Depending on their geometry, dispersive acting screw elements can break down agglomerates to a molecular level. The state of molecular dispersion is usually achieved by a combination of dispersive and distributive mixing. Furthermore, if the drug particles are small enough (agglomerate structure sufficiently broken down by mixing elements), they can dissolve in the polymer melt. The function of distributive mixing elements now is to avoid oversaturated stages of the drug in the polymer i.e. clusters of drug should be destroyed and the drug should be homogeneously distributed in the polymer melt.
<table>
<thead>
<tr>
<th>Conveying element</th>
<th>Free volume</th>
<th>Conveying effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-flighted element</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Standard element</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Shear edge element</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kneading element</th>
<th>Mixing effect (distributive)</th>
<th>Shear effect (dispersive)</th>
<th>Conveying effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Neutral</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kneading element</th>
<th>Mixing effect (distributive)</th>
<th>Shear effect (dispersive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X0</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>X0</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

Figure 2-7  -  Different screw elements and their characteristics  
(pictures courtesy of Coperion, Germany)
Mixing elements as shown are available with different staggering angles and disk widths.

**According to Kohlgrüber [39], a larger staggering angle leads to:**
- Reduction of conveying action of the melt
- Improved mixing action due to:
  - More leakage streams being generated
  - Residence time being increased

**Making the kneading discs more narrow leads to:**
- Reduced shear in the clearance between screw/screw and screw/barrel
- Increased conveying action of the melt
- Efficient mixing due to more leakage streams being generated
Since the melting process of materials is improved when the plastification zone is completely filled, it is usually recommended to install a re-conveying element at the end of the plastification zone. However, since most pharmaceutical polymers such as Soluplus® or Kollidon® VA 64 can be easily softened without high shear stress, such re-conveying elements are often not required. The disadvantage of re-conveying elements can be the high temperature peaks they can cause.

**In general it can be said that the following factors increase the dispersion effect:**
- Sufficient residence time in the mixing zone
- High screw speed
- Low throughput
- Narrow clearance between screw/screw and screw/barrel
- High melt viscosity

**Screw elements for processing shear-sensitive materials at reduced shear stress**

Kohlgrüber [39] and other reference sources, e.g. [40], list numerous different screw element geometries, all of which have the effect of exerting less shear stress on the extruded material. Many of the screw geometries are patent-protected by extruder or screw element manufacturers. Some examples of patent-protected geometries are described in the references [41, 42].

**Feeding**

Powder or granules are usually gravimetrically dosed into the extruder. The material is heated and more or less melted in the first part. Thereafter, the material is mixed and homogenized by the kneading elements, and, at the end, extruded through a die which can have various shapes. Residence times in the extruder vary depending on the size of the extruder, screw speed, screw configuration and feed rate. They range typically from 0.5 to 5 minutes.

The feeding mode of the feeders can be gravimetric and volumetric. Gravimetric feeding is typically specified for c-GMP installations.

**Feeders for pharmaceutical materials have the following characteristics:**
- They are easy to clean and disassemble
- Stainless steel components are used
- Stainless steel shrouding is used for non-stainless-steel parts
- Qualification documentation is available
Table 2-2 ▪ Feeder and feeding modes

<table>
<thead>
<tr>
<th>Gravimetric feeding</th>
<th>Volumetric feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screw rotation speed is adjusted to keep the mass-flow rate constant (quantity per unit of time)</td>
<td>Used as refill devices for gravimetric feeders</td>
</tr>
<tr>
<td>Gravimetric feeding is typically specified for GMP installations</td>
<td>High fluctuation in the mass-flow rate for metering dry ingredients into the extruder (variations in material bulk density because of handling / variations in screw flight loading)</td>
</tr>
</tbody>
</table>

Downstream processing

Downstream extrusion equipment is used to finish, shape and analyze the extruded product. After leaving the die in the form of continuous strands or ribbons, cooling and cutting is performed, resulting in the required particle size. Process Analytical Technology (PAT) instruments such as in-line NIR (Near Infrared Spectroscopy) can be used to check the homogeneity of the active ingredient in the extrudate. Different HME downstream processes (e.g. chilled rolls, calendering, pelleting devices, co-extrusion) are described in more detail in chapter 8.

Polymers for hot-melt extrusion

The polymer must exhibit thermoplastic characteristics in order to enable the hot-melt extrusion process to take place 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 2-9 ▪ Basic requirements for polymers used in HME](image)

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

Polymers with a high solubilization capacity are particularly suitable because large quantities of drugs can be dissolved. Some features like lipophilicity, hydrogen bonding acceptors or donors [43] and amide groups are basic prerequisites for a high solubilization capacity; the same applies to organic solvents. This explains why povidone, copovidone and Soluplus® are highly suitable for hot-melt extrusion. Copovidone and Soluplus® in particular are much more lipophilic than many other water-soluble polymers containing hydroxyl groups and, therefore, are best suited
Impact on solubilization capability
- Lipophilicity
- Solubility parameter
- Hydrogen bonding
- Amide structures acting as hydrogen bond acceptors

"Similia similibus solvuntur"

**Excellent solvents**
- Dimethyl acetamide
- Dimethyl formamide
- Pyrrolidone
- Methyl pyrrolidone

**Poor solvents**
- Methanol
- Acetone

**Excellent polymers**
- Soluplus®
- Kollidon® VA 64
- Kollidon® 30

**Poor polymers**
- Kollicoat® IR
- HPC

Figure 2-10  Solubilization capability

Matrix Formers
- Kollidon® VA 64 / Fine
- Kollidon® SR
- Kollidon® 12 / 17 PF
- Kollidon® 30 / 90 F
- Kollicoat® IR
- Kollicoat® Protect
- Kollicoat® MAE
- Soluplus®

Lipophilicity

Figure 2-11  Application fields of BASF pharma polymers

to the lipophilicity of poorly soluble drugs. In addition, the solubility parameter can be used to determine whether actives and polymers are compatible [44, 45].
When the drug is incorporated in a supersaturated form, the whole mixture should have a very rigid structure in order to minimize crystallization either from dissolved drug or from amorphous drug particles [46, 47]. The formulation, being a solid solution, dissolves in gastric or intestinal fluids forming a supersaturated solution of the drug in these aqueous media, thus enhancing dissolution and bioavailability [48]. Extrudability is mainly determined by the glass transition or melting temperature and melt viscosity [49]. 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 degrade sensitive drugs. As a general rule, extrusion processes can be run at temperatures 20–40 °C above glass transition temperature. Most polymers demonstrate thixotropic behavior, which means that the viscosity reduces as a function of increasing shear stress.

Plasticizers added to the polymer can reduce glass transition temperature and melt viscosity, thus facilitating the extrusion process [50]. Some actives may also have a plasticizing effect.

An extrusion temperature range of 90–140 °C for a drug containing polymer seems to be best, since the drug should survive thermal stress lasting for 0.5–5 minutes in a non-aqueous environment.

In extruded drug delivery systems, the polymer serves as a matrix and, in consequence, larger quantities are required than in its more common use as a binder or coating agent. It is crucial that the polymers are non-toxic and approved in various countries at high doses. Kollidon® VA 64 completely fulfills this requirement. Based on toxicological studies, other polymers may also be used in high doses; however, these have not yet been approved in such doses. The regulatory status of the BASF pharma polymers is summarized in chapter 19 of this compendium.

**Advantages of hot-melt extrusion in detail**

*Within the pharmaceutical industry hot-melt extrusion has been used for various purposes, such as:*

- Enhancement of the dissolution rate and bioavailability of a drug
- Controlling or modifying drug release
- Taste masking
- Stabilizing the API
- Parenteral depots and topical delivery systems

Increasing dissolution rate and bioavailability of APIs that are poorly soluble in water are important challenges in dosage form development. One approach is the formation of a solid solution/Dispersion of a drug with hydrophilic excipients. The solid solution is the ideal type for increasing drug release. In this formulation, the drug is molecularly dissolved and has a lower thermodynamic barrier for dissolution [51].
Polymer matrix acts as a solid solvent for drug molecules
- In the ideal case, the drug is molecularly dissolved in the polymer
- Enhanced rate of dissolution and solubility of drug molecules compared to the crystalline form

Figure 2-12 ▪ From poor API solubility to a final formulation

Once developed, hot-melt extrusion is a reliable and robust process offering benefits in cost-efficiency. Compared to other processes for the production of solid solutions, it is far less complex, since the manufacturing of such dosage forms requires only a few steps and avoids the use of organic solvents.
Hot-melt extrusion also has advantages over solvent-based methods of forming solid solution/dispersions:

- No need to handle explosive solvents
- Absence of residual solvents
- Possibility of continuous processing
- Fewer process steps
- High product density
- Non-dusty pellets (e.g. for HAPI formulations)
- Small-scale equipment
- Non-aqueous process

Besides oral drug formulations, the hot-melt extrusion technique can be employed to manufacture parenteral depots such as injectable implants and stents and topical delivery systems such as dermal or transdermal patches. For these applications, the extrusion process is often combined with a shaping step or injection molding.

Opportunities and advantages of the hot-melt extrusion process from the technical point of view are shown below.

| Solid dispersion | • Crystalline, amorphous or molecular dispersed  
|                 | • Can enhance solubility and hence bioavailability  
|                 | • Controlled release matrix systems |
| Temperature     | • Temperature can be set low if required for stability  
|                 | • Can be set high if required for melting API |
| Mixing          | • High dispersive mixing capability  
|                 | • Efficient and reproducible mixing due to positive mixing principle  
|                 | • Shear can be set to a very mild value |
| Process         | • Continuous for adjustable batch volumes  
|                 | • Reduced number of process steps  
|                 | • No solvents required |

Figure 2-14  • Opportunities and advantages of hot-melt extrusion
3 Process Variables of Twin-Screw Extruders

The melt extrusion process is a continuous one since it can continuously process e.g. polymer and API into a finished extrudate, shape etc. All the required process steps can be run together in series, e.g. feeding the materials (the upstream), compounding/extrusion and downstreaming (cooling/shaping). The downstream process can be continued immediately to a final product such as a tablet.

In the extrusion line, all the materials to be processed pass through the machine in a constant stream. Compared to other processes such as fluid bed systems or blenders, there is no way back for the material already in the process chain; however, there is some backflow inside the extruder (especially close to the die section) leading to some circulation of melt.

The compounding step comprises a distributive mixing step, where the materials are thoroughly mixed, and a dispersive mixing step, where agglomerates are broken down and particle size is reduced, in some cases to the molecular level. The mixing or blending process (called compounding) can be carried out either solvent-free or with solvents.

The required energy necessary for the desired transformation of material (blending, dispersing, melting etc.) can be dosed very precisely as at least 80–90% of the energy is supplied via the extrusion screws and the material gets softened and/or melted mainly by frictional heat generation which strongly depends on the viscosity of the system. This allows fine-tuning of the energy consumption by e.g. varying the screw-speed, throughput and the configuration of the screws and the barrel.

If the energy to process the materials inside the extruder comes almost entirely from the screws and there is no surplus energy that needs to be removed by the cooling system, the process is called autogenous. This is the most favorable process condition for achieving high quality extrudates with a minimum of degradation. The aspect of autogenous extrusion is also important for scale-up since the ratio of surface to volume becomes more unfavorable with increasing extruder size, especially if the process has not been developed to run autogenously on a small scale.

As the extruder is meant to be a closed system like a pipe with forced conveying by the extruder screws, the residence time distribution can be precisely adjusted and controlled. The mean residence time can be very short (less than 30 seconds) but it can also be very long (> 5 minutes). The extruder offers a broad and adjustable range for its parameters; the same applies to energy consumption.

The extruder has a small footprint, especially on a production scale, and compares very favorably with other equipment which has to process individual batches and therefore requires more space.
The melt extrusion process offers the possibility for in-line and on-line analytics. The majority of pharmaceutical processes can be equipped with analytical systems. However, attaching analytical systems to the melt extrusion process is interesting since it is a continuous process, where the material passes a certain position only once. The extrusion process can produce very large batches by running e.g. 24 hours a day, 7 days a week. The risk of not monitoring the critical process steps could incur high costs if a large amount of material turns out to be out of specification.

The extruder with its instrumentation should be seen as one system comprising a series of different process devices connected on-line to continuously manufacture a product.

One of the most critical steps in the preparation of a solid dispersion is the compounding step inside the extruder. As the extruder barrels are closed, inside viewing is difficult. Therefore, this chapter will explore the possibilities of how to develop a better understanding of the inside of an extrusion process.

Rauwendaal [52] lists the requirements for efficient extrusion which he intended for plastics extrusion but which are even more relevant in pharmaceutical melt extrusion:

- Efficient machinery
- Preventive maintenance
- Quality materials
- Trained work force
- Efficient trouble-shooting
- Design of experiments
- Statistical process control
- Instrumentation and control
- Data acquisition system
- Total line control

The last 5 points especially have to be considered within the context of process analysis and hence process understanding.

Every modern stand-alone extruder is already equipped with a certain amount of instrumentation:

- Temperature measurement and controls for the extruder barrels
- Speed measurement and control for the screw(s)
- Pressure measurement at least at the extruder die with feedback control such as emergency switch-off of the extruder in the case of over-pressure
- Torque measurement (at least relative) by measuring the power consumption of the extruder motor and feedback control for stopping the extruder screws or slowing them down in the case of too high torque being applied to the screws
Rauwendaal [52] further recommends the measuring and monitoring of at least the following parameters in an extrusion process with standard instrumentation:

- Melt pressure
- Melt temperature
- Power consumption
- Barrel and die temperatures
- Screw speed
- Energy transfer in each temperature zone (heating and cooling)
- Ambient temperature
- Relative humidity
- Temperature of feed stock entering the extruder
- Moisture level of feed stock entering the extruder
- Flow rate of cooling water
- Temperature at cooling water inlet
- Temperature at cooling water outlet
- Vacuum level at venting port (where applicable)

By monitoring these parameters, many potential problems in the extrusion process can be avoided. The process can thus be maintained and optimized and can be characterized by certain important aspects. Extrusion system parameters such as specific energy can be determined by these parameters.

The above-mentioned extruder instrumentation allows the operator to control the extruder in an optimal way. Some critical quality attributes can be linked via the extrusion system parameters to values monitored with the extruder instrumentation.

**What are the extrusion system parameters?**

Between the feeding section and the die of the extruder much happens with the processed material. Although it looks to be attractive, one should not directly link or correlate critical quality product attributes determined on the extruded material with parameters set at the beginning such as throughput, screw speed and barrel temperature. A better all-round solution is to understand exactly what happens inside the extruder with the polymer and API and to use this knowledge to optimize the process and hence the proposed formulation.

The following figure shows a possible scenario based on changing parameters too fast without adequate process analysis. The case assumes the problem to be a too high level of impurities resulting from the extrusion process. The quick assumption is that the impurities are induced by temperature and hence the extrusion temperature is reduced. This of course lowers the barrel temperature and it is therefore expected that the impurity level will decline. This can indeed be the case but it can also lead to an increase in impurities. Why is this? The lower barrel temperature will lead to a higher viscosity of melt which (still being treated with the same screw speed) means a higher shear
stress and in turn at least localized temperature increases. As a result, the higher shear with higher (real) temperatures might even lead to higher impurity levels than before.

This example shows that it takes more to make a good decision on resolving issues in the extrusion process.

Before running the extruder, it has to be set up in the right way. Based on experience, on simulation or estimations, a decision should be made on the screw and barrel design. Decisions also have to be made as to whether a degassing section or certain mixing and melting sections are required. Subsequently, the kinds of feeders, gravimetric or volumetric, for split feeding or feeding a single blend have to be selected. And selection of the right extrusion die is of course important.

Screw speed and feed rate should be based on a specific temperature profile. It is assumed here that the operator is targeting the best possible quality with the chosen set-up in the sense of the important critical quality attributes. However, how does one know which parameter to adjust and to what level? How does one know which parameter to change in order to optimize a quality attribute? How are critical quality attributes linked to the extrusion input parameters?

Extrusion system parameters are response variables which describe (abstractly) the inside of the extrusion process.
Two other very important extrusion system parameters are the residence time distribution and the specific energy consumption. Both alone and in combination allow a good description of the internal process.
Before investigating how both of these parameters can be determined, an insight of the extrusion process will be given:

The velocity of the extruded material inside the extruder basically depends on the conveying characteristics of the screw segment the material is passing. The shear stress is usually minimum at fast conveying sections and reaches its maximum on screw elements such as kneading discs, where the velocity reaches its minimum but shear reaches its maximum.

The residence time distribution expresses the different velocities of the melt inside the extruder and is hence mainly dependent on the screw geometry. Other factors are also involved but these will be discussed later. Specific mechanical energy consumption (SMEC) expresses the shear stress by the energy supplied to the extruded material. If the extrusion process is not fully autogenous, it is also important to determine the specific thermal energy.

**Determination of specific mechanical energy consumption (SMEC)**

The specific mechanical energy consumption can be calculated using the following equations:

\[
\text{SMEC} = \frac{2 \cdot \pi \cdot n \cdot \tau}{\dot{m}} \quad \text{[kWh/kg]}
\]

**Equation 3-1 [39]**

where \( n \) is the screw speed, \( \tau \) is the torque on the screw shafts and \( \dot{m} \) is the throughput.
Taking \( n \) in [rpm] and \( \tau \) in [Nm], the power \( P \) [kW] can be calculated using the following equation:

\[
P = \frac{2 \cdot \pi \cdot n \cdot \tau}{60} \quad \text{[kW]} \quad \text{Equation 3-2}
\]

The specific mechanical energy can be calculated using the following equation:

\[
\text{SMEC} = \frac{n \cdot P \cdot O}{n_{\text{max}} \cdot m} \quad \text{[kWh/kg]} \quad \text{Equation 3-3 [53]}
\]

where \( O \) is the engine loading in \% and \( n_{\text{max}} \) is the maximal screw speed in revolutions per minute [rpm] of the extruder.

Finally, we can calculate the specific mechanical energy consumption by using the equation:

\[
\text{SMEC} = \frac{\tau \cdot n}{m} \quad \text{[kJ/min]} = \frac{\text{kJ}}{\text{kg}} \quad \text{Equation 3-4 [54]}
\]

where \( \tau \) is the torque in kJ.

The specific mechanical energy consumption depends mainly on the torque.

**The torque applied to the screws by the motor is used for:**

- Turning the screws (\( \tau_{\text{empty}} \))
- Pumping the material through the die (\( \tau_{\text{pumping}} \))
- Shearing the material (\( \tau_{\text{shearing}} \)) [55]

Hence we can write the total torque \( \tau_{\text{total}} \) applied to the screws as:

\[
\tau_{\text{total}} = \tau_{\text{empty}} + \tau_{\text{pumping}} + \tau_{\text{shearing}} \quad \text{Equation 3-5}
\]

And hence we can write:

\[
\text{SMEC}_{\text{total}} = \text{SMEC}_{\text{empty}} + \text{SMEC}_{\text{pumping}} + \text{SMEC}_{\text{shearing}} \quad \text{Equation 3-6}
\]

To calculate \( \text{SMEC}_{\text{pumping}} \) we can use:

\[
\text{SMEC}_{\text{pumping}} = \frac{m \cdot \Delta P}{\omega} = \frac{\text{SFL} \cdot \Delta P}{2\pi p} \quad \text{Equation 3-7}
\]
where $\omega$ is the angular frequency and where SFL is the specific feed load and is given by:

$$\text{SFL} = \frac{\dot{m}}{n}$$  \hspace{1cm} \text{Equation 3-8}

$\Delta P$ is the measured pressure at the extruder die.

This means that the determined total specific mechanical energy consumption does not describe the energy consumed by the material by shear only. This is important to consider when linking critical quality attributes such as impurities to specific mechanical energy consumption. The energy portion which is applied for simply turning the screws is unlikely to be a cause for impurities. The SMEC$_{\text{empty}}$ can be measured directly and also includes the loss of energy on transmission within the extruder gear box.

**Determination of residence time distribution**

Another important characteristic which has a significant influence on product quality is the residence time distribution.

**Knowing the residence time distribution is important for:**
- Heat-sensitive products and for dispersion and melting [39]
- For the mixing process inside the extruder
- The average time a fluid element remains in the extruder [39]

**The most important numbers which can be calculated from the residence time distribution are:**
- The mean residence time (expresses the time where 50% of a tracer has passed the extruder)
- Variance $\sigma_t^2$ of the residence time distribution which is a measure of the axial back-mixing in the extruder
- Bodenstein No. (Bo) which is a measure of the diffusion and hence for the mixing capability
  - $\text{Bo} \rightarrow \infty$ means no axial mixing
  - $\text{Bo} \rightarrow 0$ means complete back-mixing [56]

In the simplest case, residence time is measured with an optical tracer, which has to be of a kind that does not influence the process. Colored pigments are suitable tracers.

For this method, the tracer is added to the extrusion process at $t = 0$ in the shortest possible time. Tracer concentration should be selected as low as possible. Influence of the tracer on the process (e.g. torque) should be avoided at all cost. A camera located at the end of the extruder captures a picture e.g. at one-second intervals. The lighting must be constant to obtain reliable results. The software stores the color values; these can then be used to calculate the residence time distribution.
Each run lasts 10 min (600 s + 10 s pre-run for offset determination)
- One picture should be taken per second

Simple analytical setup which works reproducibly and does not incur high cost.

Figure 3-4  ▪ Set-up for measuring tracer concentration for residence time distribution determination

The residence time distribution is represented by the exit age distribution [57]:

$$\int_0^{\infty} E(t) \, dt = 1 \quad \text{Equation 3-9}$$

$$E(t) = \frac{c}{\int_0^{\infty} c \, dt} = \frac{c}{\sum_0^{\infty} c \Delta t} \quad \text{Equation 3-10}$$

where \( c \) is the tracer concentration (intensity) at time \( t \). The exit age function has the unit of time\(^{-1}\).

The cumulative residence time distribution function can be obtained from [57]:

$$F(t) = \int_0^{t} E(t) \, dt = \sum_0^{t} E(t) \Delta t = \frac{\sum_0^{t} c \Delta t}{\sum_0^{\infty} c \Delta t} \quad \text{Equation 3-11}$$

The mean residence time is given by the first moment of the exit age function:

$$\bar{t} = \int_0^{\infty} t \cdot E(t) \, dt \quad \text{Equation 3-12}$$
Hence the mean residence time $\bar{t}$ can be calculated by using:

\[
\bar{t} = \frac{\int_{0}^{\infty} tc dt}{\int_{0}^{\infty} c dt} = \frac{\sum_{0}^{\infty} tc\Delta t}{\sum_{0}^{\infty} c\Delta t}
\]

**Equation 3-13**

The variance $\sigma_t^2$ can be calculated using:

\[
\sigma_t^2 = \frac{\sum_{0}^{\infty} t^2c\Delta t - \overline{t}^2}{\sum_{0}^{\infty} c\Delta t}
\]

**Equation 3-14**

In a first approximation, the Bodenstein No. can be calculated by using:

\[
Bo = \frac{2\overline{t}^2}{\sigma_t^2}
\]

**Equation 3-15**

This approach is valid for larger values ($Bo >> 10$). Here, the extruder is considered a one-vessel reactor. To improve the precision of the Bo determination, the steps N of the equivalent ideal vessel cascade need to be calculated first. More information on how to do this can be found in [56].

![Exit age function of residence time distribution with Soluplus®](image)

**Figure 3-5** - Exit age function of residence time distribution with Soluplus®
In general, the residence time is not plotted versus the time \( t \) but versus the dimensionless relative time \( \theta \) (simplified approach used here):
\[
\theta = \frac{t}{t'}
\]

\( \text{Equation 3-16} \)

![Cumulative function of residence time distribution with Soluplus®](image)

In both residence time distributions shown above the mixed flow curves are calculated assuming a one-vessel reactor.

**How to read the data**

When performing a series of experiments, it will soon be realized that the mean residence time in an unchanged extruder configuration is mainly dependent on the throughput. Since the extruder can extrude only the material that was fed in before, the screw speed has a minor impact since on a co-rotating twin-screw extruder the feed rate is determined by the feeder and not by the screw speed. Temperature also has a minor impact, indicating that residence time does not depend much on the viscosity.

The relationship of extrusion input variables to the specific mechanical energy consumption is a little more complex as can be seen in the next figure. These data are derived from a real design of experiment (Soluplus®) performed on a Thermo Fisher Pharmalab 16 mm co-rotating twin-screw extruder.
Any increase in throughput will result in declining SMEC. In contrast, the influence of the screw speed will result in a higher energy supply to the extruded material (and will also lead to higher product temperature). Since the viscosity will decrease at higher material temperature, less torque is necessary to extrude the material and hence the specific mechanical energy consumption will decrease. An interesting aspect would be to consider the specific feed load SFL as an independent extrusion input variable. Since it expresses the amount of material on the screws per rotation and throughput and screw speed act in the opposite way, the specific mechanical energy consumption shows a much closer dependency on SFL than on throughput or screw speed.

The absolute impact of each extrusion input variable on SMEC can be read from the maximum and minimum SMEC. The investigated temperature variation led to a variation in SMEC of 1.5 kWh/kg only whereas the specific feed load SFL shows an impact of about 2.5 kWh/kg. For the ANOVA, all factors were standardized.

Assuming again the fictive case of a too high level of impurities in the extruded product, the first assumption would be that a too high energy input led to degradation and that temperature might be the cause. As energy is expressed in the specific mechanical energy consumption as well as in the residence time distribution, a long washout phase e.g. could indicate that some material was excessively stressed on the screws.
Assuming that the experiment which led to high impurities was performed under conditions as indicated in the first two lines of the table in Figure 3-8, the specific mechanical energy consumption would appear to be quite high, as would the mean residence time. The goal is to reduce the stress on the extruded material. Therefore, the left-hand graph in Figure 3-8 implies that an increase in SFL to approximately 0.1 g/rotation will significantly reduce stress but any further increase will not have such an effect. The strategy could now be to increase the throughput and/or reduce the screw speed. This strongly depends upon whether a reduction in mean residence
time in addition to a reduction in specific mechanical energy consumption is required. Reduction of the screw speed leads to a reduction in SMEC only. Increasing the throughput will additionally also reduce the mean residence time and hence reduce exposure to stress. Both throughput and screw speed, if set as described here, would lead to a reduced product temperature, which might in turn lead to lower degradation. The graph on the right describes the impact of temperature at the set medium throughput and medium screw speed. For the ANOVA, all factors were standardized. It is thus obvious that temperature has a minor impact on SMEC only.

**Process parameter chart**

For process optimization and visualization, a process parameter chart can be useful. There is a rationale for such charts as they:
- Enable high-performance extrusion to be carried out
- Enable higher yields in production to be achieved
- Determine the suitability of changes in both the equipment and the formulation
- Define design space for the process

Usually, 2-dimensional charts are used to plot dependent versus independent variables so that the relationship between them can be seen in detail. It is recommended to do so. A chart that captures all the different facets and dimensions in such a complex process such as extrusion is certainly desirable.

**This will allow:**
- All relevant technical aspects to be displayed
- The economic effects of changes made in process design to be displayed
- Scale-up to be planned in an independent way

The proposed process parameter chart is shown in the next figure. It is an xy diagram, displaying the volume-specific feed load (VSFL) versus the extrusion temperature (mean barrel temperature).

Throughput triggers cost. The throughput in an extruder can be either torque-limited or volume-limited. In the graph there is a curve representing the determined maximum achievable VSFL values to the limit of the extruder. VSFL values above the curve cannot be reached due to torque or volume limitations of the extruder (configuration). Above a certain temperature, the viscosity will be sufficiently low so that the maximum intake capacity in the extruder is limited by volume and no longer by torque. The right-hand vertical, slightly sloping dotted line indicates the process boundary given by the maximum allowed temperature; this can be determined using the degradation points of either the active substance or any non-active ingredient in the processed formulation. For better process analysis, the design space can be filled with contour lines of extrusion system parameters such as mean residence time.
The volume-specific feed load is given by:

\[
\text{VSFL} = \frac{\dot{m}}{V_{\text{free}} \cdot n} = \frac{g}{\text{cm}^3 \cdot \text{rev}}
\]

**Equation 3-17**

where \(V_{\text{free}}\) is the free volume of the extruder.

If the process curve is determined at maximum achievable throughput for the given machine configuration, the process design space is given by the area under the curve. Its boundaries are the process curve to the left and to the top, the temperature to the right and a certain minimum volume-specific feed load, below which a process is no longer realistic.

An approach based on VSFL includes all process parameters which can be changed.

Figure 3-10 lists the most relevant influencing parameters. It shows that any change in formulation or machine configuration will result in a change in the process parameter chart.
<table>
<thead>
<tr>
<th>Material</th>
<th>Machine</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Particle size</td>
<td>• Power of motor</td>
<td>• Temperature</td>
</tr>
<tr>
<td>• Particle shape</td>
<td>• D&lt;sub&gt;2&lt;/sub&gt;/D&lt;sub&gt;1&lt;/sub&gt;</td>
<td>• Throughput</td>
</tr>
<tr>
<td>• Density</td>
<td>• Free volume</td>
<td>• Screw speed</td>
</tr>
<tr>
<td>• T&lt;sub&gt;g&lt;/sub&gt;</td>
<td>• Screw design</td>
<td></td>
</tr>
<tr>
<td>• M&lt;sub&gt;w&lt;/sub&gt;</td>
<td>• Starved or forced feeding</td>
<td></td>
</tr>
<tr>
<td>• C&lt;sub&gt;0&lt;/sub&gt;</td>
<td>• Feeder</td>
<td></td>
</tr>
<tr>
<td>• Flow properties</td>
<td>• Length/Diameter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Die</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3-10 - Parameters influencing volume-specific feed load

**Volume-specific feed load**
- Addresses economically-relevant characteristics e.g. maximum achievable throughput

**Process temperature**
- Addresses technically-relevant characteristics such as minimum and maximum temperature at minimum suitable shear

---

**Figure 3-11 - Process parameter chart showing economic and technical characteristics of the setup**
The economic impact of changes in the extruder setup or in the formulation is mainly shown by the maximum achievable throughput on the extruder. Figure 3-11 shows that this information is represented by the height of the curve. The higher the curve the higher the achievable throughput on a machine, which results in the most relevant process cost. A shift of the curve on the x-axis indicates the temperature range where the chosen setup can be operated and hence the technical feasibility for a setup.

A higher filling level usually leads to higher distributive mixing; it also leads to a shorter mean residence time, one of the influencing factors for dispersive mixing. Longer residence times often correlate with higher dispersive mixing. Changing the screw design can impact both distributive and dispersive mixing. Residence time is taken into account in the curve via the height since residence time is mainly a function of throughput and, to a minor extent, the screw speed. Specific mechanical energy consumption is also taken into account in the curve via the height. The higher the curve the lower the specific mechanical energy consumption will be at a particular temperature.

The process parameter chart becomes more powerful when two or more curves are compared.
Figure 3-12 shows an example where a set of experiments was performed. The black dots represent the experiments. The blue and orange contour lines represent the torque and pressure levels resulting from an ANOVA regression model calculation. This can be done for other parameters as well although it is recommended, for better readability, not to display too many curves in one graph. Graphs as shown in Figure 3-13 allow the process fingerprint to be expressed. Analyzing this graph step by step will result in a much better understanding of the process and how to optimize it. Since the graph is scale-independent, it can be used for scale-up purposes.

For Figure 3-13, the following parameters were determined and plotted:
- Torque
- Specific mechanical energy consumption
- Mean residence time
- Pressure at die
Of course, additional parameters, e.g. product temperature and Bodenstein number (Bo), can be added to the chart.

This graph allows a holistic view of the process. Any change in the process or formulation will likely be visualized. For detailed analysis of individual parameters, conventional two-dimensional charts are still useful (e.g. plotting standardized throughput versus diameter ratio $D_O/D_I$).

In conclusion, the process parameter chart shows all the extrusion data of a formulation regarding process parameters while allowing easy investigation of any changes in formulation, machine setup or parameters. Another advantage is its capability to directly show the economic impact of changes made to the process.

**List of abbreviations used in this compendium chapter**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\omega$</td>
<td>Angular frequency</td>
</tr>
<tr>
<td>DoE</td>
<td>Design-of-experiments</td>
</tr>
<tr>
<td>SMEC</td>
<td>Specific mechanical energy consumption</td>
</tr>
<tr>
<td>$n$</td>
<td>Extruder screw speed</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Extruder torque</td>
</tr>
<tr>
<td>$\dot{m}$</td>
<td>Extruder throughput</td>
</tr>
<tr>
<td>$P$</td>
<td>Extruder motor power</td>
</tr>
<tr>
<td>$O$</td>
<td>Extruder engine loading in %</td>
</tr>
<tr>
<td>$n_{\text{max}}$</td>
<td>Extruder maximum adjustable screw speed</td>
</tr>
<tr>
<td>$\Delta P$</td>
<td>Pressure at extruder die</td>
</tr>
<tr>
<td>SFL</td>
<td>Specific (screw) feed load</td>
</tr>
<tr>
<td>VSFL</td>
<td>Volume-specific (screw) feed load</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Melt density</td>
</tr>
<tr>
<td>RTD</td>
<td>Residence time distribution</td>
</tr>
<tr>
<td>$\bar{t}$</td>
<td>Mean residence time</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>$\text{RT}_{\text{mean}} = \bar{t}$</td>
<td>Mean residence time</td>
</tr>
<tr>
<td>Rev</td>
<td>Revolution</td>
</tr>
<tr>
<td>$V_{\text{free}}$</td>
<td>Free volume of extruder (inner barrel volume minus screw volume)</td>
</tr>
<tr>
<td>$D_O/D_I$</td>
<td>Outer screw diameter to inner screw diameter ratio</td>
</tr>
</tbody>
</table>
4 Injection Molding Combined with Hot-Melt Extrusion

Extrusion is a process for producing materials with defined physical and mechanical properties, while injection molding is one for shaping and sizing these materials to different forms for final applications. Injection molding has traditionally been used for producing parts with different sizes and different shapes from both thermoplastic and thermosetting materials. In this process, materials in the form of powder or granules are fed into a heated barrel. The barrel contains a screw which can convey and mix the materials (the degree of mixing is not comparable to extrusion). The barrel is heated externally and the heat is transferred from the barrel to the screw and hence to the materials. Due to the reciprocating action of the screw, the melt is forced by pressure into a mold cavity attached to the end of the screw. The melt cools down in the mold and acquires a defined shape. After solidification, product is released by opening the mold. Molds are generally made of steel or aluminum. The process looks simple in terms of its principle, but is complex in terms of process parameters.

The injection molding process is generally influenced by the following parameters:

- Material type (crystalline, semi-crystalline or amorphous)
- Screw (also barrel) material and its design
- Mold material and its design
- Physical properties of the melt and its solid form
- Cycle time

Although injection molding was already introduced by Speiser in 1964 as a pharmaceutical technology to produce sustained release dosage forms [58], its use within the pharmaceutical industry has been limited to date to a few specific applications. A study of the literature shows that some groups have been actively involved in utilizing the potential of injection molding for pharmaceutical applications and medical devices. One of the studies includes the development of polyethylene [59] and polyethylene glycol matrices [60] and the use of soy protein in injection [61] and co-injection-molded [62] matrices. Eith et al. evaluated the development of an injection-molded starch capsule [63]. Egalet®, a novel drug delivery system prepared using injection molding, consists of an impermeable shell of cetostearyl alcohol and ethyl cellulose enclosing a matrix plug composed of drug, polyethylene glycol monostearate and polyethylene oxide. Drug release is controlled by modulating the erosion of the matrix [64]. Recently, in order to produce sustained release matrix tablets, hot-melt extrudates of ethyl cellulose as a release-controlling polymer and hydroxypropyl methylcellulose as a hydrophilic drug release modifier together with different drugs such as ibuprofen and metoprolol tartrate were molded into tablets using a lab-scale injection molder operating at the same temperature as the extruder [65, 66].

Apart from tablet applications, considering the broad window of injection molding for different thermoplastics and biodegradable polymers, pharmaceutical polymers can be molded into films, rods, rings and shaped implants.
5 Extruder Granulation Processes

Various processes for the production of granules are described in the literature. These are also being used for pharmaceutical applications. On the one hand, there are the wet granulation methods where binder solutions agglomerate powders (e.g. mixer granulation, fluid bed granulation). On the other, there are the dry granulation methods which use mechanical pressure for agglomeration (e.g. roller compaction). Beyond that, meltable materials enable the agglomeration of small particles in so-called melt granulation processes [12]. These have not yet become very popular since, in batch processing, there are some disadvantages such as the sticking of material to the walls of mixers and in cleaning the equipment.

Continuous processes are gaining more and more in importance in the pharmaceutical industry since they offer significant cost savings and reduce the complexity of pharmaceutical manufacturing [67, 68]. Several methods for continuous wet granulation are already known and have been introduced [68, 69, 70]. In twin-screw granulation, the screws rotate inside the barrel to continuously transport, mix and agglomerate wetted particles and homogeneously distribute the binder solution inside the mixture. The extruder can be fed with the binder solution or the dry binder can be pre-blended with the other components and solvent, mainly water, introduced into the extruder via a liquid feeder. These alternatives are comparable to the regular mixer granulation processes where they are called binder- or solvent granulation. The energy required for agglomeration is provided by shear forces and pressure from screw rotation. Usually, higher temperatures are not applied, so that the extruder is not heated, the typical slight increase in temperature of the granules coming from the mechanical energy provided by the screws. In contrast to hot-melt extrusion, the mixture should not be strongly densified since denser particles result in poorer compressibility in tablet manufacturing. The die plate should thus not create high pressures; the orifices must be large or the die plate has to be removed completely. As in regular mixer granulation, the wet granules are forced through a sieve and subsequently dried.
Wet granulation performed in an extruder is highly suited to continuous manufacture; however, at some later stage, the solvent has to be evaporated off. In contrast, melt granulation avoids the addition and evaporation of solvents and therefore has additional benefits. Melt granulation is an agglomeration technique where granules are obtained due to the softening or melting of binders that are heated to near or above their melting points or glass transition temperatures [71, 72, 73].

Hydrophilic binders (e.g. polyethylene glycols, Soluplus®, poloxamers) are used for instant release formulations and hydrophobic binders (e.g. waxes, glycerol monostearates (e.g. Kolliwax® GMS I), stearic acid (Kolliwax® S Fine), stearyl alcohol (Kolliwax® SA) and other Kolliwax® grades) for sustained release formulations. The meltable binder can be preblended with all other ingredients and introduced into the extruder by one feeder or separately using a second feeder, as shown in the next figure. Heating and cooling of the various barrels of the extruder have to be adjusted to produce sufficient agglomeration on the one hand and to avoid stickiness on the other. Thus, the first barrels are not heated in order to prevent premature melting in the entry zone, the intermediate barrels are heated to melt the binder and the last barrels can be used to start cooling down the mixture. After exiting the extruder, the granules are cooled down further; the binder then solidifies and forms stable granules [67]. As these might be too large in size, a sieving step is usually added in order to achieve an even particle size distribution.
It is quite obvious that, compared to a wet granulation procedure, the binder distribution in the mixture is not as homogeneous because of its increased viscosity so that more binder is required (5–20%). Not only the type and concentration of binder have an impact on agglomeration, but also the particle size. Small particles usually improve agglomeration of the whole mixture.

To date, melt granulation is still not a common technology; however, with the increasing use of extruders in the pharmaceutical industry, it will surely become more and more popular, particularly as it offers savings in drying time and energy [68]. In addition, it is especially suitable for moisture-sensitive drugs.

**The characteristics of granules produced by extruder granulation mainly depend on:**
- Barrel temperature
- Design of the screws (kneading, mixing and conveying elements)
- Throughput rate and screw speed
- Accuracy of feeding (powder and/or liquid)
- Type of binder and other components
- Binder concentration
- Particle sizes of binder and other components
6 Spray Drying as a Solid Solution Preparation Technique

Besides the melt processes (e.g. hot-melt extrusion, spray congealing and melt granulation), solvent procedures such as spray drying, film casting and freeze drying are also common manufacturing methods for solid dispersions [74].

In general, spray drying is widely used for drying aqueous or organic solutions, emulsions and dispersions, not only in the pharmaceutical industry but also in the food and other industries. However, for solid solutions, the use of organic solvents involves some restrictions and requires particular measures for safe and environmentally friendly use [75].

Principle of spray drying

In spray drying, liquids are converted into powdered solids. The process involves atomizing the liquid into small droplets and vaporizing off the solvent used with hot drying gas [74]. Despite the energy of the gas being transferred to the droplets, these are only slightly warmed since most of the energy is used to vaporize the solvent. Therefore, in thermal terms, spray drying is a relatively gentle method. The dried powder particles are subsequently separated from the air by cyclones or filters [76, 77].

Apart from the composition of the liquid, the properties of the spray-dried powder are principally determined by the design and process conditions of the spray tower [74]. Different kinds of spray drying techniques such as co-current air flow, counter-current air flow, atomization by nozzle or rotating disc, fluidized bed spray drying (FSD or SBD) are employed to yield products with different characteristics. Sometimes an external fluidized bed is added in order to complete the drying process at low temperatures, to cool down the powder or to agglomerate particles to an even larger extent.

A standard spray-drying procedure is shown below.
For manufacturing a solid solution by spray drying, a solution of active and suitable pharmaceutical excipients in an appropriate solvent has to be prepared first. Sometimes it is not easy to find an appropriate solvent for both components because the solid content of the solution should be relatively high (≥ 20%) in order to minimize costs and increase particle size and bulk density of the resulting powder. In addition, too fine particles result in poor flow properties and require additional manufacturing steps for the production of final dosage forms. Of course, all solvents must be volatile with a boiling point < approx. 120 °C. The solubilities of the relevant BASF polymers are given in chapter 9 "General Notes on BASF Pharma Polymers"; thus, only the solubility of the actives has to be determined, which facilitates the selection of the solvent [78]. Sometimes, the solubility of the active is influenced by the polymer; this is mainly due to a solubilization effect.

**Typical solvents for spray drying are:**
Ethanol, isopropanol, methanol, acetone, 2-butanone, ethyl acetate, butyl acetate, tetrahydrofurane, methylene chloride.

The solids concentration of the organic solution is limited by viscosity since highly viscous solutions can no longer be atomized properly. This also restricts the range of polymers which can be employed. Polymers of a high molecular weight or with interacting functional groups characterized by a high viscosity are not suitable. However, the viscosities of polymers in organic solutions are commonly lower than in aqueous solutions.

**Suitable polymers for the preparation of solid solutions via spray drying are:**
Kollidon® VA 64, Soluplus®, Kollidon® 12 PF, Kollidon® 17 PF, Kollidon® 30, Kollicoat® MAE 100P.

Spray drying conditions have to be adjusted to avoid high thermal stress of the product and to yield a product without a high level of residual solvent. The inlet air temperature must considerably exceed the boiling point of the solvent in order to enable rapid vaporization and avoid the particles sticking to the tower wall and tubes. If particles cannot be dried completely within the time from leaving the nozzle to hitting the metal wall in the lower part of the tower, they will still contain organic solvent, which is a good plasticizer of the polymer and the active and which causes stickiness of the particles. In this case, the powder on the wall gets thicker and thicker, the yield declines and the process has to be terminated. Thus, drying of the particles has to be quick, a process that typically occurs within parts of a second up to a few seconds. This high speed vaporization also avoids crystallization of the active during the process, which occurs quite often when applying slower technologies such as solvent evaporation or film casting. In these cases, in parallel with evaporation of the solvent and increasing concentration of the active in the solvent, it may crystallize since the time required for complete drying is in the range of minutes rather than seconds.
Typical conditions are:
Inlet air temperatures 60–160 °C
Outlet air temperatures 40–90 °C

Of course, the spraying rate of the liquid and the inlet air volume have to be adapted to obtain a certain required temperature profile. Thus, the inlet air temperature, spraying rate and inlet air volume strongly influence the outlet air temperature. The latter is the most decisive parameter for adjusting the residual solvent level in the spray-dried powder. As a rough estimation, the particles are heated up during the process only to approximately the outlet air rather than the inlet air temperature.

The handling of organic solvents requires special measures to avoid any risk of explosion. The process is best run under nitrogen. All parts of the equipment should be grounded, vessels containing the solution should be kept tightly closed and the level of residual solvent in the powder should be low. For environment protection, the plant should be equipped with a solvent recovery system. Thus, compared to melt extrusion, the spray drying of organic formulations is a more complex and expensive technology.

In scaling up spray drying processes, one has to respect that, due to the larger nozzle diameter employed, the particle size of the powder increases. Thus, it is impossible to obtain large particles from a small spray tower.

The final product has to fulfill the specification of the relevant pharmacopoeias for residual solvents. In addition, the level in the gas phase above the powder should not exceed 40% of the lower explosion limit. Spray-dried material has a high surface area and, depending on the hygroscopicity of the formulation, it will take up moisture which can lead to crystallization of the active. Therefore, when handling the powder, contact with humid air should be avoided.

Advantages of manufacturing solid solutions by spray drying [74]:
- A one-step process from liquid to powder
- Low thermal stress
- Spray-dried powder can be directly formulated into solid oral dosage forms
- Quick drying avoids intermediate crystallization of the active
- The suitability of the technology can be tested on a small scale via film casting or solvent evaporation methods
- In large spray towers, high throughput rates are achievable

Drawbacks of manufacturing solid solutions by spray drying:
- High investment in a spray tower is necessary
- High costs of raw materials (solvent, nitrogen)
- Scaling up can be difficult
- Residual solvents may remain in the powder
- The powder is sensitive to moisture
7 Analytical Investigations of Solid Dispersions

Investigation of formulations containing APIs requires the use of several methods, depending upon the probable physical state of the API in the polymer. The methods can be used to differentiate between solid solutions (molecularly dispersed drug, without crystals), solid dispersions in which the drug is only partly molecularly dispersed (with crystals) or contained in amorphous clusters and physical mixtures of drug and carrier [74, 79]. Sometimes, it is difficult to precisely characterize and distinguish between the various systems (dissolved, amorphous or crystalline drug) due to the complexity of the systems, and different analytical methods may yield contrasting results. In many instances, a combination of two or more methods is required to obtain the complete picture [80].

Since stability of solid dispersions can be a critical point, it is important to detect phase separation in an early stage of development. In most cases, phase separation is undesirable and is considered to lead to potentially significant reductions in the therapeutic effect of a formulation because of the slower dissolution of the drug crystals compared to the molecularly dispersed form. Therefore, controlling phase separation is of critical importance in pharmaceutical solid dispersions in general and, on the basis of current interest, HME formulations in particular [81].

Commonly used analytical methods with their advantages and disadvantages are included in the following table [82].

<table>
<thead>
<tr>
<th>Analytical methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray [83, 84]</td>
<td>Non-destructive method</td>
<td>-</td>
</tr>
<tr>
<td>Powder X-ray diffraction (PXRD)</td>
<td>Qualitative and quantitative method</td>
<td>No information about the chemical structure</td>
</tr>
<tr>
<td>Single crystal X-ray diffraction (SCXRD)</td>
<td>Identification of crystalline phases</td>
<td>Single crystals of &lt; 0.1 mm are not detectable</td>
</tr>
<tr>
<td>Small angle X-ray scattering (SAXS)</td>
<td>Characterizes small and larger structures (nm to µm range)</td>
<td>Long data acquisition time and difficult interpretation of data</td>
</tr>
<tr>
<td>Thermoanalytical and gravimetric analyses [83, 84]</td>
<td>Small sample size</td>
<td>Destruction of the sample</td>
</tr>
<tr>
<td>Differential scanning calorimetry (DSC)</td>
<td>Qualitative and quantitative method</td>
<td>No information on the nature of the thermal events and potential overlapping of thermal events at the same temperature</td>
</tr>
<tr>
<td>Modulated temperature differential scanning calorimetry (MTDSC)</td>
<td>Improves clarity of small and overlapping thermal events</td>
<td>More experimental variables, long data acquisition time</td>
</tr>
<tr>
<td>Analytical methods</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Thermogravimetric (TGA) Dynamic vapor sorption (DVS)</td>
<td>Determination of solvates / hydrates and degradation</td>
<td>Interference with water-containing excipients, unsuitable for materials that degrade at low temperatures</td>
</tr>
<tr>
<td>Isothermal microcalorimetry (IMC)</td>
<td>High sensitivity, qualitative and quantitative method, stability study directly under the storage conditions, non-destructive method</td>
<td>Low specificity, larger amounts of sample (50 – 500 mg)</td>
</tr>
<tr>
<td>Solution calorimetry (SC)</td>
<td>Qualitative and quantitative method</td>
<td>Low specificity, larger amounts of sample (15 – 200 mg), long measurement time</td>
</tr>
<tr>
<td>Microscopy [83, 84]</td>
<td>Small sample size, no/less sample preparation, non-destructive method</td>
<td>-</td>
</tr>
<tr>
<td>Polarized light microscopy (PLM)</td>
<td>Good recognition of crystalline structures</td>
<td>No quantitative information available</td>
</tr>
<tr>
<td>Scanning electron microscopy (SEM)</td>
<td>Higher resolution compared to PLM</td>
<td>Requires complex sample preparation</td>
</tr>
<tr>
<td>Atomic force microscopy (AFM)</td>
<td>Provides three-dimensional surface pictures</td>
<td>Slow rate of scanning and the single scan image size compared to SEM</td>
</tr>
<tr>
<td>Spectroscopy [83, 84]</td>
<td>Small sample size, no sample preparation, non-destructive, quick data acquisition</td>
<td>-</td>
</tr>
<tr>
<td>Mid-IR (Fourier transformed infrared (FT-IR) / diffused reflectance infrared transmission spectroscopy (DRIFTS) / attenuated total reflectance (ATR))</td>
<td>Availability of spectral libraries</td>
<td>Sample preparation in FT-IR and DRIFTS can induce solid-state transformation, interference from environmental humidity</td>
</tr>
<tr>
<td>Raman</td>
<td>Ability to penetrate through glass containers, application of water is possible, fiber optic probes are available</td>
<td>Local heating of sample and sample fluorescence, photo degradation</td>
</tr>
<tr>
<td>Near infrared (NIR)</td>
<td>Ability to penetrate through glass containers, fiber optic probes are available</td>
<td>Low sensitivity and selectivity, significant baseline slope</td>
</tr>
<tr>
<td>Solid-state nuclear magnetic resonance (ss-NMR) [85]</td>
<td>Qualitative and quantitative without calibration</td>
<td>Expensive, long data acquisition time</td>
</tr>
<tr>
<td>Terahertz pulsed spectroscopy (TPS)</td>
<td>Determination of polymorphs</td>
<td>Spectrum affected by water, expensive, requires pellet compression, particle size of 100 µm is preferred to minimize scattering</td>
</tr>
</tbody>
</table>
7.1 Analytical Methods

In this chapter various analytical methods for characterizing the physical state of an API in a polymer matrix are described in more detail and illustrated by examples.

7.1.1 X-Ray Diffraction

The principle of X-ray diffraction (XRD) is based on Bragg’s Law, in which parallel incident X-rays strike the crystal planes and are then diffracted at angles related to the spacing between the planes of the molecules in the lattice. Crystallinity is indicated by a characteristic fingerprint region in the diffraction pattern. If the fingerprints of drug and carrier are not superimposed, the crystallinity of the drug and polymer following e. g. hot-melt extrusion can be determined. Thus, X-ray diffraction can be used to differentiate between solid dispersions in which the drug is amorphous and solid dispersions in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, the sensitivity of the XRD technique is limited and cannot generally detect crystallinity of less than 10% [80].

Experimental method

X-ray diffraction (XRD): XRD studies were performed by using a diffractometer D 8 Advance (Bruker / AXS, Germany).

![Graph showing XRD examples of amorphous and crystalline extrudates of Kollidon® VA 64 with the active pharmaceutical ingredient (API) Itraconazole compared to the pure and crystalline API.](image.png)
7.1.2 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analyzes the system as a function of temperature. This method has been widely used to study the thermal properties of materials used for example in hot-melt extrusion. DSC can be used for the determination of transitions (melting point ($T_m$), glass transition temperature ($T_g$)) coupled with endothermic and exothermic phase transformations. Generally, the hot-melt extrudate is scanned and compared to the results of the individual components. The lack of melting transition in the DSC scan of the hot-melt extrudate indicates that the drug is present in an amorphous or molecularly dissolved state rather than in crystalline form [80].

**Experimental method**

**Differential scanning calorimetry:** The samples were dried overnight at 70 °C (vacuum) in a 20 bar cup. The DSC studies were performed using a Q2000 (TA Instruments, USA). DSC scans were recorded at a heating rate of 20 K/min during the first heating run.

![Figure 7-2](image)

Figure 7-2  DSC examples of amorphous and crystalline extrudates of Soluplus® with the API itraconazole
Crystalline structures of itraconazole result in a melting peak at approx. 166 °C which is less or more pronounced depending on the degree of crystallinity. In contrast, the impact on the T₉ is minimal.

### 7.1.3 Microscopy

Microscopy is one of the best methods for studying the crystalline properties of hot-melt extrudates. Both optical and electron methods are suitable for examining the surface morphology of samples to check for the presence of crystalline particles or amorphous domains. It is also possible to obtain reliable particle size information using these techniques [80].

#### 7.1.3.1 Light Microscope

**Experimental method**

**Sample preparation and morphological studies:** The samples were cut using a Microtome Ultracut S (Leica Mikrosysteme GmbH, Austria) with a diamond knife Cryo 35° (DIATOME, Switzerland) at -40 °C. The crystalline structures of the cut surface were observed by optical microscope.

![Figure 7-3](image)

**Figure 7-3** Light microscope examples of crystalline extrudates of Soluplus® with the API itraconazole
In these cases crystalline structures can easily be identified and distinguished from samples without any sign of embedded crystals.

### 7.1.3.2 Scanning Electron Microscopy

**Experimental method**

**Scanning electron microscopy (SEM):** The extrudates were cut at room temperature. The crystalline structure of the cut surface was observed by using a Zeiss FE-SEM Ultra 55 (Carl Zeiss AG, Germany). The examination was carried out via emission electrons with an acceleration voltage of 6 kV at 3000-times magnification.
In contrast to the solid solution with molecularly dissolved API, the samples containing crystals showed a rough surface structure with embedded crystals.

### 7.1.4 Atomic Force Microscopy

Atomic force microscopy (AFM) is an instrument that uses a tiny probe mounted on a cantilever to scan the surface of a sample. When the probe is brought into proximity of a sample surface, forces between the probe and the sample lead to a deflection of the cantilever according to Hooke’s law. Depending on the surface of the sample, forces that are measured in AFM include mechanical forces, van der Waals forces, capillary forces etc. This analytical method is suitable for examining the surface morphology of samples to check for the presence of crystalline particles or amorphous domains.

#### Experimental method

**Sample preparation and morphological studies:** The samples were cut using a Microtome Ultracut S (Leica Mikrosysteme GmbH, Austria) with a diamond knife Cryo 35° (DiATOME AG, Switzerland) at -40 °C. The crystalline structures of the cut surface were observed using an AFM system D5 (Veeco, USA) in tapping mode with AFM tips (Olympus, Japan) and with a spring constant of 42 N/m.
Figure 7-6  ▪ AFM examples of crystalline extrudates of Soluplus® with the API itraconazole

Figure 7-7  ▪ AFM examples of amorphous extrudates of Soluplus® with the API itraconazole
Despite some irregularities that can be seen in the case of the samples with molecularly dissolved drug, crystallized samples clearly indicate larger structures that can be interpreted as crystals.

### 7.1.5 Solid-State Nuclear Magnetic Resonance

Many of the techniques mentioned provide information concerning the crystallinity or amorphicity of the API and matrix. However, they cannot usually distinguish between a molecularly dispersed drug and amorphous drug material. A worthwhile tool for addressing this problem is $^{13}$C solid-state NMR [85, 86, 87]. Therefore, the purpose of this study was to evaluate and to compare DSC, XRD and NMR for the characterization of a solid dispersion of poorly soluble itraconazole with Soluplus® (ratio 15:85, w/w%), which was prepared by hot-melt extrusion. For this purpose a 16 mm twin-screw extruder (ThermoFisher Polylab, ThermoFisher, Germany) was operated at 1 kg/h powder feed rate, 200 rpm screw speed and a barrel temperature of 150 °C [88].

#### Experimental method

1. **Differential scanning calorimetry (DSC):** DSC studies were performed using a Q 2000 (TA Instruments, USA). DSC scans were recorded at a heating rate of 20 K/min during the first heating run.

2. **X-ray diffraction (XRD):** XRD studies were performed using a diffractometer D 8 Advance (Bruker / AXS, Germany) with a radiation of 40 kV / 50 mA. The samples were step-scanned at 0.02° intervals from 2 to 80° ($2\theta$).

3. **$^{13}$C solid-state NMR:** $T_{\text{rho}(1\text{H})}$ relaxation of the solid solution, pure polymer and pure API were analyzed with a Bruker DSX 300 (Bruker, Germany) using magic angle spinning at 298 K. The spectrometer was operated at 300 MHz. Spinning rate, contact time and number of scans were optimized for each sample.

The X-ray measurements of the clear and transparent extrudates reveal an amorphous solid dispersion. No crystalline itraconazole could be detected.
DSC measurement also confirmed the amorphous state of the same solid solution. In addition, a single $T_g$ at approximately 69 °C could be found. In a further measurement, the glass transition of the pure polymer could be detected at 73 °C whereas the melting temperature of itraconazole is 166 °C. The results of both techniques stress the presence of a homogeneous and amorphous system.
However, the former crystalline itraconazole could form either amorphous clusters (solid dispersion) within the amorphous polymer or the API was molecularly dissolved (solid solution). Finally, both techniques could not properly distinguish between these two types of solid dispersions.

\(^{13}\text{C}\) solid-state NMR enables differentiation between these two systems to be made. In the case of a solid dispersion with amorphous clusters of API, this technique would detect different relaxation times for API and polymer respectively. Thus, a segregated system would consist of two phases which are at least larger than 1 nm. In the case of a molecularly dissolved API within the polymer – a one-phase system – relaxation times for API and matrix would be equal or comparable.

Finally, the results for the solid solution of itraconazole with Soluplus® confirm a true solid solution of API within the matrix polymer. Whereas the pure substances show different relaxation time decays (full symbols), no difference could be detected for the extrudate (empty symbols).
Comparison of the mean $T_{1\rho}$ relaxation time values showed no significant difference between API and matrix polymer in the solid solution.

### 7.1.6 In-Vitro Release Characteristics

In-vitro drug dissolution is also relevant and is an important tool for studying solid dispersions. It reveals whether the drug dissolves completely or not and whether the polymer prevents crystallization and keeps the drug in an oversaturated dissolved state under non-sink conditions.

These test methods can also be applied to check whether a formulation is stable after storage under various conditions. Crystallization can occur particularly when the drug has been incorporated above the saturation level, leading to a change of its biopharmaceutical properties.

The in-vitro dissolution characteristics of a drug formulation in various dissolution test models (medium composition, volume, biomimetic fluids etc.) might be different and they provide a limited indication only of efficacy in humans. However, almost complete in-vitro dissolution combined with a high degree of supersaturation maintained over a longer period of time are essential prerequisites for a significant increase in bioavailability. This does not necessarily mean, of course, that the quickest dissolution always leads to the best bioavailability. Sometimes, despite poor dissolution rates, bioavailabilities of solid solutions are still tremendously enhanced.
The figure reveals how crystallinity can affect the dissolution rate of itraconazole in Soluplus® solid dispersions. The difference in dissolution between non-crystallized and slightly crystallized material was fairly small, however; this was because only a negligible portion of the drug crystallized, whereas strongly crystallized extrudates resulted in significantly lower drug release over a period of 2 h.
8 Downstream Processing with Hot-Melt Extrusion

This chapter will discuss a few points related to the extrusion itself and to the directly following process of solidifying and shaping of the melt.

The objective is to highlight a few important aspects which can be generalized for any kind of directly connected downstream process following extrusion.

The important process steps in an extrusion process are:
- **Upstream** (material feed into the extruder)
- **Compounding** of the materials inside the extruder
- **Extrusion** of the melt through a die orifice
- **Downstreaming** the melt to cool and solidify

It all starts with the feeder

If the downstream process should result in a directly shaped dosage form (e.g. tablet, patches, stents), the dimensions of the product have to be precise. This is only possible for the extruder and subsequent downstream processing if the whole process is optimized. In chapter 3, the residence time distribution was explained. Residence time distribution simply means that the material fed into the extruder passes through it at different velocities. This results in axial mixing. In theory, a feeder should pass a constant flow of material into the extruder. In practice, however, it has to be checked whether the accuracy of the feeder is sufficient since this is not always the case (especially for solids).

This figure illustrates the material stream exiting the extruder through the die as a function of the material feed at the beginning of the extruder and of the residence time distribution. In the ideal case of a perfect feeding stream, one would expect a perfectly smooth exit stream of melt showing no fluctuations. In reality, however, the feeder
stream shows certain fluctuations. As to how well the extruder can compensate for these fluctuations depends on the spread of the residence time distribution. If this is very narrow, it results in poor axial mixing, which in turn results in fluctuation in the melt stream when exiting the extruder die. Obviously, a pulsating or fluctuating melt stream from the extruder die will influence the directly following downstream process; strand thickness e.g. would correlate directly with the fluctuation of the melt stream at the extruder die. If the amount of material fed into the extruder per unit of time is not constant and the extruder cannot compensate for the fluctuation in feed rate with a sufficiently broad residence time distribution, the melt stream exiting the extruder will also not be constant. Only if the residence time distribution is sufficiently broad can the extruder at least partially compensate for any fluctuation. It need not fully compensate for the melt stream but it should smoothen it adequately.

If the required melt stream accuracy is not achieved, the following three points (in the order as listed) should be checked:

- Optimization of the feed
- Optimization of residence time distribution
- Installation of a gear pump between extruder and downstream device

The pros and cons of a gear pump are listed in the next figure. The main advantage of a gear pump is that it can ensure a very constant melt mass flow with low pulsation. It can also be used to build up high pressures if required and, due to its power, it can handle highly viscous melts. Thus, it can process a melt stream at lower temperatures at a constant flow rate even if the viscosity varies during the process. If the melt pump is used at lower temperatures (= higher viscosity), this could lead to higher shear stress, which might well lead to an increase in melt temperature again.
Variations in extruder output

Variations in melt flow can be of the gradually increasing or decreasing type or can be cyclic. It is important to determine this first. Further variations can occur rapidly or may be slow over a period of time.

Rauwendaal [52] has mentioned a few important causes for fast variations:
- Melt fracture (caused by wall shear stress)
- Draw resonance (caused by stretching of the strand by the conveyor belt)
- Melt temperature variation
- Screw speed variation
- Take-up speed variation
- Vibration

Melt fracture is a distortion in the extrudate which can be expressed in different ways. At low extrusion rates, the extrudate usually appears with a smooth and shiny surface. At higher extrusion rates, the surface can be turbid, mat, rippled and finally distorted in a sharkskin-like pattern. This is then called a sharkskin or surface melt fracture. If the extrusion rate is further increased, the extrudate can show alternating regions of smooth and sharkskin surface. This is called stick-, slip- or spurt flow. If the extrusion rate is increased even more, the extrudate surface shows severe distortion; this is called gross melt fracture [89, 90].

Melt fracture has an effect on any downstream process such as film blowing, extrusion forming, melt spinning and cast extrusion. The causes of melt fracture are not yet fully understood, but it is believed that the wall shear stress in the die landing region has an influence. If the die wall stress exceeds a critical value, the melt flow is disturbed; the flow at the wall differs significantly from that in the core of the die. Another influencing parameter can be the backflow of melt through the barrel due to high pressure within the die region.
Rauwendaal [52] mentions a few remedies for melt fracture:

- Streamlining the flow channel
- Reducing the landing shear stress (in the die)
- Using a processing aid (e.g. PEG-based polymer or plasticizer)

Soluplus® shows superior properties in terms of melt fracture. Even under high extrusion rates, it hardly produces melt fracture.

To streamline the flow channel, the die landing temperature can be increased, a wider die could be used or the extrusion rate could be reduced. The latter option should not be preferred for economic reasons. Also, using a different material for the die in order to reduce the melt fracture effect should be carefully considered from the GMP point of view.

If cooling rate is important

In hot-melt extrusion, a solid glassy solution or amorphous suspension is often produced. Stability in the sense of avoiding re-crystallization during the shelf-life of the solid dispersion is a very important aspect of formulation and process design during the development of a solid dispersion. Thus, after extrusion, the melt should be cooled down under constant conditions.

Important parameters for cooling the melt are:

- Heat conductivity of the melt
- Melt temperature at extruder die
- Target temperature after the cooling process (usually ambient temperature)
- Cooling rate (K/min)
- Dimensions of the extruded melt
- Cooling media

Cooling is normally done by air. Depending on the thickness of the strand, the cooling will vary from the strand surface to the strand core. The melt temperature at the die is also important. The strand is usually pulled towards a cutter. The outside of the strand will solidify first and the polymer chains will have a certain orientation and elongation caused by the pulling force; however, the strand core is still viscous and the polymer chains may have another orientation. It can often be observed that the extruded material, even after the cutting process, remains relatively warm. This is caused by a certain heat capacity of the material, but it can also happen that during strand extrusion the outside section of the strand is often cooled and solidified sufficiently for cutting although the strand inner core is still warm. Polymers usually have a low heat conductivity and poor cooling characteristics. Water would be a more efficient cooling medium but cannot be used as the extrudate would begin to dissolve.

Bourry [91] found that the morphology is critically determined in the melt itself and not during the melting process. The morphology is obtained quite rapidly. He also found
that the last flow environment experienced by the blend melt controls the morphology. However, as he investigated the extrusion process only, he indicated that the screw design and the die might play a critical role in morphology determination. This thought has to be extended to the downstream process where the melt is still in flow until solidification. To obtain repeatable results in morphology it seems to be important to keep this last flow environment as constant as possible. This might be very difficult to achieve in extruding a strand since the change in environment temperature already made would change the cooling process. Therefore, attention should be directed to another downstream possibility, the chill roll.

Figure 8-4  ■ Thermo Fisher Pharmalab 24 mm with chill roll attached  
(photo is courtesy of Thermo Fisher Scientific, Germany)

The principle of the chill roll is to place the melt between two rolls with a defined gap between them and a defined roll speed. Furthermore, the temperature of the rolls can be adjusted to match the requirements for the cooling rate of the extrudate. This cooling results in a strand which is conveyed on a short conveyor belt to a crushe

r which breaks the extruded strand into smaller flakes for further processing.
BBA innovations introduced the chill rolls CCR (without integrated mill) and CCRM-20/12-PH. CCRM-20/12-PH is the first chill roll with an integrated mill and which is supplied by Frewitt (Switzerland). The major advantage of this chill roll is that it continuously produces a powder which can be easily further processed into a final dosage form such as a tablet using established techniques.

The product to be cooled is rolled out to a film between two rolls, the roll gap being adjustable. The synthetic pre-tensioned belt holds the product tight against the cooling roll. In the flaker, the cooled formulation is broken into defined pieces. Different designs of flakers to influence the flake size are available.
The advantages of a chill roll are to ensure a repeatable, constant cooling process for the extrudate by:

- Defined temperatures and sufficient cooling capacity of the rolls
- A defined gap between the rolls which remains constant and always ensures the same temperature gradient, even if the melt feed rate varies (in which case the spread of the melt will be wider on the rolls only)
- Constant contact area for cooling, depending on roll size and position
- Precisely controllable and constant roll speed

Besides these advantages, the chill roll has a very small footprint and allows a compact extrusion line as shown in Figure 8-4. Chill rolls are available for small and high throughput rates. They allow the process to run unattended compared to strand extrusion where the strand continuously needs to be monitored in case of rupture before reaching the cutting device.

This kind of cutting/pelletizing device is displayed in the following figure. The pharmaceutical formulation exits the die in the form of continuous strands; the strands become solidified on a conveyor belt and are then cut into small cylindrical pieces. The pelletizer allows pellet length to be controlled between approximately 1 and 3 mm. The pelletizer consists of a rotating knife with several cutting faces and a rubber wheel for adjusting to constant feeding of the strands into the cutting device. The cut strands can be milled and subsequently blended with suitable excipients for compression into tablets.
Calendering allows direct shaping of the melt and solidification into tablet- or capsule-like forms. This is an integrated process where the API and excipients are fed to the extruder and a short period of time later finished dosage forms exit. The calender consists of 2 counter-rotating rolls with numerous cavities in half the form of the desired tablet. When the rolls rotate, the jointly formed space is filled with melt, the melt is cooled down for solidification and, by subsequent rotation, the tablet is ejected. There is a certain similarity to soft gel manufacturing; however, in calendering, no encapsulation step is involved.

Although the process looks simple, it is quite difficult to perform in pharmaceutical manufacturing. The basic prerequisites are precise adjustments of the 2 counter-rotating rolls in 2 dimensions, on the one hand to minimize the gap between the rolls and on the other hand to avoid any displacement of the cavities, which would generate irregular dosage forms. Furthermore, the melt flow coming from the extruders needs to be balanced with the throughput of the calender. Throughput is mainly based on the roll speed but is usually limited by the required cooling rate and consistency of the forms.
However, in contrast to a tablet, such an extruded form does not have any porosity with all the associated benefits such as small volume; however, it does have the disadvantage of relatively slow release. Usually, subsequent treatment – such as abrasion – has to be added in order to remove sharp edges caused by the small gap between the rolls. Also, the so-called cold flow needs to be considered as this can lead to a change in tablet dimensions and structure, even when the tablets are stored at room temperature.

Besides the above-mentioned downstream processes, two further interesting technologies exist: Injection molding and co-extrusion. Injection molding will be discussed in a separate chapter in this compendium. Co-extrusion is an interesting technique for special applications.
Basically, in co-extrusion, two or even more melt streams are united in layers. The most relevant characteristics are:

- Applicable for multi-layered systems
- Each layer can contribute specific functionality
- Specific dies are necessary
- The cooling characteristics of the layers should be similar for maintaining shape

The layers can consist of different polymeric carriers but their properties, such as cooling ability, should be similar to avoid separation of the layers due to different softening and shrinking processes upon cooling. Co-extrusion allows the development of very sophisticated systems.

Other downstream processes

Further downstream systems are:

- Cooling of the extrudates with air or nitrogen on stainless steel or PTFE conveyors or in a non-solvent medium
- Hot die face pelletizer (with rotating knife blades)
- Film and lamination systems for transmucosal / transdermal applications
- Cyclic molding
- Torque winders for cooling and collecting the extrudates
BASF SE offers a variety of polymers based on different monomers and chemical structures which can be employed in hot-melt extrusion applications. The portfolio comprises homopolymers, copolymers, amphiphilic copolymers as well as solubilizers and plasticizers, which are described in this chapter in more detail [92, 93, 94]. Kolliphor® HS 15 (Solutol® HS 15) and Kolliphor® EL (Cremophor® EL) can also be used in hot-melt extrusion but are not described here in detail.

Table 9-1  List of BASF pharmaceutical excipients suitable for hot-melt extrusion and their pharmacopoeial monographs

<table>
<thead>
<tr>
<th>New Product Name *</th>
<th>Old Product Name</th>
<th>Ph. Eur. Monograph</th>
<th>USP-NF Monograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>Kollidon® VA 64</td>
<td>Copovidone</td>
<td>Copovidone</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>Soluplus®</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kollidon® 12 PF</td>
<td>Kollidon® 12 PF</td>
<td>Povidone (K-value 12)</td>
<td>Povidone (K-value 12)</td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td>Kollidon® 17 PF</td>
<td>Povidone (K-value 17)</td>
<td>Povidone (K-value 17)</td>
</tr>
<tr>
<td>Kollidon® 30</td>
<td>Kollidon® 30</td>
<td>Povidone (K-value 30)</td>
<td>Povidone (K-value 30)</td>
</tr>
<tr>
<td>Kollidon® 90 F</td>
<td>Kollidon® 90 F</td>
<td>Povidone (K-value 90)</td>
<td>Povidone (K-value 90)</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>Kollidon® SR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kollicoat® MAE 100P</td>
<td>Kollicoat® MAE 100P</td>
<td>Methacrylic acid – ethacrylate copolymer 1:1</td>
<td>Methacrylic acid copolymer type C</td>
</tr>
<tr>
<td>Kollicoat® IR</td>
<td>Kollicoat® IR</td>
<td>Macrogol polyvinyl alcohol grafted copolymer</td>
<td>Ethylene glycol and vinyl alcohol graft copolymer</td>
</tr>
<tr>
<td>Kollicoat® Protect</td>
<td>Kollicoat® Protect</td>
<td>Macrogol polyvinyl alcohol grafted copolymer + poly(vinyl alcohol)</td>
<td>Ethylene glycol and vinyl alcohol graft copolymer + polyvinyl alcohol</td>
</tr>
<tr>
<td>Kolliphor® P 188 / Kolliphor® P 188 micro</td>
<td>Lutrol® F 68 / Lutrol® micro 68</td>
<td>Poloxamer 188</td>
<td>Poloxamer 188</td>
</tr>
<tr>
<td>Kolisolv™ PEG grades</td>
<td>Lutrol® E grades</td>
<td>Macrogols</td>
<td>Polyethylene glycols</td>
</tr>
<tr>
<td>Kolliphor® RH 40</td>
<td>Cremophor® RH 40</td>
<td>Macrogolglycerol hydroxystearate 40</td>
<td>Polyoxyl 40 hydrogenated castor oil</td>
</tr>
<tr>
<td>Kolliphor® TPGS</td>
<td>Spezial® TPGS PHARMA</td>
<td>-</td>
<td>Vitamin E polyethylene glycol succinate</td>
</tr>
</tbody>
</table>

* In 2012 BASF SE rebranded its solubilizers, emulsifiers and cosolvents in order to simplify the structure of the whole excipients portfolio.
Solubilities in solvents

The individual chapters on products contain information on solubilities in various solvents.

Solubility of polymer in solvent: Different concentration levels of the polymer (1 %, 10 %, 25 %, 40 % (w/w)) in solvent were prepared with a magnetic or paddle stirrer at room temperature. Evaluation of the samples was after 24 hours (dissolved or not dissolved). Higher concentrations than 40 % were not tested and thus values of 40 % in the figures mean that the solubility is probably higher than 40 %. In some cases, particularly with high molecular weight polymers, the high viscosity prevented the testing of high concentrations. The solvents varied from high lipophilicity to high hydrophilicity and thus the results reveal whether a polymer is more lipophilic or hydrophilic. To ease recognition of this characteristic, the solvents in all figures are arranged according to increasing hydrophilicity (from left to right). The solubilities of polymers in various solvents are also of significant importance when selecting a suitable solvent for the preparation of solid solutions by spray drying, where polymer and drug must be dissolved in a volatile solvent.

9.1 Kollidon® VA 64/VA 64 Fine

The Kollidon® VA 64 grades are manufactured by free-radical polymerization of 6 parts of N-vinylpyrrolidone and 4 parts of vinyl acetate. Vinilpyrrolidone is a hydrophilic, water-soluble monomer whereas vinyl acetate is lipophilic and water-insoluble. The ratio of the monomers is balanced in such a way that the polymer is still freely water soluble.

Figure 9-1 — Properties and structural formula of Kollidon® VA 64
Pharmaceutical applications in addition to HME:
Kollidon® VA 64 is used in the pharmaceutical industry as a binder in the production of granules and tablets by wet granulation, as a dry binder in direct compression, as an additional film former in coatings on tablets, as a protective layer and sub-coat for tablet cores and as a film-forming agent in sprays.

Intended release profile of extrudates:
Since Kollidon® VA 64 is readily soluble in aqueous media, the release profile of these formulations is mostly instant release; however, it can also be used in modified release drug delivery systems.

9.2 Soluplus®
Soluplus® is a polyvinylcaprolactam – polyvinyl acetate – polyethylene glycol graft copolymer. It has an amphiphilic structure and can be regarded as a polymeric solubilizer. This innovative excipient was launched in 2009 and was designed to be used in hot-melt extrusion and to solubilize poorly soluble actives.
**Pharmaceutical applications in addition to HME:**

Soluplus® acts as a matrix polymer for solid solutions prepared for instance by spray drying or evaporation techniques. It can also be used as a wet or dry binder, film former in oral strips, solubilizer, emulsion stabilizer and protective colloid. In most of these applications, it improves formulation characteristics by its outstanding solubilizing effect. Furthermore, Soluplus® can increase the bioavailability of poorly soluble drugs.
**Intended release profile of extrudates:**
Soluplus® is expected to show an instant release profile.

### 9.3 Kollidon® 12 PF, Kollidon® 17 PF, Kollidon® 30 and Kollidon® 90 F

The soluble Kollidon® grades are obtained by free-radical polymerization of vinylpyrrolidone. The current range of soluble Kollidon® grades consists of pharmaceutical grade products with different nominal K-values.

<table>
<thead>
<tr>
<th>Kollidon® grade</th>
<th>M_W [g/mol]</th>
<th>K-value (1 or 5% solutions in water)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® 12 PF</td>
<td>~2500</td>
<td>11 – 14</td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td>~9000</td>
<td>16 – 18</td>
</tr>
<tr>
<td>Kollidon® 30</td>
<td>~50000</td>
<td>28 – 32</td>
</tr>
<tr>
<td>Kollidon® 90 F</td>
<td>~1250000</td>
<td>85 – 95</td>
</tr>
</tbody>
</table>

**Properties**
- Polyvinylpyrrolidone
- Appearance
  - Almost white free-flowing powder

**Figure 9-5** Properties and structural formula of polyvinylpyrrolidone (povidone)
Increasing hydrophilicity

Figure 9-6  Solubility of Kollidon® 12 PF in different solvents

Figure 9-7  Solubility of Kollidon® 17 PF in different solvents
Figure 9-8  Solubility of Kollidon® 30 in different solvents

Figure 9-9  Solubility of Kollidon® 90 F in different solvents
**Pharmaceutical applications in addition to HME:**
The relevant properties of the soluble Kollidon® grades for pharmaceuticals are solubility in numerous conventional solvents, adhesive- and binding power, film formation, affinity to hydrophilic and hydrophobic surfaces, ability to form water-soluble complexes and thickening. Thus, they are mainly used as binders, crystallization inhibitors, protective colloids, suspension stabilizers, thickeners and wetting agents.

**Intended release profile of extrudates:**
All PVP powders are readily water-soluble and therefore intended to be used for instant release dosage forms.

### 9.4 Kollidon® SR

Kollidon® SR is a spray-formulated mixture of polyvinyl acetate and polyvinylpyrrolidone (povidone) in the ratio of 8:2.

**Properties**
- Polyvinyl acetate/polyvinylpyrrolidone
  - 80/20
- Appearance
  - White or slightly yellowish, free-flowing powder
- Molecular weight
  - Polyvinyl acetate: ~ 450 000 g/mol
  - Povidone: ~ 50 000 g/mol
- K-value (1 % in tetrahydrofuran)
  - 60–65

**Figure 9-10** Properties and structural formula of Kollidon® SR
Pharmaceutical applications in addition to HME:
Kollidon® SR can be used for the production of sustained release matrix preparations in the form of tablets, pellets and granules. The recommended technology for the production of sustained release matrix tablets based on Kollidon® SR is direct compression, but roller compaction and wet granulation can also be used. It is characterized by outstanding compressibility, resulting in extremely high hardness of the tablets.

Intended release profile of extrudates:
Kollidon® SR is insoluble in water and is designed to deliver the active in a sustained release manner [95, 96].

9.5 Kollicoat® MAE 100P

This copolymer consists of methacrylic acid and ethyl acrylate in a ratio of 1:1. It is an anionic copolymer with a neutralization degree of 6 mol %. This can be further neutralized by bases such as sodium hydroxide.
**Properties**

- Methacrylic acid / ethyl acrylate
- 50 / 50
- Appearance
  - White redispersible powder with a faint characteristic odor
- Molecular weight
  - ~ 250 000 g/mol

![Properties and structural formula of Kollicoat® MAE 100P](image)

**Pharmaceutical applications in addition to HME:**
The main application of Kollicoat® MAE 100P is as a film former in enteric coatings for solid dosage forms such as enteric tablets and pellets.

**Intended release profile of extrudates:**
Kollicoat® MAE 100P is intended to be used as an enteric matrix in hot-melt extrusion formulations, the drug being released mainly in the intestine.

![Solubility of Kollicoat® MAE 100P in different solvents](image)
9.6 Kollicoat® IR and Kollicoat® Protect

Kollicoat® IR powder (polyethylene glycol – polyvinyl alcohol graft copolymer) comprises polyethylene glycol and polyvinyl alcohol in the ratio of 25:75 (w/w%). The polyethylene glycol chain forms a backbone onto which side chains of polyvinyl alcohol are grafted.

Kollicoat® Protect is a formulated mixture of Kollicoat® IR and polyvinyl alcohol.

Properties and structural formula of Kollicoat® IR

- Polyethylene glycol/polyvinyl alcohol
  - 25/75
- Appearance
  - White to faintly yellow free-flowing powder
- Molecular weight
  - ~ 45 000 g/mol
Properties

- **Kollicoat® IR/polyvinyl alcohol**
  - 60/40
- **Appearance**
  - White to off-white free-flowing powder
- **Molecular weight**
  - ~30000 g/mol

Figure 9-16  Properties of Kollicoat® Protect
**Pharmaceutical applications in addition to HME:**
Kollicoat® IR acts as a flexible film forming agent in instant release coatings, as a water-soluble binding agent in wet granulation, as a pore-forming agent for adjusting release rates, as a film former in oral strips, as a protective colloid and as a stabilizer of emulsions and suspensions. Kollicoat® IR combines enormous flexibility with extremely low viscosity in water.

Kollicoat® Protect can be used as a protective film against oxidation and hydrolysis of the active ingredient. It can be used to mask taste, to facilitate the swallowing of tablets, to improve their appearance or as a sub-coating. Kollicoat® Protect possesses all the advantages of Kollicoat® IR, e.g. rapid dissolution in water, a high degree of adhesion – also on lipophilic surfaces, enormous flexibility and low viscosity in water.

**Intended release profile of extrudates:**
Due to the excellent water solubility of Kollicoat® IR and Kollicoat® Protect, an instant release profile can be expected [54].
9.7 Kolliphor® P 407, Kolliphor® P 407 micro (Poloxamer 407) and Kolliphor® P 188, Kolliphor® P 188 micro (Poloxamer 188)

The Kolliphor® P grades P 188/P 407 and Kolliphor® P 188 micro/P 407 micro are synthetic copolymers of ethylene oxide (a) and propylene oxide (b) where \( a = \) approx. 80 and \( b = \) approx. 27 for Kolliphor® P 188/Kolliphor® P 188 micro and \( a = \) approx. 101 and \( b = \) approx. 56 for Kolliphor® P 407/Kolliphor® P 407 micro. Principally, the Kolliphor® P grades are amphiphilic molecules where polyoxypropylene represents the lipophilic and polyethylene glycol the hydrophilic part. Typically, Kolliphor® P gels show increased viscosities when the temperature increases from room temperature to 40 °C.

The 3 other poloxamers Kollisolv® P 124 (poloxamer 124, Lutrol® L 44), Kolliphor® P 237 (poloxamer 237, Lutrol® F 87) and Kolliphor® P 338 (poloxamer 338, Lutrol® F 108) are also covered by the poloxamer monograph and are suitable for pharmaceutical applications.

### Properties

- Ethylene oxide/propylene oxide
  - Different ratios
- Appearance Kolliphor® P 188/P 407
  - White, coarse-grained powders with a waxy consistency
- Appearance Kolliphor® P 188 / P 407 micro
  - White microprilled powders with a weak odor
- Molecular weight
  - Kolliphor® P 188 / P 188 micro: \(~8500\) g/mol
  - Kolliphor® P 407 / P 407 micro: \(~12000\) g/mol

![Figure 9-18](image)

Figure 9-18  Properties and structural formula of Kolliphor® P 188 / Kolliphor® P 188 micro and Kolliphor® P 407 / Kolliphor® P 407 micro
Figure 9-19  ▪ Solubility of Kolliphor® P 188 in different solvents

Figure 9-20  ▪ Solubility of Kolliphor® P 407 in different solvents
Pharmaceutical applications in addition to HME:
Kolliphor® P 188 is employed as an emulsifier and solubilizer, also in drug formulations for parenteral use. Furthermore, it is used as a dispersing and wetting agent for preparing solid dispersions and for improving the solubility, absorption and bioavailability of poorly soluble actives in solid oral dosage forms. The formulations are usually processed by melt- and spray granulation.

Kolliphor® P 407 is used primarily as a thickening agent and gel former, but also as a co-emulsifier and consistency enhancer in creams and liquid emulsions. It is also used as a solubilizer for certain active substances in pharmaceutical and cosmetic formulations.

Kolliphor® P 188 micro / P 407 micro are poloxamers designed for direct compression, roller compaction, wet- or melt granulation and hot-melt extrusion. This is because they have a much smaller particle size (approx. 50 µm) than the prilled grades, which renders them compatible with the particle sizes of actives and other excipients. Thus, these fine grades can be blended with drug mixtures without segregation, often somewhat risky when using the prilled Kolliphor® P grades. Their functionality is mainly for improving the wetting and dissolution of poorly soluble drugs. In addition they can also act as water-soluble lubricants in tablet formulation.

Intended use in HME:
Poloxamers are intended to be used as plasticizers and as wetting and dissolution enhancers. Kolliphor® P micro grades can be preblended with other components and also mix more homogeneously in the extruder.

9.8 Kolliphor® RH 40

Kolliphor® RH 40 (macrogolglycerol hydroxystearate 40) is a non-ionic solubilizer and emulsifying agent.

Properties
- Kolliphor® RH 40 consists of:
  - Hydrophobic part: glycerol polyethylene glycol hydroxystearate, together with fatty acid glycerol polyglycol esters;
  - Hydrophilic part: polyethylene glycols and glycerol ethoxylate
- Appearance
  - White to yellowish paste at 20 °C
- Solubility
  - Soluble in water, ethanol, 2-propanol, n-propanol, ethyl acetate, chloroform, carbon tetrachloride, toluene, xylene

Pharmaceutical applications in addition to HME:
The main application is as a solubilizer and emulsifier in oral and topical liquid and semi-solid dosage forms.

Intended use in HME:
Kolliphor® RH 40 is intended to be used as plasticizer or solubility enhancer for actives that are poorly soluble in water.
9.9 Polyethylene Glycols

Polyethylene glycols (PEGs) are liquids or low-melting solids depending on their molecular weights. They are prepared by the polymerization of ethylene oxide and are commercially available with a wide range of molecular weights. The numbers that are often included in the names of PEGs indicate their average molecular weights, e.g. a PEG with \( n = 9 \) would have an average molecular weight of approximately 400 g / mole and would be labeled PEG 400 (e.g. Kollisolv® PEG 400).

**Properties**
- Polyethylene glycols
- Appearance
  - Liquids or low-melting solids
- Molecular weight
  - \( \sim 300 \) to \( \sim 10000000 \) g/mol
- Solubility
  - Polyethylene glycols are readily soluble in water, ethanol, acetone, glycols and chloroform

**Pharmaceutical applications in addition to HME:**
PEGs of different molecular weights are used as co-solvents, plasticizers, thickening agents and as matrix formers in oral, dermal and parenteral dosage forms.

**Intended use in HME:**
The various PEGs are intended to be used as plasticizers.

![Properties and structural formula of PEG](figure)

9.10 Kolliphor® TPGS

Kolliphor® TPGS (d-\( \alpha \)-tocopheryl polyethylene glycol 1000 succinate) is a D-alpha vitamin E ester derived from natural vitamin E. Kolliphor® TPGS is manufactured by esterification of natural d-\( \alpha \)-tocopheryl succinate with polyethylene glycol 1000 [74].

The product is a mixture containing mainly monoester, a certain amount of diester and residual free PEG 1000.

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 [74].
Properties

- **D-α-tocopheryl polyethylene glycol 1000 succinate**
- **Appearance**
  - Waxy solid, white to light brown
- **Molecular weight**
  - ~ 1500 g/mol
- **Solubility**
  - Miscible in all parts with water

Figure 9-23 • Properties and structural formula of Kolliphor® TPGS

![Structural formula of Kolliphor® TPGS]

**Figure 9-24 • Solubility of Kolliphor® TPGS in different solvents**
Pharmaceutical applications in addition to HME:
For tableting or filling hard capsules, hot-melt granulation can be performed using TPGS as a binder for granulation. APIs can be admixed to the binder in the molten state if they are not heat-sensitive. In general, Kolliphor® TPGS can be used to improve the solubility of poorly soluble drugs in tablets or capsules and as carrier for dermal applications [74].

TPGS is described in the literature as a strong p-glycoprotein inhibitor and can thus be used to enhance the bioavailability of BCS class III and IV drugs [74].

Intended use in HME:
Kolliphor® TPGS is intended to be used as a solubilizer for poorly soluble drugs, a bioavailability enhancer for BCS class II, III and IV drugs, as a stabilizer for amorphous drugs in solid dispersions and as a thermal binder for hot-melt granulation and extrusion [74].
10 Physico-Chemical Characteristics – Processability

Polymers for hot-melt extrusion must exhibit thermoplastic characteristics in order to make the hot-melt extrusion process possible and they must be thermally stable at the extrusion temperatures employed. Other relevant characteristics are: suitable glass transition and melting temperatures ($T_g$ or $T_m$) of 50–180 °C, low hygroscopicity and no toxicity since larger amounts of polymer are used [34]. The extrudability of a polymer is mainly determined by $T_g$ or $T_m$ and melt viscosity [49]. Polymers with a high molecular weight exhibit high melt viscosity and are difficult to extrude. Moreover, a high $T_g$ or $T_m$ requires a high processing temperature, which can cause degradation of sensitive actives [97]. As a general rule, an extrusion process should be run at temperatures 20–40 °C above the $T_g$. Most polymers demonstrate thixotropic behavior, which means that the viscosity reduces as a function of increasing shear stress.

10.1 Glass Transition and Melting Temperatures

To determine the glass transition temperature and the melting points of the polymers, differential scanning calorimetry (DSC) analysis was performed. These values should prove helpful in determining the lowest process temperatures that can be used for the polymers in hot-melt extrusion.

**Experimental method**

1. Differential scanning calorimetry:
DSC studies were performed using a Q2000 (TA Instrument, USA). DSC scans were recorded at a heating rate of 20 K/min in the second heating run.

1.1 Additional experimental parameters for measurements on pure polymers, plasticizers and polymer-plasticizer mixtures:
All measurements were performed in a 2-bar pressurized pan except for Kolliphor® RH 40 and Kolliphor® P 407, which were tested in an open pan.

The drying conditions of polymers and plasticizers had to be adjusted for every single sample to ensure complete drying (drying above the $T_g$) without decomposition. The vacuum drying temperature varied from 140 °C to 200 °C.

1.2 Additional experimental parameters for measurements on polymer mixtures:
The polymer blends were predried in open pans for ten minutes inside the DSC apparatus. The drying temperature varied from 160 °C to 200 °C.
10.1.1 DSC Analysis of Polymers and Plasticizers/Solubilizers

The glass transition temperature of PVP homopolymers increases from 90 °C to 156 °C as a function of molecular weight. The relatively low glass transition temperature of Kolliodon® VA 64 is caused by the soft monomer vinyl acetate and in Soluplus® by the covalently bound PEG moiety. Soluplus® can be regarded as an internally plasticized molecule. The PEGs, poloxamers and Kolliphor® TPGS exhibit glass transition temperatures below freezing point; thus, only the melting point is given here.

10.1.2 DSC Analysis of Polymer-Plasticizer Mixtures

DSC is also an excellent tool for studying the impact of plasticizers in polymers on glass transition temperature. For this reason, extrudates and cast films consisting of polymer and plasticizer were analyzed concerning their $T_g$.

**Experimental methods**

1. **Polymer-plasticizer extrudates (extrusion):** The hot-melt extrusion of the polymer-plasticizer mixtures was performed using a twin-screw extruder ZSK 25 (Coperion Werner & Pfleiderer, Germany) with a screw diameter of 25 mm and a length-to-diameter ratio of 34. Several extrusion parameters were varied: Loading of the extruder from 2.5 to 5 kg/h, extrusion temperature of 60–200 °C and the
speed of the extruder screws from 100 to 150 rpm. The screw configuration for all experiments was kept constant. After extrusion, the samples were cooled down on a conveyor belt and subsequently granulated.

2. Polymer-plasticizer films (film casting): Polymer and plasticizer were dissolved in water and the solution cast using a Coatmaster (Erichsen Testing Equipment, Germany) using knives with different die gaps (150–500 µm) and then dried at 40 °C.

Figure 10-2 - $T_g$ of pure polymers in comparison with polymer-plasticizer combinations (extrudates and films (*), 9:1, w/w%)
It is a well-known fact that the glass transition temperature can be reduced by the addition of plasticizers. However, the additives tested acted in a different way. Whereas PEG 1500 and Kolliphor® RH 40 decreased the glass transition temperatures in all systems significantly, Kolliphor® P 188 had no effect on several polymers and Kolliphor® TPGS decreased the Tg in all tested systems except for Kollidon® 30 and Kollidon® 90 F. From these results, it can be concluded that PEG 1500 and Kolliphor® RH 40 dissolve more homogeneously in most of the polymers tested than Kolliphor® P 188 and Kolliphor® TPGS.

### 10.1.3 DSC Analysis of Polymer Mixtures

In these experiments, the extrudates of completely molten polymer mixtures were used as samples. If the polymers are completely miscible, only one T_g should occur. For an immiscible mixture, two glass transition temperatures (T_g signals of polymers) should be found. Similar principles also apply to the melting peaks of the crystalline polymers. Partial miscibility would also result in two glass transition temperatures where at least one is shifted [44].
### Table 10-1  ▪ Tested polymer combinations (extrudates) by DSC-analysis

<table>
<thead>
<tr>
<th>Matrix polymer</th>
<th>Kollidon® SR</th>
<th>Kollicoat® IR</th>
<th>Kollidon® 30</th>
<th>Kollidon® 90 F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>30:70</td>
<td>30:70</td>
<td>30:70</td>
<td>-</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>30:70</td>
<td>30:70</td>
<td>30:70</td>
<td>-</td>
</tr>
</tbody>
</table>

### Experimental method

**Preparation of the polymer mixtures by extrusion (for more detailed information, see chapter: 10.1.2 DSC-Analysis of Polymer-Plasticizer Mixtures):**

- Extruder: ZSK 25 (Coperion Werner & Pfleiderer, Germany)
- Throughput: 4 – 5 kg/h
- Extrusion temperature: 120 – 200 °C
- Screw speed: 100 – 150 rpm
**Kollidon® VA 64 and Soluplus® with Kollidon® SR**

Despite the fact that Kollidon® VA 64 and Kollidon® SR contain the same monomers but in a different polymer structure, they are obviously not miscible, since all glass transition temperatures remained almost the same. The slight increase in the $T_g$ of Kollidon® VA 64 can be attributed to a lower water content of the extrudates or a partial mixing of the PVP contained in Kollidon® SR with Kollidon® VA 64.

The DSC curves of the Soluplus® – Kollidon® SR extrudates show comparatively wide and unsharp peaks. However, partial miscibility is obvious since with 30 % Kollidon® SR, no PVP peak with a molecular weight of ~50000 Daltons can be detected. With larger quantities (70 % Kollidon® SR) the typical $T_g$ of PVP of approx. 160 °C is still visible. Parallel to this, the $T_g$ of Soluplus® increases.

![Figure 10-4](image)

*Glass transition temperatures of the pure polymers and combinations of Kollidon® VA 64 and Soluplus® with Kollidon® SR (extrudates)*
Kollidon® VA 64 and Soluplus® with Kollicoat® IR
Kollidon® VA 64 and Soluplus® in combination with Kollicoat® IR are not completely miscible in the tested concentrations, as can be seen from the melting point of Kollicoat® IR. The decrease in glass transition temperature of Soluplus® and Kollidon® VA 64 in combination with Kollicoat® IR seems to be affected by the low T_g of this compound.

Figure 10-5  Glass transition temperatures of the pure polymers and combinations of Kollidon® VA 64 and Soluplus® with Kollicoat® IR (extrudates)
Kollidon® VA 64 and Soluplus® with Kollidon® 30 and Kollidon® 90 F
The extrudates of Kollidon® VA 64 and Soluplus® with Kollidon® 30 and Kollidon® 90 F demonstrate that these polymers are not miscible by melting and homogenizing in a hot-melt extrusion process.

All experiments with Soluplus® and Kollidon® VA 64 in combination with PVP have shown that the glass transition temperatures of the used components remain almost unchanged. Slight variations in the glass transition temperature of the polymers can be explained by the different drying method used compared to the experiments with the pure polymers.

Figure 10-6: Glass transition temperatures of the pure polymers and combinations of Kollidon® VA 64 and Soluplus® with Kollidon® 30 (extrudates)
**Kollidon VA 64 with polyvinyl acetate**

The miscibility of the polymer Kollidon® VA 64 used in combination with polyvinyl acetate in different ratios of 70:30, 50:50, 30:70 (w/w%) was determined by determination of the \( T_g \)s by DSC analysis.

**Experimental method**

1. **Melt extrusion:** HME was performed using a twin-screw extruder PolyLab OS (ThermoFisher, Germany) with a screw diameter of 16 mm and a length-to-diameter ratio of 40D. After extrusion, the samples were cooled down on a conveyor belt and subsequently pelletized.

- Throughput: 0.5 kg/h
- Extrusion temperature: 160 °C
- Screw speed: 100 rpm

2. **Differential scanning calorimetry (DSC):** DSC studies were performed using a Q2000 (TA Instruments, USA). DSC scans were recorded at a heating rate of 20 K/min during the second heating run.

Based on the DSC results, it can be concluded that polyvinyl acetate forms a two-phase mixture when being melt-extruded with Kollidon® VA 64. This is because two \( T_g \)s were found but no shift in the \( T_g \)s of Kollidon® VA 64 and polyvinyl acetate, showing that these components could not be blended homogeneously on a molecular basis. Despite the similarity in structure, both compounds contain acetate ester functions, lipophilicity strongly differs (Kollidon® VA 64 is water-soluble, polyvinyl acetate is not extrudable).

---

**Figure 10-7** Glass transition temperatures of the pure polymers and combinations of Kollidon® VA 64 and Soluplus® with Kollidon® 90 F (extrudates)
water-insoluble), which together with the relatively high molecular weight of both compounds results in a two-phase system. This does not mean that the combination cannot be used for drug formulation based on extrusion. Kollidon® VA 64 serves as a tool for adjusting drug release from extruded Kollidon® SR matrices by forming pores and channels upon contact with water.

Figure 10-8 - DSC plots of different ratios of Kollidon® VA 64 with polyvinyl acetate and pure polyvinyl acetate

Table 10-2 - $T_g$s of pure polyvinyl acetate in comparison with Kollidon® VA 64-polyvinyl acetate combinations

<table>
<thead>
<tr>
<th>Polymer combination</th>
<th>$T_g$s [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64 / polyvinyl acetate (70:30, w/w%)</td>
<td>41 / 107</td>
</tr>
<tr>
<td>Kollidon® VA 64 / polyvinyl acetate (50:50, w/w%)</td>
<td>43 / 107</td>
</tr>
<tr>
<td>Kollidon® VA 64 / polyvinyl acetate (30:70, w/w%)</td>
<td>44 / 112</td>
</tr>
<tr>
<td>Polyvinyl acetate</td>
<td>43</td>
</tr>
</tbody>
</table>

10.2 Melt Viscosity

Besides the glass transition temperature, the melt viscosity is another crucial factor in determining extrudability.
Experimental method

**Viscosity:** Viscosity studies were performed using a shear stress-controlled rotational rheometer (SR5 Rheometrics, USA) at three different temperatures with a plate-to-plate measuring geometry (diameter of 25 mm, height of 1 mm).

### 10.2.1 Melt Viscosity of Polymers

It is worthwhile obtaining these values in order to get some idea about the lowest process temperature to be used for the polymers in the hot-melt extrusion process. The influence of shear rate and temperature on the melt viscosity characteristics of the polymers was investigated.

**Influence of shear rate on melt viscosity**

All the polymers tested showed a decrease in dynamic melt viscosity with increasing angular frequency and shear rate respectively. Some of the tested polymers showed an unproportional increase in dynamic viscosity at higher temperatures and lower angular frequencies. This might well indicate an initiating cross-linking of the polymer chains. The influence of frequency/shear on the melt viscosity of the polymers is displayed for temperatures within the process temperature range of the pure polymers.
Influence of temperature on melt viscosity

With increasing temperature, the dynamic viscosity of all tested polymers decreased. Only Kollicoat® IR showed a slightly higher viscosity at 190 °C compared to the viscosity at 180 °C. This can probably be explained by an initiating cross-linking of the polymer chains. All the values presented in this chapter were determined at 16 rad/s.

Melt viscosity is influenced by molecular weight and any interaction between the functional groups of the polymer chains. Thus, significant differences between the various polymers were found. Melt viscosity increased strongly when going from Kollidon® 12 PF (~ 2500 Dalton) to Kollidon® 17 PF (~ 9000 Dalton), Kollidon® 30 (~ 50000 Dalton) and Kollidon® 90 F (1250000 Dalton). Despite a high molecular weight, Soluplus® (118000 Dalton) results in a similar viscosity to Kollidon® VA 64 (~ 45000 Dalton). For a small-scale extruder, the limitation is at approximately 10000 Pa*s since higher viscosities generate too much torque. On the other hand, the polymer should not exhibit a very low viscosity because of problematic downstream processing.
Figure 10-11  Melt viscosity of pure polymers as a function of temperature

Figure 10-12  Melt viscosity of Kolliphor® P 407 as a function of temperature
10.2.2 Influence of Plasticizers on Melt Viscosity

Sometimes melt viscosities have to be lowered in order to be able to run a smoother process. This can be achieved by adding plasticizers. We recommend not using liquid plasticizers but solid or at least semi-solid ones since their diffusivity in the matrix is limited; this leads to better stability. Kolliphor® RH 40, Kolliphor® P 188 and PEG 1500 are all effective in reducing viscosity, the most pronounced effect being with Kolliphor® RH 40 and PEG 1500. All the values were determined at 1 rad/s.

![Graph showing influence of plasticizers on melt viscosity of Kollidon® VA 64](image)

10.3 Decomposition by TGA

In principle, all organic materials can be degraded by increasing temperature. Thermal gravimetric analysis (TGA) is a suitable tool for examining the thermal sensitivity of a polymer. At least at the extrusion temperature, which is usually between 100 °C and 200 °C, it must be stable. Even if this method is not capable of delivering detailed information about cross-linking of the polymer chains and a few other possible reactions, it provides at least an idea about the changes that take place upon heating. Thus, changes in the mass with increasing temperature and the kind of reactions (endothermic or exothermic) can be determined. One more thing which has to be considered, is the time during which the material is exposed to the temperature. Long
heat exposure might lead to decomposition, while the material is stable for a shorter time at the same temperature. Exemplarily, a TGA diagram of Soluplus® is shown in this chapter.

**Experimental method**

**Thermo gravimetric analysis (TGA):** TGA was performed using a Netzsch STA 409 C/CD instrument (USA). TGA scans were recorded at a heating rate of 5 K/min up to 450°C (air atmosphere).

![TGA diagram example of Soluplus®](image)

**10.3.1 TGA of Polymers**

The difference between glass transition temperatures ($T_g$) or melting temperature ($T_m$) and $T_{degradation}$ serves as an indication of the extrusion range, which is defined as the temperature range within which extrusion can be performed from a process and stability point of view. The broadest range by far was found with Soluplus®, followed by Kollidon® VA 64, Kollidon® 12 PF and Kolliphor® P 407. Materials with a high $T_g$ can only be extruded within a small, relatively high temperature range.
10.3.2 TGA of Plasticizers

Since plasticizers are often included in formulations for extrusion, they must also be stable at high temperatures. Based on the results obtained, PEG 1500 can be used at up to 175 °C, Kolliphor® P 188 at up to 180 °C, Kolliphor® RH 40 at up to 200 °C and Kolliphor® TPGS at up to 215 °C.
10.3.3 TGA of Active Pharmaceutical Ingredients

The TGA results of the three model drugs fenofibrate, carbamazepine and itraconazole indicate that these can be extruded at temperatures up to at least 180 °C. Of course, for a detailed investigation, HPLC analysis should be performed.
10.4 Specific Heat Capacity of Polymers

The specific heat capacity is the amount of heat that must be added (or removed) from a unit mass of a substance to change its temperature by one degree Kelvin.

This was determined by DSC experiments and is helpful in designing the screw configuration for the extrusion of the polymer. The higher the specific heat capacity, the more energy has to be generated and transferred into the polymer to melt it. Principally, such a polymer requires a more aggressive screw configuration.

**Experimental method**

**Differential scanning calorimetry (DSC):** DSC studies were performed using a Q2000 (TA Instrument, USA). DSC scans were recorded at a heating rate of 20 K/min during the second heating run.

<table>
<thead>
<tr>
<th>Sample</th>
<th>(c_p) (25.0 °C) [J/gK]</th>
<th>(c_p) (100.0 °C) [J/gK]</th>
<th>(c_p) (175.0 °C) [J/gK]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>1.228</td>
<td>1.634</td>
<td>2.137</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>1.396</td>
<td>1.937</td>
<td>2.100 (145 °C)</td>
</tr>
<tr>
<td>Kollidon® 12 PF</td>
<td>1.263</td>
<td>1.740</td>
<td>2.170</td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td>1.205</td>
<td>1.508</td>
<td>2.061</td>
</tr>
<tr>
<td>Kollidon® 30</td>
<td>1.235</td>
<td>1.573</td>
<td>2.142</td>
</tr>
<tr>
<td>Kollidon® 90 F</td>
<td>1.233</td>
<td>1.563</td>
<td>2.142</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>1.270</td>
<td>1.857</td>
<td>2.073</td>
</tr>
<tr>
<td>Kollicoat® MAE 100P</td>
<td>1.298</td>
<td>1.694</td>
<td>2.149 (150 °C)</td>
</tr>
<tr>
<td>Kollicoat® IR</td>
<td>1.880</td>
<td>2.340</td>
<td>3.046</td>
</tr>
<tr>
<td>Kollicoat® Protect</td>
<td>1.703</td>
<td>2.487</td>
<td>3.668</td>
</tr>
<tr>
<td>Koliphor® P 407</td>
<td>1.809</td>
<td>2.111</td>
<td>x</td>
</tr>
</tbody>
</table>

The polymers tested showed specific heat capacities in a range of 1.5 to 2.5 J/gK. The highest values were found for Kollicoat® IR and Kollicoat® Protect. For processing these polymers, more energy has to be transferred in the hot-melt extrusion process.
A potential affinity between polymers and a drug that is poorly soluble in water can be pretested using various methods. The solubilization capacity of the different polymers can be tested by determining the saturation solubility of such a poorly soluble drug in a polymer solution. Using phosphate buffer as a solvent (e.g. pH 7.0) ensures comparable conditions when testing ionic solubilizers or drugs. Thus, solubility effects due to pH shifts can be avoided.

**Experimental method**

**Solubilization procedure:** A 10% polymer solution in phosphate buffer is oversaturated with a discrete drug and stirred for 72 h at room temperature. The resulting suspension is filtered through 0.45 µm filter and the content of solubilized drug is determined in the filtrate by UV spectroscopy with the 8453 UV-Visible spectrophotometer (Agilent, USA).
The following figures show the results of the solubility enhancement of different polymers and PEG 1500 as a plasticizer for various water-insoluble drugs in comparison with the API solubilities in phosphate buffer at pH 7.0. Soluplus® outperformed by far all other polymers and resulted in an enhancement of the saturation solubility for all tested drugs. From these results it is obvious that Soluplus® is capable of effectively solubilizing these water-insoluble drugs. Higher solubilities were achieved only in the case of piroxicam with other polymers, in particular for Kollidon® VA 64; this was caused by a specific complexation of this drug with the vinylpyrrolidone and vinyl acetate moiety.

In contrast, Soluplus® increases drug solubility mainly by forming micelles, which can take up lipophilic drugs almost independently of their structures.
10.6 Calculation of Solubility Parameters of Polymers, Plasticizers and APIs

The computer program SPWin (version 2.1) was used for calculation of the three-dimensional solubility parameters for polar systems according to Hansen [98]. This program contains an advanced parameter set based on the group contribution methods of Fedors [99] and Van Krevelen and Hohtyzer [100]. Group contribution by Fedors and Van Krevelen and Hohtyzer were combined by Braun and Gröning [101] and were modified and optimized by Breitkreutz for the software SPWin 2.1.

For the calculation, the structures of the polymers, plasticizers and drugs have to be divided into functional groups, whereby each atom may only occur once. The determining factor for the affiliation to a group is its priority in chemical nomenclature. The solubility parameters of polymers and plasticizers are always related to an approximate molecular weight given in the chapter 9. The number of groups can be determined from the molecular weight of the polymer or plasticizer and the structure of the monomer. For Kolliphor® RH 40 containing different structures, the calculation of the solubility parameter was not meaningful [102].
Solubility parameters were defined as:

- \( \delta_d \) dispersion components
  Components of intermolecular dispersion or Van der Waals’ forces

\[
\delta_d = \frac{\sum_i F_{di}}{\sum_i V_i}
\]

**Equation 10-1**

- \( \delta_p \) polar components
  Components of intermolecular polar forces

\[
\delta_p = \sqrt{\sum_i \frac{F^2_{pi}}{V_i}}
\]

**Equation 10-2**

- \( \delta_h \) hydrogen bonding components
  Components of intermolecular hydrogen bonding

\[
\delta_h = \sqrt{\sum_i \frac{E_{hi}}{V_i}}
\]

**Equation 10-3**

- \( \delta_v \) calculation of the combined solubility parameters \( \delta_d \) and \( \delta_p \)

\[
\delta_v = \sqrt{\delta^2_d + \delta^2_p}
\]

**Equation 10-4**

- \( \delta_{\text{total}} \) calculation of the combined solubility parameters \( \delta_d, \delta_p \) and \( \delta_h \)

\[
\delta_{\text{total}} = \sqrt{\delta^2_d + \delta^2_p + \delta^2_h}
\]

**Equation 10-5**

The calculated solubility parameter can be used as an initial tool to predict the miscibility of compounds. Agents with similar \( \delta \) values are expected to be miscible.

The polymers and plasticizers show quite similar \( \delta_d, \delta_p, \delta_h, \delta_v \) and (\( \delta_{\text{total}} \)) solubility parameters (except Kollicoat® IR, Kollicoat® Protect). The parameters for the APIs display compliance between fenofibrate and itraconazole and a higher deviation for carbamazepine.
Table 10-4 - Three-dimensional (δ₃, δ₄, δ₅), combined (δᵥ) and total (δₜₐₜ₉) solubility parameters of different polymers

<table>
<thead>
<tr>
<th>Polymer</th>
<th>δ₃</th>
<th>δ₄</th>
<th>δ₅</th>
<th>δᵥ</th>
<th>δₜₐₜ₉</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>17.4</td>
<td>0.5</td>
<td>9.2</td>
<td>17.4</td>
<td>19.7</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>17.4</td>
<td>0.3</td>
<td>8.6</td>
<td>17.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Kollidon® 12 PF</td>
<td>17.3</td>
<td>2.4</td>
<td>8.5</td>
<td>17.5</td>
<td>19.4</td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td>17.4</td>
<td>1.3</td>
<td>8.6</td>
<td>17.5</td>
<td>19.4</td>
</tr>
<tr>
<td>Kollidon® 30</td>
<td>17.4</td>
<td>0.6</td>
<td>8.6</td>
<td>17.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Kollidon® 90 F</td>
<td>17.4</td>
<td>0.1</td>
<td>8.6</td>
<td>17.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>17.4</td>
<td>0.1</td>
<td>10.2</td>
<td>17.4</td>
<td>20.2</td>
</tr>
<tr>
<td>Kollicoat® MAE 100P*</td>
<td>18.3</td>
<td>0.1</td>
<td>11.1</td>
<td>18.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Kollicoat® IR</td>
<td>20.8</td>
<td>0.6</td>
<td>24.9</td>
<td>20.8</td>
<td>32.5</td>
</tr>
<tr>
<td>Kollicoat® Protect</td>
<td>21.3</td>
<td>0.6</td>
<td>26.5</td>
<td>21.3</td>
<td>34.0</td>
</tr>
<tr>
<td>Kolliphor® P 407</td>
<td>17.6</td>
<td>0.8</td>
<td>9.5</td>
<td>17.7</td>
<td>20.1</td>
</tr>
</tbody>
</table>

* Calculated for the acid form

Table 10-5 - Three-dimensional (δ₃, δ₄, δ₅), combined (δᵥ) and total (δₜₐₜ₉) solubility parameters of different plasticizers

<table>
<thead>
<tr>
<th>Plasticizer</th>
<th>δ₃</th>
<th>δ₄</th>
<th>δ₅</th>
<th>δᵥ</th>
<th>δₜₐₜ₉</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolliphor® P 188</td>
<td>17.8</td>
<td>1.0</td>
<td>9.8</td>
<td>17.8</td>
<td>20.3</td>
</tr>
<tr>
<td>PEG 1500</td>
<td>18.0</td>
<td>2.5</td>
<td>11.2</td>
<td>18.2</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Table 10-6 - Three-dimensional (δ₃, δ₄, δ₅), combined (δᵥ) and total (δₜₐₜ₉) solubility parameters of different APIs

<table>
<thead>
<tr>
<th>API</th>
<th>δ₃</th>
<th>δ₄</th>
<th>δ₅</th>
<th>δᵥ</th>
<th>δₜₐₜ₉</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate</td>
<td>19.8</td>
<td>4.2</td>
<td>6.7</td>
<td>20.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>23.7</td>
<td>8.0</td>
<td>10.2</td>
<td>25.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>19.4</td>
<td>5.4</td>
<td>10.3</td>
<td>20.1</td>
<td>22.6</td>
</tr>
</tbody>
</table>
11 Extrusion Experiments

The hot-melt extrusion technique was used to process BASF pharma polymers in the absence and presence of different plasticizers. Moreover, different blends were also produced using combinations of some of these polymers. This chapter mainly provides detailed information on the hot-melt extrusion set up, experimental procedure, processing conditions, effect of plasticizers on processing of the polymers and handling of the extruded products.

11.1 Extrusion of Polymers

The following pure BASF pharma polymers were investigated:

- Kollidon® VA 64
- Soluplus®
- Kollidon® 12 PF
- Kollidon® 17 PF
- Kollidon® 30
- Kollidon® 90 F
- Kollidon® SR
- Kollicoat® MAE 100P
- Kollicoat® IR
- Kollicoat® Protect
- Kolliphor® P 407

11.1.1 Extrusion Temperature Range of Polymers

The polymers were processed at different temperatures in a co-rotating twin-screw extruder. The temperature range selected was the lowest possible processing temperature to the highest. The lowest temperature was determined by various factors such as \( T_g \) or \( T_m \), the melt viscosity, the power consumption of the twin-screw extruders (by means of Ampere) and the pressure in the extruder. The highest possible processing temperature was determined by the thermal stability of the polymers.

Experimental method

Extrusion (for more detailed information, see chapter: 10.1.2 DSC-Analysis of Polymer-Plasticizer Mixtures):

- Extruder: ZSK 25 (Coperion Werner & Pfleiderer, Germany)
- Throughput: 2 to 5 kg/vh
- Extrusion temperature: 60–200 °C
- Screw speed: 100–150 rpm

Taking the \( T_g \) or \( T_m \) (by DSC), the melt viscosity and the \( T_{\text{degradation}} \) (indicated by start of mass reduction by TGA or discoloration) and the determination of the lowest and
highest processing temperatures by hot-melt extrusion into consideration, Kollidon® VA 64, Soluplus®, Kollidon® 12 PF and Kolliphor® P 407 demonstrated excellent suitability for extrusion. Kollidon® 17 PF, Kollidon® SR, Kollicoat® IR and Kollicoat® Protect were difficult to extrude because of a higher T$_g$ or T$_m$, melt viscosities and the smaller difference of T$_{(\text{degradation})}$ to T$_g$/T$_m$. Povidones of higher molecular weight (Kollidon® 30 and Kollidon® 90 F) and Kollicoat® MAE 100 P as pure polymers were not processed by HME due to their degradation.

Figure 11-1  Temperature ranges for the extrusion of pure polymers
11.1.2 Appearance and Pelletizing Characteristics of Extrudates

Appearance and pelletizing behavior of the extrudates are important characteristics from the product and process point of view.

**Appearance of Kollidon® VA 64**
The extrudates of Kollidon® VA 64 look quite clear, glassy and regular. With increasing extrusion temperature, the color turns yellowish and brownish. Above 220 °C extrusion temperature, pelletizing – under the set extrusion conditions – becomes quite difficult.

![Image of Kollidon® VA 64 extrudates at different temperatures]

**Appearance of Soluplus®**
Soluplus® also appears clear, glassy and regular as an extrudate at low temperatures. Above 200 °C, the color changes slowly into yellowish/golden.

![Image of Soluplus® extrudates at different temperatures]
Appearance of Kollidon® 12 PF
The extrudates of Kollidon® 12 PF are quite clear and brittle; this leads to a wide particle size distribution and irregular shapes.

Figure 11-4  •  Extrudate of Kollidon® 12 PF

Appearance of Kollidon® 17 PF
The extrudate of Kollidon® 17 PF appears quite clear and brittle; this leads to a wide particle size distribution and irregular shapes.

Figure 11-5  •  Extrudate of Kollidon® 17 PF

Appearance of Kollidon® SR
Extrudates of Kollidon® SR are yellowish opaque. Kollidon® SR remains flexible for a comparatively long time (after leaving the extruder). For this reason, pelletizing of the strands of pure polymer is challenging.

Figure 11-6  •  Extrudate of Kollidon® SR
Appearance of Kollicoat® IR
The extrudate of Kollicoat® IR looks quite clear and regular. With increasing extrusion temperature, the color becomes slightly darker. However, Kollicoat® IR extrudates processed at temperatures of 160 °C are no longer completely water-soluble.

Appearance of Kollicoat® Protect
The extrudate appears quite clear to cloudy and regular. With increasing extrusion temperature, the color becomes slightly darker. However, Kollicoat® Protect extrudates processed at temperatures of 160 °C are no longer completely water-soluble.

Appearance of Kolliphor® P 407
Kolliphor® P 407 melts at a comparatively low temperature and shows an extremely low viscosity already around 60 °C, so that cooling and pelletizing is a challenge. The extrudate of Kolliphor® P 407 is white.
Soluplus® and Kollidon® VA 64 extrudates have a clear appearance and show good pelletizing behavior. Fairly good results for pelletizing were achieved with Kollicoat® IR, Kollicoat® Protect and Kollidon® SR. Within the range of PVP polymers, Kollidon® 12 PF demonstrated better pelletizing behavior than Kollidon® 17 PF although both polymers have a tendency to create brittle extrudates. The pelletizing of Kolliphor® P 407 was impossible because of the low viscosity of the extrudate at 60 °C.

### Table 11-1: Overview of the appearance and pelletizing behavior of pure polymer extrudates

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Processing temperature [°C]</th>
<th>Characteristics</th>
<th>Pure polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>150</td>
<td>Appearance: Clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: + (Regular pellets)</td>
<td></td>
</tr>
<tr>
<td>Soluplus®</td>
<td>120</td>
<td>Appearance: Clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: + (Regular pellets)</td>
<td></td>
</tr>
<tr>
<td>Kollidon® 12 PF</td>
<td>100</td>
<td>Appearance: Quite clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: + (Irregular pellets, brittle extrudates)</td>
<td></td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td>175</td>
<td>Appearance: Quite clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: 0 (Brittle extrudate)</td>
<td></td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>135</td>
<td>Appearance: Opaque, slight yellowish</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: + (Regular pellets)</td>
<td></td>
</tr>
<tr>
<td>Kollicoat® IR</td>
<td>160</td>
<td>Appearance: Quite clear</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: + (Regular pellets)</td>
<td></td>
</tr>
<tr>
<td>Kollicoat® Protect</td>
<td>160</td>
<td>Appearance: Quite clear to cloudy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: + (Regular pellets)</td>
<td></td>
</tr>
<tr>
<td>Kolliphor® P 407</td>
<td>60</td>
<td>Appearance: White</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelletizing: - (&gt; 60 °C low viscous liquid)</td>
<td></td>
</tr>
</tbody>
</table>
11.1.3 Dissolution Characteristics of Polymer Extrudates

In order to determine the dissolution characteristics of the extrudates, dissolution experiments in different media were performed.

**Experimental method**

**Dissolution:** These investigations were conducted in a USP-conform dissolution apparatus with 900 mL volume at 100 rpm. The cylindrical extrudates of approximately 2 cm length and a diameter of 4 mm were tested in several buffer media with different pH-values (1.1, 6.8 and 9.0).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Extrusion temperature [°C]</th>
<th>Dissolution time [h:min]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pH-value 1.1</td>
</tr>
<tr>
<td>Kollidon® VA 64</td>
<td>180</td>
<td>00:17</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>145</td>
<td>01:15</td>
</tr>
<tr>
<td>Kollidon® 12 PF</td>
<td>130</td>
<td>00:04</td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td>175</td>
<td>00:08</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>180</td>
<td>&gt; 24:00</td>
</tr>
<tr>
<td>Kollicoat® IR</td>
<td>160</td>
<td>&gt; 24:00</td>
</tr>
<tr>
<td>Kollicoat® Protect</td>
<td>160</td>
<td>&gt; 24:00</td>
</tr>
<tr>
<td>Kolliphor® P 407</td>
<td>100</td>
<td>01:01</td>
</tr>
</tbody>
</table>

Kollidon® VA 64, Soluplus®, Kollidon® 12 PF, Kollidon® 17 PF and Kolliphor® P 407 dissolved completely in aqueous media of various pH within a short period of time. As expected, Kollidon® SR extrudates did not dissolve since they contained polyvinyl acetate as a water-insoluble polymer. Surprisingly, Kollicoat® IR and Kollicoat® Protect, as water-soluble polymers, also did not dissolve completely. This effect might be a result of a cross-linking reaction caused by the high extrusion temperatures. Other experiments with Kollicoat® IR in combination with plasticizer and at lower extrusion temperature showed complete dissolution in aqueous media.

11.1.4 Decomposition of Polymers During Extrusion

In addition to TGA analysis, GPC (gel permeation chromatography) of Kollidon® VA 64 and Soluplus® was performed. The GPC was conducted in order to capture cross-
linking or split of the polymer chains. Additionally, chemical test parameters according to the Certificate of Analysis were performed to study the stability of Kollidon® VA 64 and Soluplus® in the hot-melt extrusion process.

11.1.4.1 Kollidon® VA 64 During Extrusion

Melt extrusion was performed using a twin-screw extruder PolyLab OS (ThermoFisher, Germany) with a screw diameter of 16 mm and a length to diameter ratio of 40D. After extrusion, the samples were cooled down on a conveyor belt and subsequently pelletized.

**Experimental method**
- Throughput: 0.5 kg/h
- Extrusion temperature: 160 °C, 180 °C, 200 °C, 220 °C
- Screw speed: 150 rpm

As the curves show, there was no change in molecular weight distribution after extrusion at 160 °C to 220 °C. Furthermore, the chemical parameters reveal no significant difference; in particular no saponification of the ester group or a split-off of the pyrrolidone ring from the polymer chain could be determined. Backsplit of the polymer chain into monomers was also not observed.

![Molecular weight distribution curves of Kollidon® VA 64 (powder) and Kollidon® VA 64 (extrudates)](image-url)
<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Requirements</th>
<th>Powder</th>
<th>160 °C</th>
<th>180 °C</th>
<th>200 °C</th>
<th>220 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinyl acetate [mg/kg]</td>
<td>max. 10</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Vinylpyrrolidone [mg/kg]</td>
<td>max. 10</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Acetaldehyde [mg/kg]</td>
<td>max. 500</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Peroxide [mg/kg]</td>
<td>max. 400</td>
<td>45</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>2-Pyrrolidone [g/100 g]</td>
<td>0.5</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Saponification value [mg KOH/g]</td>
<td>230 – 270</td>
<td>239</td>
<td>243</td>
<td>241</td>
<td>244</td>
<td>242</td>
</tr>
<tr>
<td>pH-value (10% in solution)</td>
<td>min. 3.0, max. 7.0</td>
<td>4.0</td>
<td>3.9</td>
<td>4.0</td>
<td>3.9</td>
<td>4.0</td>
</tr>
<tr>
<td>K-value (1% aqueous solution)</td>
<td>min. 25.2, max. 30.8</td>
<td>25.7</td>
<td>25.7</td>
<td>25.7</td>
<td>25.6</td>
<td>25.6</td>
</tr>
</tbody>
</table>

### 11.1.4.2 Soluplus® During Extrusion

Melt extrusion was performed using a twin-screw extruder PolyLab OS (ThermoFisher, Germany) with a screw diameter of 16 mm and a length to diameter ratio of 40D. After extrusion, the samples were cooled down on a conveyor belt and subsequently pelletized.

#### Experimental method
- **Throughput:** 1.0 kg/h
- **Extrusion temperature:** 160 °C, 180 °C, 200 °C, 220 °C
- **Screw speed:** 200 rpm

Comparable to Kollidon® VA 64, Soluplus® also showed no degradation. The molecular weight remained constant, as did the chemical parameters. A slight increase of the parameter acetic acid / acetate could be detected, but these results were still within the specification.
Figure 11-11  Molecular weight distribution curves of Soluplus® (powder) and Soluplus® (extrudates)

Table 11-4  Stability of Soluplus® during extrusion at 160 °C, 180 °C, 200 °C and 220 °C

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Requirements</th>
<th>Powder</th>
<th>160 °C</th>
<th>180 °C</th>
<th>200 °C</th>
<th>220 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification (IR)</td>
<td>conf.</td>
<td>conf.</td>
<td>conf.</td>
<td>conf.</td>
<td>conf.</td>
<td>conf.</td>
</tr>
<tr>
<td>pH-value</td>
<td>3.0 – 5.5</td>
<td>4.0</td>
<td>3.9</td>
<td>3.9</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Ester value [mg KOH / g]</td>
<td>146 – 236</td>
<td>192</td>
<td>193</td>
<td>193</td>
<td>194</td>
<td>193</td>
</tr>
<tr>
<td>Vinyl acetate [ppm]</td>
<td>max. 100</td>
<td>&lt; 2</td>
<td>&lt; 2</td>
<td>&lt; 2</td>
<td>&lt; 2</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Vinylcaprolactam [ppm]</td>
<td>max. 100</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Caprolactam [g / 100g]</td>
<td>max. 1.0</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Ethylene glycol [ppm]</td>
<td>max. 620</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Acetic acid / Acetate [ppm]</td>
<td>max. 5000</td>
<td>760</td>
<td>860</td>
<td>910</td>
<td>1010</td>
<td>1480</td>
</tr>
<tr>
<td>Peroxide [ppm]</td>
<td>max. 85</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Molecular weight Mw [g / mol]</td>
<td>90,000 – 140,000</td>
<td>120,900</td>
<td>120,800</td>
<td>121,000</td>
<td>120,700</td>
<td>121,500</td>
</tr>
</tbody>
</table>
11.2 Extrusion of Polymer-Plasticizer Combinations

The specific objective was to investigate the effect of various plasticizers on the processing temperature of different polymers.

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Plasticizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>Kolliphor® P 188</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>Kolliphor® RH 40</td>
</tr>
<tr>
<td>Kollidon® 12 PF</td>
<td>PEG 1500</td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td></td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td></td>
</tr>
<tr>
<td>Kollicoat® IR</td>
<td></td>
</tr>
<tr>
<td>Kollicoat® Protect</td>
<td></td>
</tr>
</tbody>
</table>

11.2.1 Extrusion Temperature Range of Polymer-Plasticizer Combinations

Three plasticizers – Kolliphor® P 188, Kolliphor® RH 40 and PEG 1500 – were investigated. In general, it was found that 10 % (w/w) of the plasticizers were sufficient for a significant decrease in extrusion temperatures. Kolliphor® P 188 and PEG 1500 could be added in powder form using a separate powder feeder. Kolliphor® RH 40 was added in molten form using a melt pump. The temperature range for extrusion was determined according to the method employed for the pure polymers.

Experimental method

Extrusion (for more detailed information, see chapter: 10.1.2 DSC-Analysis of Polymer-Plasticizer Mixtures):

- Extruder: ZSK 25 (Coperion Werner & Pfleiderer, Germany)
- Throughput: 2.5 to 5 kg/h
- Extrusion temperature: 60–200 °C
- Screw speed: 100–150 rpm

It is obvious that all the polymer-plasticizer combinations could be processed below the processing temperatures of the pure polymers; however, this reduction was not the same for all the polymers. The highest reduction of 50 °C was observed for Kollidon® SR with all three plasticizers. This is in line with previous studies on the plasticizing effects in film coatings based on polyvinyl acetate, where small amounts also showed a tremendous effect.
The type of plasticizer also had a significant impact since PEG 1500 decreased the extrusion temperatures more than the others. This can probably be attributed to the low molecular weight of this plasticizer.

Figure 11-12  Temperature range for extrusion of polymer / Kolliphor® P 188 combinations (9:1, w/w%)

Figure 11-13  Temperature range for extrusion of polymer / Kolliphor® RH 40 combinations (9:1, w/w%)
11.2.2 Appearance and Pelletizing Characteristics of Polymer-Plasticizer Extrudates

The appearance of the polymer-plasticizer extrudates and pelletizing behavior are important characteristics, particularly for downstream processing. The type of plasticizer had a significant impact since PEG 1500 only slightly deteriorated the appearance and pelletizing behavior of the polymer-plasticizer extrudates compared to the extrudates of pure polymer. More deviation of appearance and pelletizing was observed for Kolliphor® P 188, the strongest deviation being observed for Kolliphor® RH 40. In general, the addition of plasticizers made pelletizing more difficult. Quite often, appearance changed from clear to opaque.
Table 11-5 Overview of appearance and pelleting behavior of different extrudates in the presence of plasticizers (ratio polymer to plasticizer 9:1, w/w%)

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Characteristics</th>
<th>Plasticizer 10 % (w/w%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Kolliphor® P 188</td>
</tr>
<tr>
<td><strong>Kollidon® VA 64</strong></td>
<td>Appearance: Opaque</td>
<td>Opaque</td>
</tr>
<tr>
<td></td>
<td>Pelletizing: + (150 °C) (Irregular pellets)</td>
<td>+ (150 °C) (Irregular pellets)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o (135 °C)</td>
</tr>
<tr>
<td><strong>Soluplus®</strong></td>
<td>Appearance: Clear</td>
<td>Clear</td>
</tr>
<tr>
<td></td>
<td>Pelletizing: + (120 °C) (Regular pellets)</td>
<td>o (120 °C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o (100 °C)</td>
</tr>
<tr>
<td><strong>Kollidon® 12 PF</strong></td>
<td>Appearance: Opaque</td>
<td>Opaque</td>
</tr>
<tr>
<td></td>
<td>Pelletizing: o (60+100 °C)</td>
<td>o (60+100 °C)</td>
</tr>
<tr>
<td><strong>Kollidon® 17 PF</strong></td>
<td>Appearance: Opaque</td>
<td>Opaque</td>
</tr>
<tr>
<td></td>
<td>Pelletizing: 0 (165+175 °C) (Brittle extrudate)</td>
<td>0 (165+175 °C) (Brittle extrudate)</td>
</tr>
<tr>
<td><strong>Kollidon® SR</strong></td>
<td>Appearance: Opaque (Yellowish)</td>
<td>Opaque (Yellowish)</td>
</tr>
<tr>
<td></td>
<td>Pelletizing: + (135 °C) (Regular pellets)</td>
<td>o (135 °C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o (85 °C)</td>
</tr>
<tr>
<td><strong>Kollicoat® IR</strong></td>
<td>Appearance: Opaque</td>
<td>Opaque</td>
</tr>
<tr>
<td></td>
<td>Pelletizing: o (160 °C)</td>
<td>o (160 °C)</td>
</tr>
<tr>
<td><strong>Kollicoat® Protect</strong></td>
<td>Appearance: Opaque</td>
<td>Opaque</td>
</tr>
<tr>
<td></td>
<td>Pelletizing: + (160+180 °C) (Irregular pellets)</td>
<td>0 (160+180 °C)</td>
</tr>
</tbody>
</table>
11.2.3 Miscibility of Polymer-Plasticizer Combinations

The miscibility of the polymers used in combination with the plasticizers (polymer-plasticizer combinations of 9:1, w/w%) was determined by visual inspection of the mixtures and by determination of the $T_g$s and $T_m$s by DSC analysis. A homogeneously clear sample is expected to represent completely miscible combinations. In these experiments, the mixtures were produced using two different experimental methods.

**Experimental method**

1. **Extrusion** (for more detailed information, see chapter: 10.1.2 DSC-Analysis of Polymer-Plasticizer Mixtures):
   - Extruder: ZSK 25 (Coperion Werner & Pfleiderer, Germany)
   - Throughput: 2.5 to 5 kg/h
   - Extrusion temperature: 60–200 °C
   - Screw speed: 100–150 rpm

2. **Polymer-plasticizer films (film casting)**: A polymer and a plasticizer were dissolved in an appropriate solvent. The solution was cast by Coatmaster (Erichsen Testing Equipment, Germany); the knife had different die gaps (150–500 µm) and the solvent was evaporated until a uniform film remained.

---

**Polymer**
- Kollidon® VA 64
- Soluplus®
- Kollidon® 12 PF
- Kollidon® 17 PF
- Kollidon® 30
- Kollidon® 90 F
- Kollidon® SR
- Kollicoat® MAE 100P
- Kollicoat® IR
- Kollicoat® Protect
- Kolliphor® P 407

**Plasticizer**
- Kolliphor® P 188
- Kolliphor® RH 40
- PEG 1500
3. Differential scanning calorimetry (DSC): DSC studies were performed using a Q2000 (TA Instruments, USA). DSC scans were recorded at a heating rate of 20 K/min during the second heating run.

Table 11-6 - Appearance of polymer-plasticizer combinations tested by film casting experiments/hot-melt extrusion and evaluated by visual inspection

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Kolliphor® P 188</th>
<th>Kolliphor® RH 40</th>
<th>PEG 1500</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Film</td>
<td>Extrudate</td>
<td>Film</td>
</tr>
<tr>
<td>Kollidon® VA 64</td>
<td>9:1</td>
<td>9:1</td>
<td>9:1</td>
</tr>
<tr>
<td>Kollidon® 30</td>
<td>9:1</td>
<td>-</td>
<td>9:1</td>
</tr>
<tr>
<td>Kollidon® 90 F</td>
<td>9:1</td>
<td>-</td>
<td>9:1</td>
</tr>
<tr>
<td>Kollicoat® MAE 100P</td>
<td>9:1</td>
<td>-</td>
<td>9:1</td>
</tr>
</tbody>
</table>

The extrudates of Kollidon® VA 64 in combination with Kolliphor® P 188 and Kolliphor® RH 40 were opaque, while the extrudate obtained using PEG 1500 was transparent. Based on the DSC results (Figures 11-16 to 11-18) and visual inspection, it can be concluded that PEG 1500, in contrast to the others, forms a single-phase mixture when melt-extruded with Kollidon® VA 64. This is because, in DSC, no melting point for PEG 1500 was found but rather a shift in the T_g of Kollidon® VA 64. In the case of Kolliphor® P 188 and Kolliphor® RH 40, melting points could still be detected, showing that these components could not be incorporated homogeneously and completely. Visual inspection of films can be employed as a good indicator for miscibility of components.
Figure 11-16  DSC plots of Kollidon® VA 64, pure Kolliphor® P 188 and the Kollidon® VA 64 / Kolliphor® P 188 combination (extrudate, 9:1, w/w%).

Figure 11-17  DSC plots of Kollidon® VA 64, pure Kolliphor® RH 40 and the Kollidon® VA 64 / Kolliphor® RH 40 combination (extrudate, 9:1, w/w%).
11.3 Extrusion of Polymer Mixtures

Kollidon® VA 64 and Soluplus® were selected as two different matrix polymers which were then combined with Kollidon® SR, Kollicoat® IR, Kollidon® 30 and Kollidon® 90 F to produce different blends.

11.3.1 Extrusion Temperature Range of Polymer Mixtures

The polymer ratios were varied from 100:0 to 0:100 (w/w%) in order to investigate the effect of polymer composition on the minimum processing temperature by extrusion.
### Table 11-7  ■ Tested polymer combinations by hot-melt extrusion

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Kollidon® SR</th>
<th>Kollicoat® IR</th>
<th>Kollidon® 30</th>
<th>Kollidon® 90 F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>50:50</td>
<td>50:50</td>
<td>50:50</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>30:70</td>
<td>30:70</td>
<td>30:70</td>
<td>-</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>50:50</td>
<td>50:50</td>
<td>50:50</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>30:70</td>
<td>30:70</td>
<td>30:70</td>
<td>-</td>
</tr>
</tbody>
</table>

### Experimental method

**Extrusion (for more detailed information, see chapter: 10.1.2 DSC-Analysis of Polymer-Plasticizer Mixtures):**

- Extruder: ZSK 25 (Coperion Werner & Pfleiderer, Germany)
- Throughput: 4 to 5 kg/h
- Extrusion temperature: 120 – 200 °C
- Screw speed: 100 – 150 rpm

In the case of Kollidon® SR, almost no effect of Kollidon® VA 64 on the processing temperature was observed. For all compositions with Kollicoat® IR, it was possible to process the blends at 150 °C. It proved impossible to extrude pure polymers Kollidon® 30 and Kollidon® 90 F due to their high T_g and melt viscosities. In the presence of Kollidon® VA 64, Kollidon® 30 could be melt-processed successfully. Moreover, relatively low processing temperatures were required with an increasing amount of Kollidon® VA 64. For Kollidon® 90 F, processing of the mixture was possible only with 70 % (w/w) of Kollidon® VA 64. However, the appearance of the extrudates of this blend was inhomogeneous.

The blends of Soluplus® with Kollidon® SR could be processed at 135 °C. For all compositions with Kollicoat® IR, the processing temperature could be reduced with increasing amounts of Soluplus®. Also, in the presence of Soluplus®, Kollidon® 30 could be melt-extruded successfully at relatively low processing temperatures by increasing the Soluplus® concentration.

The combination of Soluplus® with Kollidon® 90 F behaved similarly to the combination of Kollidon® VA 64 with Kollidon® 90 F but at slightly lower processing temperatures. The blends were also inhomogeneous because of the high molecular weight of Kollidon® 90 F.
Figure 11-19  ■ Minimum processing temperature of polymer blends Kollidon® VA 64 and Soluplus® with Kollidon® SR

Figure 11-20  ■ Minimum processing temperature of polymer blends Kollidon® VA 64 and Soluplus® with Kollicoat® IR
Figure 11-21  Minimum processing temperature of polymer blends Kollidon® VA 64 and Soluplus® with Kollidon® 30

Figure 11-22  Minimum processing temperature of polymer blends Kollidon® VA 64 and Soluplus® with Kollidon® 90 F
11.3.2 Appearance and Pelletizing Characteristics of Extrudates of Polymer Mixtures

The appearance of the extrudates and pelletizing behavior of the polymer mixtures are important characteristics, particularly for downstream processing.

The two different matrix polymers Kollidon® VA 64 and Soluplus® in combination with Kollidon® SR, Kollicoat® IR, Kollidon® 30 and Kollidon® 90 F showed good pelletizing behavior. The appearance of the extrudates of these blends was opaque and displayed the inhomogeneous nature of the systems.

Table 11-8 • Overview of appearance (A) and pelletizing (P) behavior of polymer mixtures

<table>
<thead>
<tr>
<th></th>
<th>Kollidon® SR</th>
<th>Kollicoat® IR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>A</td>
</tr>
<tr>
<td>Kollidon® VA 64</td>
<td>+</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>50:50</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>30:70</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0:100</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>+</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>50:50</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>30:70</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0:100</td>
</tr>
<tr>
<td>Kollidon® 30</td>
<td>+</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>50:50</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>30:70</td>
</tr>
<tr>
<td></td>
<td>Not processable!</td>
<td>0:100</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>+</td>
<td>100:0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>70:30</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>50:50</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>30:70</td>
</tr>
<tr>
<td></td>
<td>Not processable!</td>
<td>0:100</td>
</tr>
</tbody>
</table>

- **Clear sample**
- **Almost clear sample**
- **Opaque sample**
- **+ Good pelletizing behavior**
- **◦ Poor pelletizing behavior**
11.4 Solubilization Capacity of Active Ingredients in Polymers for Hot-Melt Extrusion

The solubilization capacity of active pharmaceutical ingredients in solid solutions of the following polymers was investigated.

- Kollidon® VA 64 Kollidon® 30 with 10 % PEG 1500 (w/w%)
- Soluplus® Kollidon® 90 F with 20 % PEG 1500 (w/w%)
- Kollidon® 12 PF Kollicoat® MAE 100 P with 10 % PEG 1500 (w/w%)
- Kollidon® 17 PF Kollicoat® IR with 10 % PEG 1500 (w/w%)
- Kollidon® SR Kollicoat® Protect with 10 % PEG 1500 (w/w%)
- Kolliphor® P 407

The APIs fenofibrate, carbamazepine and itraconazole were used as model drugs because of their low solubility. Some polymers had to be combined with 10 – 20 % (w/w) PEG 1500 in order to enable extrusion processing at appropriate temperatures.

The solubilization capacity of the APIs in the solid solutions of the polymers was determined using the two different methods of film casting and hot-melt extrusion.

![Chemical structures of model drugs](image-url)

Fenofibrate (antihypertensive) ~0.0001 g / 100 mL in phosphate buffer pH 7.0

Carbamazepine (antiepileptic) ~0.013 g / 100 mL in phosphate buffer pH 7.0

Itraconazole (fungicide) ~0.0001 g / 100 mL in phosphate buffer pH 7.0

The solubilization capacity of the APIs in the solid solutions of the polymers was determined using the two different methods of film casting and hot-melt extrusion.
11.4.1 Film Casting

Solubilization capacity was determined by film casting experiments using fenofibrate, carbamazepine and itraconazole as model drugs in combination with the polymers or polymer-plasticizer combinations described below.

Experimental method

Film casting: An appropriate solvent that dissolves the API, the polymer and the 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 applied for the film casting method (5 to 50 % (w/w) API content in 5 % steps). The higher the clearly dissolved drug concentration, the higher 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.

Figure 11-24 - Film casting procedure

- Preparation of films from 5% to 50% (w/w) drug content in 5% steps
- Observation of film stability
  - drug must not re-crystallize
Soluplus®, Kollidon® VA 64 and Kollidon® SR showed the highest solubilization capacity. Kollidons of lower molecular weight such as Kollidon® 12 PF and Kollidon® 17 PF dissolved only smaller amounts. For the systems comprising Kollicoat® MAE 100 P, Kollicoat® IR and Kollicoat® Protect in combination with itraconazole, no appropriate solvent could be found that dissolved all components.

### Table 11-9  ■ Solubilization capacity of fenofibrate, carbamazepine and itraconazole in polymers or polymer-plasticizer combinations

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Drug content [% dissolved in polymer]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fenofibrate</td>
</tr>
<tr>
<td>Kollidon® VA 64</td>
<td>25</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>35</td>
</tr>
<tr>
<td>Kollidon® 12 PF</td>
<td>20</td>
</tr>
<tr>
<td>Kollidon® 17 PF</td>
<td>15</td>
</tr>
<tr>
<td>Kollidon® 30 *</td>
<td>20</td>
</tr>
<tr>
<td>Kollidon® 90 F **</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td>30</td>
</tr>
<tr>
<td>Kollicoat® MAE 100 P *</td>
<td>15</td>
</tr>
<tr>
<td>Kollicoat® IR *</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Kollicoat® Protect *</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Kolliphor® P 407</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

*With 10 % PEG 1500  **With 20 % PEG 1500
11.4.2 Extrusion

Besides the film experiments, solubilization capacity was also determined using hot-melt extrusion of carbamazepine and itraconazole as model drugs in combination with the following polymers and polymer-plasticizer combinations:

- Kollidon® VA 64
- Soluplus®
- Kollidon® 12 PF
- Kollidon® 17 PF
- Kollidon® SR
- Kolliphor® P 407

- Kollidon® 30 with 10% PEG 1500 (w/w%)
- Kollidon® 90 F with 20% PEG 1500 (w/w%)
- Kollicoat® MAE 100 P with 10% PEG 1500 (w/w%)
- Kollicoat® IR with 10% PEG 1500 (w/w%)
- Kollicoat® Protect with 10% PEG 1500 (w/w%)

Drug content in the extrudates was increased from 5% to 50% (w/w) in 5% steps. All extrudates were investigated by XRD or DSC in order to determine the physical state of the incorporated drug. Since stability of solid dispersions can be a critical point, the extrudates were stored in open glass bottles at 25 °C/60% r.h. for 3 months and tested for physico-chemical changes. In addition dissolution studies were also performed.

**Figure 11-25** Appearance of extrudates with increasing drug concentration

---

**Experimental method**

**Extrusion:** Melt extrusion was performed using a twin-screw extruder PolyLab OS (ThermoFisher, Germany) with a screw diameter of 16 mm and a length-to-diameter ratio of 40D. Several extrusion parameters were varied such as the loading of the extruder (from 0.3 to 0.8 kg/h), extrusion temperature (90–180 °C) and the speed of the extruder screws (from 50 to 250 rpm). The active ingredient was fed to the
extruder via a separate feeder, since this allows a simple and quick change of the active concentration in the extrudate. After extrusion, the samples were cooled down on a conveyor belt and subsequently pelletized.

2. X-ray diffraction (XRD): XRD studies were performed using a diffractometer D 8 Advance (Bruker/AXS, Germany).

3. Differential scanning calorimetry (DSC): DSC studies were performed using a Q2000 (TA Instruments, USA). DSC scans were recorded at a heating rate of 20 K/min during the first heating run.
<table>
<thead>
<tr>
<th>Polymer</th>
<th>Drug content [% dissolved in polymer]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carbamazepine [mp: 190 – 193 °C]</td>
<td>Itraconazole [mp: 166 °C]</td>
</tr>
<tr>
<td><strong>Kollidon® VA 64</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>150 – 160°C</td>
<td>155 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Soluplus®</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>150 – 160 °C</td>
<td>160 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>30%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>30%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>30%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td><strong>Kollidon® 12 PF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>120 – 130 °C</td>
<td>130 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>5% (DSC)</td>
<td>5% (DSC)</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>5% (DSC)</td>
<td>5% (DSC)</td>
</tr>
<tr>
<td><strong>Kollidon® 17 PF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>160 – 170 °C</td>
<td>150 – 160 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>15% (DSC)</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Kollidon® 30 + 10 % PEG 1500</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>140 – 170 °C</td>
<td>160 – 170 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>35%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>35%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>10%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Polymer</td>
<td>Drug content [% dissolved in polymer]</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carbamazepine [mp: 190 – 193 °C]</td>
<td>Itraconazole [mp: 166 °C]</td>
</tr>
<tr>
<td>Kollidon® 90 F + 20 % PEG 1500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>180 °C</td>
<td>160 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>&gt; 50%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>10%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>10%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Kollidon® SR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>150 °C</td>
<td>150 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>25%</td>
<td>45%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>25%</td>
<td>45%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>20%</td>
<td>45%</td>
</tr>
<tr>
<td>Kollicoat® MAE 100P + 10 % PEG 1500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>Not processable!</td>
<td></td>
</tr>
<tr>
<td>Kollidicon® IR + 10 % PEG 1500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>140 °C</td>
<td>140 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Kollicoat® Protect + 10 % PEG 1500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>140 °C</td>
<td>145-150 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Kolliphor® P 407</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process temperature</td>
<td>140 °C</td>
<td>140 °C</td>
</tr>
<tr>
<td>Extrudates (initial value)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Extrudates (1 month)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Extrudates (3 months)</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>
Carbamazepine extrudates

Principally, there are two types of polymer – those that can solubilize higher concentrations and those of rather poor performance in this respect. Differences were also found when storing the solid solutions for a longer period of time. Kollidon® VA 64 and Soluplus® could solubilize ≥ 30% (w/w) carbamazepine and kept it in solution for more than 3 months. The other polymers such as Kollidon® 12 PF, Kollidon® SR, Kollicoat® IR, Kollicoat® Protect and Kolliphor® P 407 were less effective for the solubilization of carbamazepine (< 30% (w/w)). Some polymers resulted in quite high concentrations at the beginning (Kollidon® 17 PF, Kollidon® 30 and Kollidon® 90 F); however, the drug crystallized upon storage and the concentration of dissolved drug decreased significantly.

![Graph showing solubilization capacity of polymers for carbamazepine](image)

Figure 11-27 - Stability of carbamazepine extrudates stored in open glass bottles at 25 °C / 60 % r.h. over a period of 3 months

Itraconazole extrudates

Most of the polymers dissolved itraconazole better than carbamazepine and concentrations of ≥ 40% (w/w) could mostly be achieved. Best performance > 50% was obtained for Soluplus®, Kollidon® 30 + 10% PEG 1500 and Kollidon® 90 F + 20% PEG 1500 followed by Kollidon® SR with 45%, Kollidon® VA 64 and Kollidon® 17 PF with 40%. Kollicoat® IR, Kollicoat® Protect and Kolliphor® P 407 are too hydrophilic by far to dissolve lipophilic actives. Changes upon storage occurred only with Kollicoat® IR, whereas all the others remained stable.
11.4.3 Results and Comparison

The solubilization capacity of the APIs carbamazepine and itraconazole in solid solutions of the polymers was determined using the two different methods of film casting and hot-melt extrusion. Extruders require considerable quantities of drugs, which are not often available at the early development stage when pilot studies are undertaken. In contrast to extrusion studies, film tests can be performed with small amounts of drugs. Should there be a correlation between extrusion and film tests, the latter can serve as an indicator for solid solutions, provide an approximate drug/excipient ratio and minimize the number of extrusion experiments. For this comparison, solubilization capacities from film casting (7 days/23 °C/54 % r.h.) and extrusion (1 month at 25 °C/60 % r.h.) were used. Differences in results between the two methods might well be because, in hot-melt extrusion, no solvent is used and the drug is incorporated by temperature and shear only, whereas in film casting the solid solution is formed by evaporation of the solvent.

Solubilization capacities of carbamazepine

A good correlation of film casting and extrusion results was achieved for carbamazepine extrudates with Kollidon® VA 64, Soluplus®, Kollidon® 17 PF, Kollidon® 90 F + 20 % PEG 1500, Kollicoat® IR + 10 % PEG 1500, Kollicoat® Protect + 10 % PEG 1500 and Kolliphor® P 407. The other systems (except Kollidon® 30 + 10 % PEG 1500) showed higher solubilization capacities in film casting experiments.
Solubilization capacities of itraconazole

The combinations of itraconazole with Soluplus®, Kollidon® 17 PF, Kollidon® 30 + 10% PEG 1500, Kollidon® 90 F + 20% PEG 1500, Kollidon® SR and Kolliphor® P 407 revealed good correlation between extrusion and film casting. Higher solubilization capacities in film casting were observed with the other combinations.

In principle, solubilization capacities determined by extrusion and film casting correlate well and therefore the film casting method is a suitable tool for predicting the maximum concentration of dissolved drug in the polymer. The solubilization capacities determined by film casting have a tendency to produce higher values compared to the results obtained by extrusion.
Solubilization capacity API [%]

Kollidon VA 64
Kollidon 12 PF
Kollidon 17 PF
Kollidon 30*
Kollidon 90 F**
Kollidon SR
Kolliphor P 407

* Polymer + 10% PEG 1500
** Polymer + 20% PEG 1500
↓ Solubilization capacity API below the tested concentration
↑ Solubilization capacity API above the tested concentration

Figure 11-30 - Comparison of the solubilization capacity of itraconazole determined by film casting (visual inspection 7 days after storage at 23 °C / 54 % r.h.) and extrusion (XRD 1 month after storage in open glass bottles at 25 °C / 60% r.h.)
12 Injection Molding Experiments

A physical blend of Soluplus® with 15% (w/w) itraconazole was used to prepare a specimen tablets via injection molding. The study investigated mainly the difference in preparing the material for injection molding by having a hot-melt compounding step prior to injection molding (experimental method 1) or without the compounding step (experimental method 2). The tablets were analyzed for drug release characteristics and compared to cut melt extrudates and pure itraconazole [103]. These injection molding trials were conducted in cooperation with Thermo Fisher Scientific in Karlsruhe, Germany.

Experimental method

1. Hot-melt extrusion & injection molding: Melt extrusion was performed using a conical small-scale extruder – Pharma mini HME (Thermo Scientific, Germany). After extrusion, the extruder fed the melt directly into the reservoir of the injection molding device (Thermo Scientific Haake Minijet, Thermo Scientific, Germany) from where oblong tablets of dimensions 20 x 6 mm were prepared by injection molding [103].

- Formulation: Soluplus® with 15% (w/w) itraconazole
- Extrusion temperature: 170 °C
- Screw speed: 150 rpm
- Torque: 0.5 Nm

Parameters for injection molding:
- Reservoir temperature: 195 °C
- Injection pressure I: 400 bar, applied for 10 s
- Injection pressure II: 150 bar, applied for 10 s

2. Injection molding: In a second set of experiments, the physical powder blend was fed manually into the reservoir of the Minijet (Thermo Scientific, Germany) without prior melt extrusion and tablets were prepared by injection molding. The conditions for the injection molding process were kept constant in both cases for comparison purposes [103].

Parameters for injection molding:
- Reservoir temperature: 195 °C
- Injection pressure I: 400 bar, applied for 10 s
- Injection pressure II: 150 bar, applied for 10 s

3. Drug release: Drug release was tested according to USP, with apparatus 2, 50 rpm 700 mL HCl (0.08 N) under non-sink conditions. Release was determined using cut extrudates (3 mm in length and diameter), the 2 different formulations of Soluplus® with 15% itraconazole produced by injection molding and pure itraconazole. During dissolution, samples were automatically passed through a 45 µm and measured by the 8453 UV-VIS spectrophotometer (Agilent, USA).
Tablets could be obtained from the injection molding process independently of whether the material was first melt-extruded or not. Tablets obtained from the physical blend (non-extruded) contained more air bubbles, which were caused by the process. The prior extrusion process is a good tool for homogenizing the blend and getting rid of air bubbles. Both injection molded forms appeared translucent, indicating that itraconazole was dissolved within the polymer [103].

In terms of drug release, both series of tablets, with and without a prior extrusion step, showed a similar performance. Dissolution of itraconazole was enhanced by both preparation methods. Compared to the pure itraconazole, a strong increase in solubility was observed. It is also obvious that cut extrudates with a particle size of approximately 3 mm resulted in even faster dissolution than the tablets prepared by injection molding. This is not a result of the process itself or a different state of the active within the polymer, but only because of the surface area of the forms tested. All formulated products had no or no significant porosity and thus drug release kinetics are mainly determined by dissolution of the polymeric matrix, in this case Soluplus® [103]. The hydration and dissolution speeds of a polymer are dependent on the molecular weights and other polymer characteristics; however, they are usually not as quick as in the case of a low molecular weight compound. It also means that large bolus forms without any porosity, such as injection molded tablets, cannot generate very fast drug release. Soluplus® offers the particular benefit that the poorly soluble itraconazole is completely dissolved and precipitation and crystallization are prevented for the entire test period (6 h).
Injection molding provides the opportunity to prepare solid solutions and perform final shaping into a final dosage form in a single step or in directly linked steps. Other industries have already shown just how cost-efficient this technology can be since it is widely used to manufacture small plastic items. However, it also competes with the calendering of melts, which can also be directly linked to melt extrusion. As pointed out already, injection molding is not a technology for generating quickly dissolving dosage forms but dosage forms with a controlled release pattern. This pattern can be adjusted by the polymer and additives used as well as by the dimensions of the form. The larger the dimensions and the smaller the surface area, the slower the release profile.
13 Melt Granulation Experiments

Soluplus® and Kolliphor® P 407 micro were investigated concerning their melt binding properties using highly dosed caffeine as a model drug [104].

Experimental method

1. Melt granulation & post-processing: Caffeine/polymer preblends were agglomerated using a twin-screw extruder PolyLab OS (ThermoFisher, Germany) with a screw diameter of 16 mm and a length-to-diameter ratio of 40D.

Tested Formulations:
- 80 % (w/w) caffeine / 20 % (w/w) Soluplus®
- 90 % (w/w) caffeine / 10 % (w/w) Soluplus®
- 80 % (w/w) caffeine / 20 % (w/w) Kolliphor® P 407 micro
- 85 % (w/w) caffeine / 15 % (w/w) Kolliphor® P 407 micro

Agglomeration:
- Feed rate: 1 kg/h
- Barrel temperature: 50 °C (Kolliphor® P 407 micro mixtures)
- Barrel temperature: 120 °C (Soluplus® mixtures)
- Screw configuration: 1 kneading block with 5 x 0.25 D kneading elements at 90°
- Screw speed: 200 rpm
- Torque: 0.5 Nm

2. Sieving: The produced granules were passed through an oscillating sieve of 1000 µm mesh size.

3. Granule friability: Granules were stressed using an air jet sieve of 125 µm mesh. The fines were removed at a flow rate of 20 m³/h for 1 minute before stressing the granules for 10 minutes at 70 m³/h flow rate. The friability of granules was defined as mass loss in % after 10 minutes [105].

Caffeine was successfully granulated with both polymers. At 20 % binder concentration, Soluplus® and Kolliphor® P 407 micro resulted in similar particle size distributions, despite the much finer particles of the micronized poloxamer binder (approx. 50 µm). The better binding strength of the Soluplus® polymer compensated for its larger particles (approx. 340 µm). This finding is further supported by the results obtained using lower binder concentrations; this is because – in contrast to Soluplus® – Kolliphor® P 407 micro could not be reduced to 10 % without losing proper agglomeration behavior during processing (not shown in the figure). Even the 15 % binder concentration of the poloxamer generated smaller particles than the 10 % of Soluplus®.
Bulk densities and flowabilities were significantly increased for all formulations compared to pure caffeine.

Granule friability as an indicator of granule strength was excellent at 20% binder concentration irrespective of the chosen binder. At lower binder concentrations, granule strength strongly decreased resulting in high friability values. It is expected that granule strength can be improved even at lower binder concentrations by optimizing the extruder settings and processing conditions.
Drug release of the granules was completed within the first 20 minutes for both formulations at 20% binder concentration.

Figure 13-2  Granule friability of different formulations (fraction 125–1000 µm)

Figure 13-3  Drug release of granules (fraction 315–500 µm, 100 mg API) containing 20% (w/w) polymeric binder
In summary, Soluplus® showed stronger melt binding properties compared to Kolli-
phor® P 407 micro. The binder concentration could be decreased to 10% enabling
highly dosed caffeine granules to be formed. Melt granulation with polymeric solu-
bilizers offers the possibility of agglomerating and solubilizing actives that are poorly
soluble in water as well as moisture-sensitive drugs [104].
14 Spray Drying Experiments

The solubilization capacity of the APIs fenofibrate, carbamazepine and itraconazole in solid solutions of the polymers Kollidon® VA 64 and Soluplus® produced by spray drying was investigated. All formulations were analyzed by differential scanning calorimetry (DSC) or X-ray diffraction (XRD) in order to determine the physical state of the incorporated drug.

**Experimental method**

**Spray drying:**

**Liquid:** The APIs and polymers were dissolved under stirring in an appropriate solvent (formulations with fenofibrate: acetone; formulations with carbamazepine and itraconazole: dichloromethane). Concentrations of the organic solutions ranged from 10 to 20 % (w/w).

<table>
<thead>
<tr>
<th>Table 14-1</th>
<th>API – Kollidon® VA 64 combinations in spray drying</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymer</strong></td>
<td><strong>Formulations</strong></td>
</tr>
<tr>
<td>Kollidon® VA 64</td>
<td>Fenofibrate Carbamazepine Itraconazole</td>
</tr>
<tr>
<td>Inlet air [°C]</td>
<td>91–92 83–86 85</td>
</tr>
<tr>
<td>Outlet air [°C]</td>
<td>51–52 55–56 54–56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 14-2</th>
<th>API – Soluplus® combinations in spray drying</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymer</strong></td>
<td><strong>Formulations</strong></td>
</tr>
<tr>
<td>Soluplus®</td>
<td>Fenofibrate Carbamazepine Itraconazole</td>
</tr>
<tr>
<td>Inlet air [°C]</td>
<td>60–85 85 85–91</td>
</tr>
<tr>
<td>Outlet air [°C]</td>
<td>44–56 54–57 59–87</td>
</tr>
</tbody>
</table>

**Results**

Due to the small scale spray dryer used, small particles were produced; in general, these have a stronger tendency to stick to the wall than larger ones. Due to the plasticizing effect of the API and, especially, of fenofibrate on the polymers, some formulations were very difficult to spray-dry. In contrast, APIs with higher melting points and subsequently lower plasticizing effects revealed better spray drying behavior.
Kollidon® VA 64 and Soluplus® dissolved \( \geq 30\% \) (w/w) carbamazepine and 40\%–50\% (w/w) itraconazole. Both polymers dissolved itraconazole better than carbamazepine.

Good correlation of spray drying, film casting and extrusion results was achieved for carbamazepine and itraconazole formulations with Kollidon® VA 64 and Soluplus®.

In principle, solubilization capacities determined by spray drying, film casting and extrusion correlate well and therefore the film casting method is also a suitable tool for predicting the maximum concentration of dissolved drug in the polymer.
Figure 14-1  ■ Comparison of the solubilization capacity of carbamazepine in polymers determined by film casting (visual inspection 7 days after storage at 23 °C / 54 % r.h.), extrusion (XRD 1 month after storage in open glass bottles at 25 °C / 60 % r.h.) and spray drying.

Figure 14-2  ■ Comparison of the solubilization capacity of itraconazole in polymers determined by film casting (visual inspection 7 days after storage at 23 °C / 54 % r.h.), extrusion (XRD 1 month after storage in open glass bottles at 25 °C / 60 % r.h.) and spray drying.
15 In-Vitro / In-Vivo Characteristics of HME Formulations

15.1 In-Vitro Release Characteristics

Drug dissolution is an important parameter for the characterization of a solid dispersion since it reveals whether the drug dissolves completely or not and whether the polymer prevents crystallization and keeps the drug in an oversaturated dissolved state. Thus, all experiments were carried out without the addition of any further solubilizer in the dissolution medium (non-sink conditions).

Three different types of behavior of drugs formulated with water-soluble polymers can occur:
1. The drug dissolves and no recrystallization takes place.
2. The drug dissolves and recrystallization occurs later, leading to a decrease of dissolution.
3. Crystallization occurs quickly and almost simultaneously with the matrix dissolving, leading to very low and incomplete dissolution.

It is quite obvious that the targeted profile is behavior No. 1 – complete dissolution without recrystallization.

Experimental method

1. Drug release: Drug release was tested according to USP, with apparatus 2, 50 rpm, 700 mL HCl (0.08 N) under non-sink conditions. Release was determined using cut extrudates of comparable length (3 mm in length and diameter, except Kolliphor® P 407, as this could not be cut directly into pellets). The amount of API used was 100 mg. During dissolution, samples were automatically passed through a 45 µm filter and immediately measured by spectrophotometer.

All polymers or polymer-plasticizer combinations with itraconazole showed an enhanced dissolution rate of the drug (except Kollidon® SR) compared to the crystalline itraconazole.
Soluplus® outperformed all other polymers by far and resulted in almost complete dissolution. From these results, it is obvious that Soluplus® is capable of solubilizing itraconazole effectively, not only in a solid state but also in an aqueous environment; it is also capable of preventing crystallization. In this case a high level of supersaturation (approx. 20-fold) is achieved and maintained. Satisfactory results were found with Kollicoat® IR and Kollidon® VA 64.

Within the range of PVP homopolymers, Kollidon® 90 F produced significant dissolution of itraconazole, whereas, with decreasing molecular weight of the PVP homopolymer, dissolution decreased.
15.2 In-Vivo Behavior

When developing formulations for poorly soluble drugs, the general goal is to increase bioavailability. This cannot be tested in in-vitro experiments but only in in-vivo studies, either in animals or in humans. Of course, the in-vitro dissolution characteristics give some indication of efficacy in humans but often there is no exact in-vitro – in-vivo correlation; the dissolution behavior of a drug formulation in a glass vessel and in the intestine under the influence of ingested food and intestinal motility might well be different. However, almost complete in-vitro dissolution combined with a high degree of supersaturation maintained over a longer period of time are essential prerequisites for a significant increase in bioavailability. This does not necessarily mean, of course, that the quickest dissolution always leads to the best bioavailability.

15.2.1 In-Vivo Behavior of Itraconazole Formulations

In order to show the potential of HME formulations for increasing bioavailability, a study on itraconazole as a model drug was performed.

**Experimental method**

The following drug formulations were produced and used:

1. **Solid solution**: Itraconazole was extruded with Soluplus® to give a 15% (w/w) solid solution. The extrudates were milled, blended with 5% (w/w) of disintegrant and filled into gelatine capsules.
2. Physical mixture: Itraconazole, Soluplus® and disintegrant were blended in the same proportions as in the solid solution and filled into gelatine capsules.

3. Crystalline drug: Itraconazole was blended with disintegrant and filled into gelatine capsules.

Animal study:
The formulations were applied to 5 beagle dogs (in fasting state) in a dose of 10 mg/kg body weight. Plasma samples were taken at predetermined time points and analyzed for itraconazole concentration.

The plasma curves reveal that itraconazole is a drug which is poorly absorbed without special formulations. The crystalline drug as well as the physical mixture with Soluplus® did not result in significant plasma levels. In contrast, the solid solution of itraconazole in Soluplus® significantly enhanced the absorption by a factor of approximately 25. This study demonstrates that the physico-chemical properties and the in-vitro characteristics of Soluplus® are capable of achieving the desired in-vivo performance.
15.2.2 In-Vivo Behavior of Fenofibrate Formulations

This study was performed similar to the itraconazole study, except that a 20% solid solution of fenofibrate in Soluplus® was prepared and administered.

The solid solution of fenofibrate in Soluplus® as well as, surprisingly, the physical mixture with Soluplus®, significantly enhanced absorption. In contrast, the crystalline drug did not result in high plasma levels. The outcome of this study also demonstrates that, in certain cases, the physical blending or mixing of an API with Soluplus® may enhance its bioavailability. This may well hold true for APIs which show a certain level of bioavailability already as crystalline compounds and which can be increased by improved wetting and dissolution of the crystals with Soluplus®.

15.2.3 In-Vivo Behavior of Danazol Formulations

This study was performed similar to the itraconazole study, except that dosing to animals was 30 mg/kg.
This figure reveals that danazol is poorly absorbed without a special formulation. The crystalline drug and the physical mixture did not lead to significant plasma levels of the drug. In contrast, the solid solution with Soluplus® enhanced absorption significantly by a factor of 15.

### 15.3 Comparison of the Performance of Soluplus® Formulations with Marketed Drugs

This study compared the in-vitro and in-vivo performance of a commercially available itraconazole drug product (Sempera®) with a Soluplus®-based formulation [106].

**The following drug formulations were produced and used:**

1. **Itraconazole, crystalline:** Itraconazole with a mean particle size of 2.5 µm was used.

2. **Sempera® (Jansen-Cilag):** Hard gelatine capsules containing 100 mg itraconazole in the form of drug-layered pellets.

3. **Itraconazole-Soluplus® extrudate:** Itraconazole-Soluplus® extrudate (ratio 20:80) was prepared by melt extrusion with a 16 mm twin screw extruder PolyLab OS (ThermoFisher, Germany) at 160 °C, 200 rpm and a feed rate of 1000 g/h. Extrudates were milled to a size of max 250 µm.
15.3.1 In-Vitro Performance of Sempera® and a Soluplus®-Based Formulation

Experimental method for in-vitro drug release:
Dissolution tests were conducted with a USP apparatus #2 (paddle) operating at 50 rpm and using 700 mL hydrochloric acid (0.08 molar), pH 1.1 (simulated gastric fluid) as dissolution medium. Samples were taken manually through a 0.2 µm filter. Since Soluplus® forms large drug-loaded micelles, a 10 µm filter was used for the analysis of these samples. The amount of dissolved itraconazole was immediately measured by UV-Vis spectrophotometer (Agilent, USA) at 258 nm [106].

The samples (standardized to a content of 100 mg itraconazole) were added to the dissolution medium as powders – and in the case of Sempera® as pellets – but all without capsules.

Crystalline itraconazole has very poor solubility and did not dissolve in the dissolution medium. Both formulations, itraconazole in the form of a solid solution with Soluplus® and the commercial Sempera®, significantly improved dissolution and enabled supersaturated solutions to be obtained.
15.3.2 In-Vivo Performance of Sempera® and a Soluplus®-Based Formulation

Experimental method for in-vivo drug release:
The formulations were administered to beagle dogs as gelatine capsules containing mixtures of 70% test formulation, 15% Avicel® PH 102 and 15% Kollidon® CL at a dose of 10 mg/kg body weight [106].

The itraconazole-Soluplus® and Sempera® formulations achieved a significant increase in bioavailability compared to crystalline itraconazole. However, the bioavailability of the Soluplus® formulation was 2.3 times higher than that of Sempera®. This superior performance can be explained by the capability of Soluplus® to form stable solid solutions and by the formation of itraconazole-loaded micelles upon dissolution [106].

Results from in-vitro dissolution tests and in-vivo bioavailability studies normally correlate only partially. The in-vivo performance of the itraconazole Soluplus® extrudate was much better than expected from its dissolution behavior [106].
16 Manufacture of Final Dosage Forms

The extrusion process leads to a strand leaving the die in a more or less molten or softened state; this then solidifies upon cooling and is commonly cut into pieces in the mm range by a pelletizer. The still soft strand or ribbon can also be directly shaped into forms similar to tablets by a calender, which consists of two co-rotating rolls with cavities. The principle of manufacturing has some similarities with the soft gel capsule manufacturing process.

The cut extrudates can be filled directly into hard gelatine capsules; however, they are usually milled in order to speed up the release rate. Such milled solid solutions can be blended with other excipients and either filled into capsules or compressed into tablets. In each case water-insoluble excipients that act as so-called spacers between the solid solution particles should be used in order to avoid lumping effects when the dosage form comes into contact with water. Such lumping can negatively affect the dissolution rate due to the reduced surface area and longer diffusion pathways. Water-insoluble excipients separate the particles of the solid solution and prevent lumping. Best results were found with crospovidone (Kollidon® CL, CL-F, CL-SF) and microcrystalline cellulose, but dicalcium phosphate and other inorganic excipients can also be employed.

Typically, tablets containing solid solution particles require higher disintegrant concentrations (5 to 20 %) than common ones (3 to 5 %). Here, crospovidone, due to its limited swelling behavior, outperforms all other superdisintegrants (croscarmellose sodium, sodium starch glycolate), which are of unlimited swelling and form gels upon contact with water.

Examples of dosage forms

1. Capsule formulation:
   - Solid solution 70 % (w/w)
   - Kollidon® CL 15 % (w/w)
   - Microcrystalline cellulose 15 % (w/w)

2. Tablet formulation:
   - Solid solution 60 % (w/w)
   - Microcrystalline cellulose (Avicel® PH 102) 29 % (w/w)
   - Kollidon® CL 10 % (w/w)
   - Magnesium stearate 0.5 % (w/w)
   - Aerosil® 200 0.5 % (w/w)
The following flow chart shows the development process from screening to a final pharmaceutical formulation using hot-melt extrusion.

### Polymeric Material/API/Additive
Selection by:
- Chemical structure
- Solubility
- Glass transition temperature (Tg)
- Melt viscosity
- Lipophilicity
- Dissolution profile
- Stability

### API
Relevant characteristics:
- Solubility
- Melting point (Tm)
- Lipophilicity
- Stability

### Additive
Selection by:
- Physical state
- Plasticizing effect
- Lubricating effect
- Stability

#### Pre-study:
Film casting trials

#### Hot-melt extrusion

#### Extrudate

#### Stability tests

#### Milling/tableting/capsule filling

#### Stability tests

#### Final oral dosage form

**Figure 17-1** From screening to a final pharmaceutical formulation
Hot-melt extrusion (HME) is a relatively new process which has not yet become well established in the pharmaceutical industry. As there is therefore a lack of practical experience, formulators have had to start from scratch. In this chapter, first recommendations for carrying out extrusion experiments are given.

**General recommendation for the process**

1. **Impact of ingredient characteristics**

When starting the development process for pharmaceutical formulations using HME, it is important to select suitable polymers and additives, as described in the flow chart illustrated in chapter 17.

**Important factors that influence the process parameters in HME are:**

- **Polymer characteristics:**  Glass transition temperature or melting temperature, melt viscosity and thermal stability
- **Additive characteristics:**  Thermal stability, plasticizing effect and lubricating effect
- **API characteristics:**  Thermal stability, plasticizing effect and melting point

2. **Correlation between the extrusion parameters**

The impact of the so-called independent variables such as screw speed, feed rate and temperature on parameters such as torque and residence time should be known for each extruder and basic formulation. This allows a better comparison and a better understanding of extrusion experiments carried out at different settings. In particular, it is a prerequisite for the scale-up of extrusion processes from small extruders (16 or 18 mm screw diameter) to pilot plant scale (approximately 25 mm screw diameter) and hence to production scale (40 to 70 mm screw diameter).

3. **Constant and equilibrated process**

In principle, extrusion is a continuous process where materials enter the machine at one end and leave it at the other. All settings should be such that the whole process runs in a constant, equilibrated and smooth manner. This is of particular importance when taking samples from the extruded material for further analysis. Torque, throughput and die pressure are good indicators for such a process and they should not vary much.

**Feeder**

1. **Demixing of the blend during feeding**

- Verification of homogeneous mixing of the blend by horizontal and vertical mixing in the feeder.
- Separate feeding of ingredients should be used in case of segregation of a mixture. Generally, this allows quick changes of the formulation. If the active is fed by a separate feeder, its concentration in the polymer matrix can be changed simply by adjusting its feed rate while keeping the feed rate of the other ingredients constant.
2. Segregation of blends
To avoid segregation, powders of almost the same particle size should be used. For instance, Kolliphor® P micro grades usually do not segregate because they have a similar particle size (50 µm) to actives in contrast to the Kolliphor® P grades, which are in the mm-range. If segregation cannot be avoided, the ingredients should be fed to the extruder by separate feeders.

3. Electrostatic charge on the substances
- Equipment should be grounded.
- The screw tube should be well designed.
- There should be no electrostatic charge on the API: polymer/API premix preparation can avoid this.
- Anti-static devices (e.g. U-electrodes) should be used to generate positive and negative ions evenly and hence remove charges from the substance.

4. Inconstant feeding
An appropriate twin-screw for the feeder should be selected. It should run well within the feeding range of the twin-screw expressed as kg/h. Particle size and other physical characteristics of the formulation determine the screw geometry/design of the feeder.

5. Gravimetric feeding systems
Gravimetric feeding systems should be run in a constant and protected environment without vibrations and infiltration (drafts!).

**Feeding section of the twin-screw extruder**

1. Cooling the feeding section
   The powder must not melt within the first barrels after the feeding sections to avoid blocking the barrel opening.

2. Screw configuration
   Only conveying elements should be used in the feeding section and afterwards for a certain distance. A short distance between the barrel opening and the first kneading block can lead to backflow of powder and hence inconstant throughput.

**Melting section of the twin-screw extruder**

1. Melting of the formulation should be brought about by a balanced combination of thermal and mechanical energy. Factors to be taken into consideration are glass transition temperature or melting temperature and melt viscosity of the ingredients, screw speed, feed rate, screw configuration, barrel temperature etc. The energy input caused by friction should not dominate the process as high temperature peaks can occur within small areas.

2. Start-up of a twin-screw extruder
   - Start with a moderate screw speed.
Adjust the feed rate according to the melt viscosity of the material (a high melt viscosity of the powder means a lower feed rate).

**Mixing section of the twin-screw extruder**

1. **Adjustment of mixing intensity**
   In principle, as much as needed but as low as possible. Parameters: Length of the mixing section and configuration of the kneading elements (a strong increase in temperature in the kneading sections should be avoided!).

2. **Screw configuration**
   For thermal- and shear-sensitive polymers and APIs, a screw configuration providing low shear should be selected.

**Degassing section of the twin-screw extruder**

1. **Residual moisture**
   Residual moisture of the powder in the extrusion process should be removed.

2. **Application of vacuum**
   This results in quicker removal of moisture and entrapped air and gas bubbles.

3. **Screw configuration**
   Conveying elements only should be used in the degassing section.

**Die**

1. **Bulky surface of the extrudates**
   Reduction of die temperature for increasing die pressure; pressures can also be changed by altering the dimensions of the die.

**Cleaning procedure of the extruder**

**Example:** Twin-screw extruder PolyLab OS (ThermoFisher, Germany) with a screw diameter of 16 mm and a length to diameter ratio of 40D.

**Procedure:**

1. Stop feeding the formulation and allow the extruder to run until empty.

2. Heat up the feeding section and adjust the temperature to the temperature of the melting, mixing and shaping section (for example: 150 °C, 200 rpm).

3. Add approximately 200 g cleaning polymer (a polymer with higher melt viscosity) to the feeding section to remove the residual formulation (for example: 150 °C, 200 rpm).

4. Add a small amount of water (approximately 30 mL) to the feeding section (for example: 150 °C, 200 rpm).
5. Add approximately 200 g cleaning polymer to the feeding section (for example: 150 °C, 200 rpm).

6. Allow the extruder to run until empty.

7. Allow the extruder to cool down (feeding, melting, mixing and shaping section) to approximately 100 °C.

8. Disassemble the extruder (remove the upper barrel of the extruder and the die) and remove the screws. Protect your hands against heat!

9. Remove the residual cleaning polymer from the barrel, die and the screws with your protected hands.

10. To remove the residual impurities, use a brass wire brush and/or an appropriate solvent.

**Pelletizing device**

1. Poor pelletizing properties of extrudates caused by stickiness
   Improvement can be achieved by pre-cooling the extrudates with cold air between the die and the pelletizing device.

2. Poor pelletizing properties of extrudates caused by brittleness
   Pelletizing of strands immediately cooled to room temperature can be difficult if the material becomes brittle upon cooling. In this case, prevent the temperature of the strands from reaching a low value before pelletizing.

**Sampling**

1. All samples should be taken from a constant and equilibrated process.

2. If release rates are to be determined from pelletized extrudates, the geometry of the pellets (diameter, length, surface area) should be very similar.
19 Regulatory Aspects

In this chapter, an overview is given on the regulatory status of the BASF pharma polymers.

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>Europe</th>
<th>Japan</th>
<th>GRAS Status USA</th>
<th>Maximum Potency * [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon® VA 64</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+**</td>
<td>854</td>
</tr>
<tr>
<td>Kollidon® 30</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+****</td>
<td>80</td>
</tr>
<tr>
<td>Polyvinyl acetate</td>
<td>+</td>
<td>+</td>
<td></td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>Kollicoat® MAE 30 DP</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>100</td>
</tr>
<tr>
<td>Kollicoat® IR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Expected Q4 2012</td>
<td>20.4***</td>
</tr>
<tr>
<td>Kolliphor® P 407</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>107</td>
</tr>
<tr>
<td>Kolliphor® P 188</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>66.9</td>
</tr>
<tr>
<td>Kolliphor® RH 40</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>405</td>
</tr>
<tr>
<td>PEG 1500</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>4.2******</td>
</tr>
<tr>
<td>Kolliphor® TPGS</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>300.0</td>
</tr>
</tbody>
</table>

Typically, in extruded formulations, more polymer is used compared to common applications such as coatings or binders since the polymer serves as a matrix. BASF pharma polymers either benefit from prolonged use in pharmaceutical applications (e.g. older products such as Kollidon® 30) or they have been tested over the full range of toxicological studies (e.g. newer products such as Soluplus® or Kollicoat® IR). In most cases, the results obtained from toxicological studies justify higher doses than the ones given in the previous table of the FDA Inactive Ingredient Guide.

Toxicological reports are available upon request.
20 Literature References


41 P. Andersen, Multi-shaft extruder kneading discs, kneading disc blocks and extruder, US 6,170,975 B1.
42 H. Wobbe, E. Uhland, Screw kneader for plastic material having a controlling mixing section, Patent number: 5,318,358.
<table>
<thead>
<tr>
<th>Page</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>G. Cuff, F. Raouf, A preliminary evaluation of injection moulding as a technology to produce tablets, Pharm. Technol. 6, 96–106 (1998).</td>
</tr>
<tr>
<td>68</td>
<td>C. Vervaet, J. P. Remon, Continuous granulation in the pharmaceutical industry, Chemical Engineering Science 60, 3949-3957 (2005).</td>
</tr>
</tbody>
</table>


92 V. Bühler, Kollidon®: Polyvinylpyrrolidone excipients for the pharmaceutical industry, BASF SE, 9th revised edition (2008).
93 V. Bühler, Kollicoat® Grades: Functional polymers for the pharmaceutical industry, BASF SE (2007).
100 D. W. Van Krevelen, P. J. Hoftyzer, Properties of polymers. Their estimation and correlation with chemical structures, Amsterdam: Elsevier (1976).
Note

This document, or any answer or information provided herein by BASF, does not constitute a legally binding obligation on the part of BASF. While the descriptions, designs, data and information contained herein are presented in good faith and believed to be accurate, it is provided for your guidance only. Because many factors may affect processing or application / use, we recommend that you make tests to determine the suitability of a product for your particular purpose prior to use. It does not relieve our customers from the obligation to perform a full inspection of the products upon delivery or any other obligation. No warranties of any kind either express or implied, including warranties of merchantability or fitness for a particular purpose are made regarding products described or designs, data or information set forth, or that the products, designs, data or information may be used without infringing the intellectual property rights of others. In no case shall the descriptions, information, data or designs provided be considered a part of our terms and conditions of sale.

October 2012
21 Alphabetical Index

A  
Active pharmaceutical ingredients 119, 148  
Agglomeration 13, 19, 55–57, 162  
Ambient temperature 22, 37, 77  
Amide structure 14, 31  
Amorphous 10, 12–15, 17, 18, 31, 34, 54, 61, 63–71, 73, 77, 102, 167  
Amorphous drug 12, 14, 31, 69, 102  
Amorphous glass suspension 13, 14  
Amorphous solid dispersion 12, 13, 15, 69  
Amorphous state 12, 14, 70  
Amphiphilic 17, 84, 86, 97, 100  
Analytical method 61–63, 67  
ANOVA 46, 48, 52, 53  
API solubility 19, 33, 121  
Appearance polymer extrudates 128–131  
Appearance polymer mixtures 147  
Appearance polymer-plasticizer extrudates 138–143  
Atomic force microscopy (AFM) 62, 67  
Attenuated total reflectance (ATR) 62  
Autogenous extrusion 35  
Axial flight width 23  
Axial mixing 42

B  
Barrel diameter 23  
Barrel temperature 37–39, 48, 51, 52, 57, 69, 162, 180  
Binder 32, 55–57, 86, 87, 91, 102, 162–165, 183  
Bioavailability 10, 13, 19, 20, 31, 32, 34, 72, 87, 99, 102, 171–174, 176, 178  
Biopharmaceutics classification system (BCS) 10, 11  
Blending 35, 173  
Bodenstein-No 42, 44  
Bulk density 25, 30, 59

C  
Calendering 22, 30, 33, 81, 82, 161  
Carbamazepine 119, 122–125, 148–151, 153, 155–157, 166, 168  
Channel width 23  
Chill roll 78–80  
Cinnarizine 122, 123  
Cleaning procedure 179, 181  
Clotrimazole 122, 123
Co-extrusion 82, 83
Compounding 21, 35, 36, 74, 159, 186
Continuous processes 55
Conveying 21–29, 35, 40, 57, 180, 181
Conveying effect 27
Conveying elements 24, 29, 57, 180, 181
Cooling 17, 21, 22, 30, 35, 37, 56, 77–83, 130, 177, 180, 182
Copovidone 30, 31, 84
Co-rotating 16, 22, 45, 126, 177, 186
Counter-rotating 22, 81
Crystalline 12–15, 18, 33, 43, 54, 61–69, 71, 73, 106, 149
Crystalline glass suspension 13
Crystalline state 12, 14
Danazol 122, 123, 173, 174
Decomposition (GPC) Kollidon® VA 64 133, 134
Decomposition (GPC) Soluplus® 134–136
Degassing 22, 24, 25, 38, 181
Design of experiments 36, 53
Design space 48, 49, 51
Die 20–22, 29, 30, 35–39, 41, 42, 50–53, 55, 74–78, 80, 83, 105, 140, 177, 179, 181, 182
Die geometry 39
Die temperature 22, 37, 181
Differential scanning calorimetry (DSC) 14, 61, 64, 69, 103, 111, 120, 141, 152, 166
Diffused reflectance infrared transmission spectroscopy (DRIFTS) 62
Discharging 25
Disintegrant 171, 172, 177
Dispersing 23–25, 35, 99
Dispersive mixing 26, 28, 34, 35, 51
Dissolution characteristic polymer extrudates 132
Dissolution kinetics 11
Dissolution rate 10–12, 17, 32, 72, 73, 169, 177, 186, 188
Distributive mixing 26, 27, 35, 51
Dosage form 10, 19, 20, 32, 33, 54, 59, 60, 74, 79, 81, 91, 93, 99, 100, 161, 177, 178, 187
Double flighted 22
Downstream 16, 21, 30, 35, 74–76, 78, 82, 83, 114, 138, 147
Downstream device 75
Downstream processing 16, 30, 74, 114, 138, 147
Downstreaming 35, 74
Drug delivery system 19, 32, 54, 86, 187
Drug release 19, 32, 54, 73, 112, 159–161, 164, 169–171, 175, 176, 184
Dry granulation 55
Dynamic vapour sorption (DVS) 62

Economic effects 48
Economic impact 51, 53
Electrostatic charge on the substances 180
Energy state 12
Estradiol 122, 123
Ethylene glycol and vinyl alcohol graft copolymer 84
Extruder equipment 20, 152
Extrusion process 18–25, 30, 32, 34–38, 40, 42, 120, 133, 148, 160, 177, 179, 181
Extrusion temperature 30, 32, 37, 48, 103, 104, 107, 111, 116, 126, 128, 130, 132–134, 136, 137, 140, 143, 144, 151, 159
Extrusion temperature range polymer mixtures 143–146
Extrusion temperature range polymer-plasticizer combinations 136–138
Extrusion temperature range polymers 126, 127

Feed rate 29, 38, 39, 45, 69, 75, 80, 162, 174, 179–181
Feeder 21, 29, 30, 38, 43, 45, 50, 55–57, 74, 78, 82, 136, 152, 179, 180
Feeding section 21, 24, 37, 180–182
Fenofibrate 119, 122–125, 148–150, 166, 167, 173
Film casting 58–60, 105, 141, 148, 149, 156–158, 160, 167, 178
Final dosage form 59, 79, 161, 177
Flight 23, 30
Flight width 23
Fourier transformed infrared (FT-IR) 62
Fox equation 15
Free volume 23, 27, 49, 50, 53
Freeze drying 16, 58, 188

Gear-pump 76
Gordon-Taylor equation 15
Granule friability 162–164
Gravimetric feeding 29, 30, 180
Griseofulvin

**H**
- Heat conduction: 25
- Heat flux: 25
- Helix angle: 23
- Homogenizing: 25, 110, 160
- Hot die face pelletizer: 83
- Hot-melt compounding: 159
- Hot-melt extrusion (HME): 9, 14, 16–21, 30, 32–34, 54, 55, 58, 63, 64, 69, 74, 77, 84, 93, 99, 103, 104, 110, 113, 120, 126, 127, 133, 144, 148, 156, 159, 178, 179, 184, 185, 189
- Hydrogen bonding: 12, 14, 30, 31, 124, 186
- Hydrophilic binders: 56
- Hydrophobic binders: 56

**I**
- Impurities: 37, 38, 39, 42, 46, 47, 182, 185
- Injection molding: 9, 20, 34, 54, 82, 159–161
- Inner diameter: 23
- In-vitro characteristics HME formulations: 169–171, 175
- In-vivo characteristics HME formulations: 171–174, 176
- Isothermal microcalorimetry (IMC): 62

**K**
- Ketoconazole: 122, 123
- Kneading: 21, 23–25, 27–29, 40, 57, 162, 186
- Kneading elements: 23, 24, 29, 162, 181
- Kollicoat® MAE 100P: 31, 59, 84, 92, 93, 120, 125, 126, 140, 141, 150, 154
- Kollidon® CL: 176, 177
Kolliphor® P 188 84, 97–99, 106, 116, 118, 125, 136–142, 183
Kolliphor® P 188 micro 84, 97, 99
Kolliphor® P 237 97
Kolliphor® P 338 97
Kolliphor® P 407 micro 84, 97, 162, 165
Kolliphor® RH 40 84, 99, 103, 106, 116, 123, 136–142, 183
Kolliphor® TPGS 84, 100, 101, 102, 104, 106, 118, 183
Kollisolv® P 124 97

Macrogol polyvinyl alcohol grafted copolymer 84
Macrogol polyvinyl alcohol grafted copolymer + poly(vinyl alcohol) 84
Macrogolglycerol hydroxystearate 40 84, 99
Macrogols 84
Melt conveying 25, 26
Melt fracture 76, 77, 189
Melt granulation 55–58, 99, 102, 162, 165, 187–189
Melt pressure 22, 37
Melt stream 75, 76, 82, 83
Melt temperature 22, 37, 39, 75–77
Melt viscosity 29, 32, 103, 112–116, 126, 178–181
Melting enthalpy 25
Melting point 39, 56, 64, 103, 104, 109, 141, 166, 178, 179
Melting zone 21
Methacrylic acid – ethacrylate copolymer 1:1 84
Methacrylic acid copolymer type C 84
Miscibility polymer-plasticizer combinations 140–143
Mixing effect 26, 27
Mixing zone 26, 29
Modulated temperature differential scanning calorimetry (MTDSC) 61
Molecularly dispersed 11–15, 61, 69
Multi-layered systems 83

Near infrared (NIR) 62
Noyes-Whitney-equation 11

Outer diameter 23

Screw length 23
Screw root 23
Screw shafts 40
Segregation of blends 180
Sempera® 174–176
Shaping 20, 21, 33–35, 54, 74, 81, 161, 181, 182
Shaping section 21, 181, 182
Shear effect 27
Shelf-life 17, 77
Single crystal X-ray diffraction (SCXRD) 61
Single-phase system 14
Single-screw extruder 23
Small angle X-ray scattering (SAXS) 61
Solid dispersion 10, 12–19, 26, 34, 36, 58, 61, 63, 69, 71–73, 77, 99, 102, 151, 169, 185, 186, 189
Solid feeding 26, 26
Solid glassy solution 13–17, 77
Solidifying 74
Solid-state nuclear magnetic resonance (ss-NMR) 62
Solubilities in solvents 85
Solubility parameter 9, 31, 123–125, 186, 189
Solubilization capability 30, 31
Solubilization capacity by film casting 149, 150
Solubilization capacity by HME 151–156
Solubilization capacity by spray drying 166–168
Solution calorimetry (SC) 62
Solvent-free 16, 19, 35
Specific feed load 42, 46, 48–52
Specific heat capacity 25, 39, 120, 121
Specific mechanical energy consumption 40–42, 45–48, 51–53
Specific temperature 38
Spray drying 14, 16, 17, 58–60, 85, 87, 166–168, 186, 188
Spray drying conditions 58
Spray-dried powder 58, 60
Stability of solid dispersions 61, 151
Stainless steel 29, 83
Standard spray-drying 58
Supercritical fluid drying 16
Super-saturated state 14, 17
Supersaturation 72, 170, 171

**T**
- Temperature range 5, 14, 17, 32, 51, 113, 117, 126, 127, 136–138, 143
- Terahertz pulsed spectroscopy (TPS) 62
- Thermal gravimetric analysis (TGA) 116
- Throughput 20, 25, 29, 35, 37, 40, 45–51, 53, 57, 60, 80, 81, 107, 111, 126, 133, 134, 136, 140, 144, 179, 180
- Torque 22, 36, 39–42, 46, 48–53, 83, 114, 159, 162, 178, 179
- Torque winders 83
- Torque-limited 48–50
- Tracer 42, 43, 44, 45
- Twin-screw extruder 2, 4, 16, 22, 23, 26, 35, 45, 69, 104, 111, 126, 133, 134, 151, 162, 180, 181, 184, 186, 187, 189
- Two-phase system 14, 112

**U**
- Upstream 21, 35, 74, 75

**V**
- Vacuum 22, 25, 37, 64, 103, 149, 181
- Velocity 40
- Volume-limited 48–50
- Volume-specific feed load 48–52
- Volumetric feeding 22, 30

**W**
- Wet granulation 55–57, 86, 92, 96, 187
- Wettability 11

**X**
- X-ray diffraction (XRD) 63, 69, 152, 166
Contacts

E-mail:
solid-dispersion@basf.com

Web Page:
http://www.innovate-exipients.basf.com
This book is intended for all researchers and developers in pharmaceutical technology who are already, or are considering, working with solid dispersions and hot-melt extrusion.

The relevant properties of the various BASF pharma polymers, plasticizers and solubilizers as well as combinations of these are described in detail.

Furthermore, it provides information on how to process actives in hot-melt extrusion, how to characterize the resulting formulations and how to develop stable drug delivery systems. Particular emphasis is placed on the important process variables of twin-screw extrusion, adequate downstream processes and practical recommendations for hot-melt extrusion.

In addition, other manufacturing processes for solid dispersions such as spray drying and injection molding are briefly described.