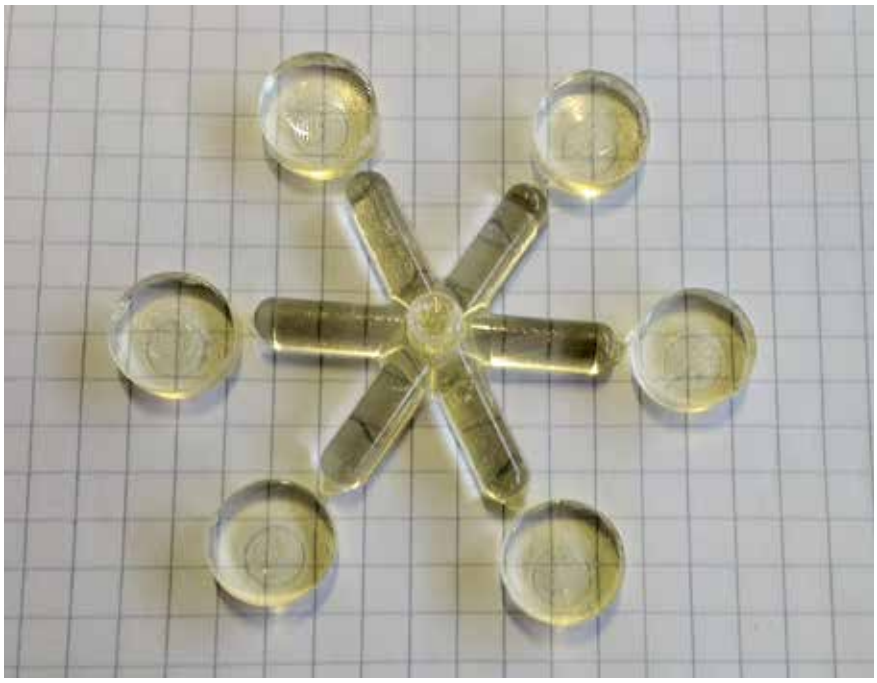
Tablets from the Injection Molding Machine

Certain Pharmaceutical Dosage Forms Can Be "Effectively" Injection Molded in a Single Step

Some 40 percent of all active pharmaceutical ingredients (APIs) currently in the development pipelines of the pharmaceutical industry are sparingly soluble in water. At the same time the cost of medicines is soaring. Consequently, in order that a wide demographic may continue to have guaranteed access to medicines, two things must happen: the industry needs to develop new, economic manufacturing processes and, through new dosage forms, it must ensure APIs which are sparingly soluble in water can be released and absorbed in the human body. Injection molding affords a new way of accomplishing this.



The tablets (here with manifold runner, but without sprue gate) were produced in a single-step process from Soluplus pellets with 10 % API content (fenofibrate)

In order for an API to be released from a solid oral administration form and to reach its target and be absorbed there, it must first dissolve. The state-of-the-art way to improve solubility is to produce solid dispersions. The API therein is embedded in a matrix of a water-soluble polymer that serves as excipient and solubilizer [1]. Nowadays, solid dispersions are prepared by hot-melt extrusion in a multistep compounding process (**Fig. 1**). This entails processing the excipient polymer, together with the API in crystalline form above their glass transition temperatures, followed by conversion into an amorphous melt system.

Uniform incorporation of the APIs is ensured by passing the mixture of polymer and API through various shearing and mixing zones. For successful compounding, vent zones are also required, because the polymer is usually highly amphiphilic and the residual moisture needs to be removed from the system. The extrudate is pelleted and then the pellets themselves are re-ground for the next step of the tablet pressing line.

Pharmaceutical Polymers as the Basis

For experts in polymer processing, complicated multiple passes through various operations might remind them of classic thermoset processing. Injection molding, by contrast, offers the advantage of combining many of these separate processing steps into a single integrated process. This knowledge together with the vast market potential – one study estimates that pharmaceutical expenditure in 2017 will be approx. 1.2 trillion USD, 22 % higher than in 2012 [2] – provided the motivation to devise the basics for injection molding of pharmaceutical dosage forms. Participants in the research project include the Institute for Polymer Injection Molding Technology and Process Automation (IPIM) at the Johannes Kepler University in Linz and injection molding machine manufacturer Engel Austria GmbH, Schwertberg, both in Austria.

The research is divided into two development steps. Development step I is

currently fully underway, while initial steps have been taken on development step II (single-step process with in-line compounding) (**Fig. 1**). Implementation is posing a number of challenges for the development team:

- Dosing of polymer and API (both in powder form),
- Compounding on a reciprocating-screw plasticizing unit,
- Moisture absorption by the excipient polymers,
- Demolding of a tablet with uniform API distribution,
- The use of process simulation for analysis.

The research was conducted on pharmaceutical polymers from the Soluplus program of BASF SE, Ludwigshafen, Germany. Compared with thermoplastics of the kind used in medical technology, Soluplus polymers have a much less-pronounced shear-thinning behavior (decrease in viscosity with increase in shear). This property (**Fig. 2**) requires a higher torque during plasticizing and high injection pressures for cavity filling.

Soluplus is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. The backbone consists of ethylene glycol (PEG 6000) with one or two grafted vinyl acetate side chains, which are polymerized with vinyl caprolactam. The model API is fenofibrate, a lipid-lowering agent which is classified as having poor solubility in water [3]. Lipid-lowering APIs are prescribed for the treatment of dyslipidemia and prevention of cardiovascular disease.

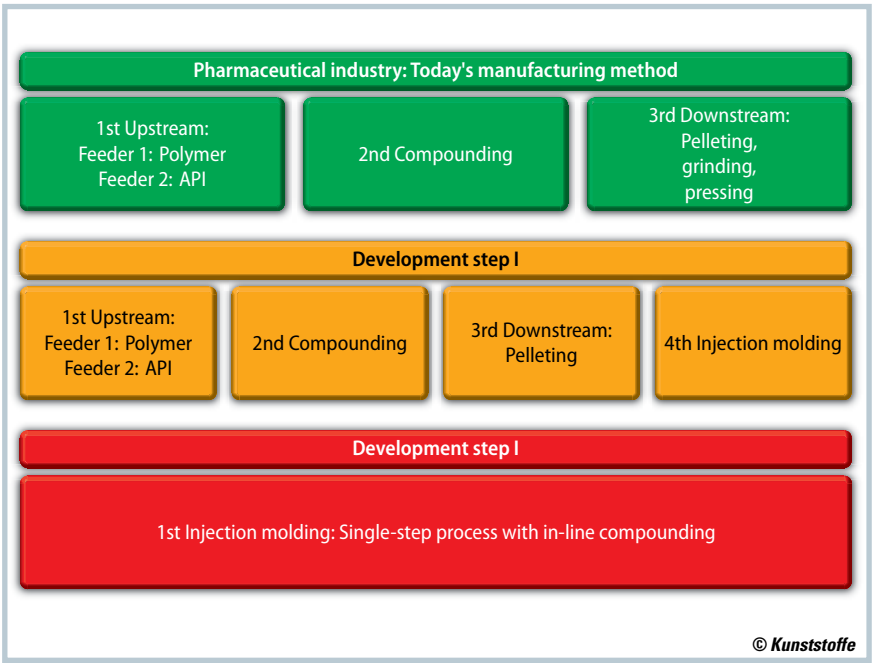


Fig. 1. The path to a one-step injection molding process skips the compounding step (figures: IPIM)

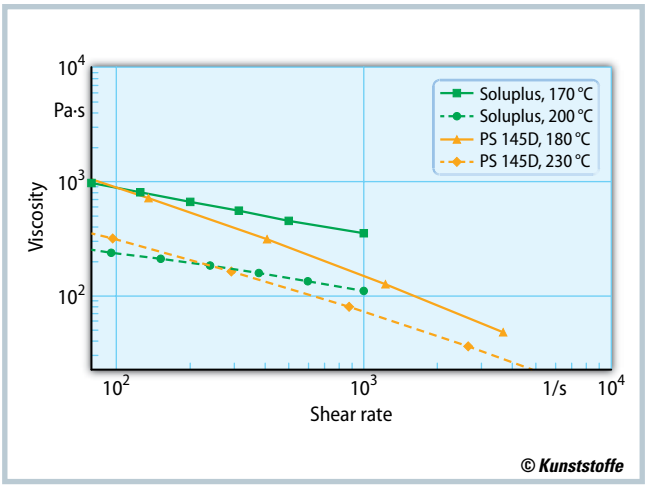


Fig. 2. Comparison of the shear-dependent viscosities of Soluplus and polystyrene 145D (manufacturer in each case: BASF) reveals that inter alia the pharmaceutical polymer requires a higher injection pressure

Six-Cavity Proving Mold for Tablet Production

The glass transition temperatures for both Soluplus and fenofibrate lie in the range 70 to 80 °C. This similarity in glass transition temperature is essential for the preparation of solid dispersions.

For the studies, a tablet 13 mm in diameter and 4 mm high was defined as the pharmaceutical dosage form. Shaping is performed in an injection mold with six cavities and a naturally balanced radial runner system in conjunction with a sprue gate (**Fig. 3**). On the nozzle side, a sensor measures the mold cavity pressure. The various polymer-API systems are processed on an all-electric injection molding machine (type: Engel e-mac 50/50) with a clamping force of 500 kN and a reciprocating-screw plasticizing unit fitted with an 18-mm three-section screw.

Simulation Tracks Homogeneous Distribution of API

When polymers are being pigmented, the goal is to obtain a uniform distribution of the pigments over the surface of the component – this usually involves pigmenting the entire polymer melt during plasticizing. In pharmaceutical dosage forms, uniform distribution of the API over the entire height of the tablet represents the ideal. Here, uniform "pigmenting" is not only desirable, but essential.

Through the use of flow simulations based on CFD (computational fluid dynamics) (used programs: Sigmasoft; supplier: Sigma Engineering GmbH, Aachen, Germany, and OpenFoam; supplier: OpenCFD Ltd., Bracknell, Berkshire/UK), the distribution of the API in dynamic shear and mixing sections of a reciprocating-screw plasticizing unit and during shaping can be simulated based on the input process parameters.

Filling simulation followed by analysis of the API distribution allows the following questions to be answered:

- How is API distribution affected by different injection flow rates during cavity filling – starting with the sprue bushing of the manifold system? »

Fig. 3. Cross-section through the injection mold for pharmaceutical production (left). The tablets are connected via a star-shaped runner system with sprue gate (right)

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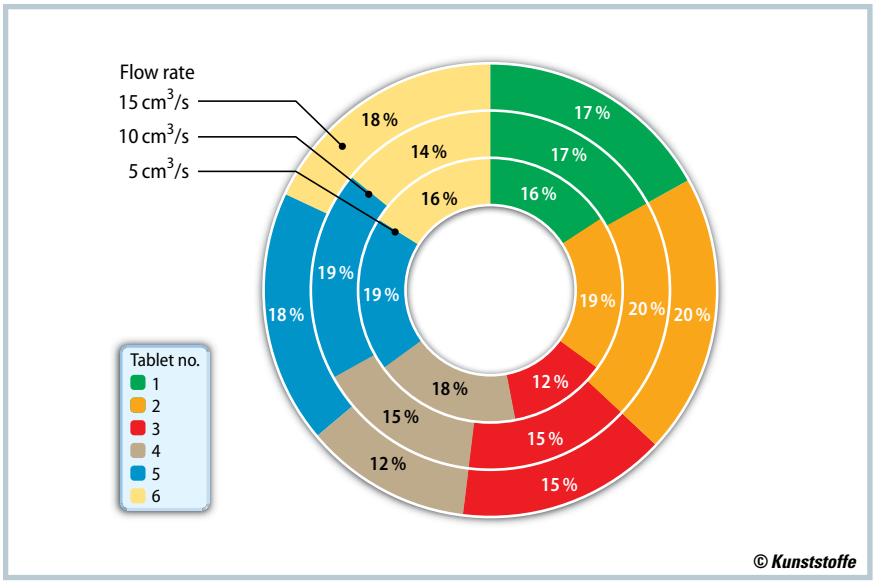

Fig. 4. Percentage API distribution in the tablets at three different flow rates is broadly consistent across the six cavities

- How much API (in percent) is present in the individual tablets at the end of the filling process?
- How homogeneously is the API distributed across all cavities?

The homogeneity in the individual cavities was determined with the aid of Shannon entropy S [4, 5]. This index uses statistical methods to describe the mixing of substances. It is calculated from the probability p_j and tracer number c_j:

$$S = -\sum_{j=1}^{M} p_j \ln p_j \quad \text{where} \quad p_j = \frac{C_j}{N}$$

p_j expresses the probability of an API tracer lying in a bin. The tablet is divided into virtual planes spaced 1 mm apart. On each plane is placed a grid consisting of a certain number of quadrants (in this case: 12), N is the total number of active tracers in one plane.

When the distribution of APIs at different injection flow rates is analyzed, a direct comparison of the flow rates in the three concentric rings at 5, 10 and 15 cm^3/s reveals a uniform distribution pattern of API tracer across all six cavities (**Fig. 4**). Here, the number of tracers detected per cross-sectional plane was added up and listed as a percentage. The different flow conditions arising from varying the injection flow rates did not significantly affect the distribution of the tracers. However, API distribution is influenced by the lateral gating of the tablet and the conditions of flow during cavity filling.

The Shannon entropy calculated in four different sectional planes (1, 2, 3,

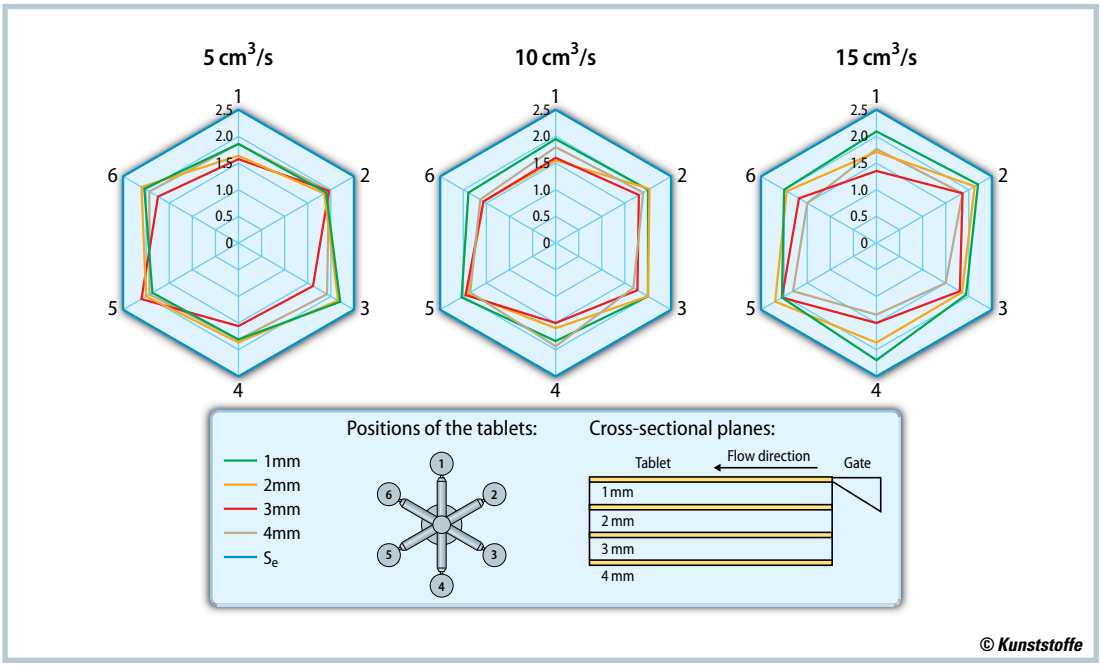

Fig. 5. Analysis of API distribution by means of Shannon entropy in the four cross-sectional planes (1, 2, 3, 4 mm) of the six tablets at three different injection flow rates (5, 10 or 15 cm^3/s): The closer the values for S are to the limit value (2.5), the more uniformly the API is distributed within the cross-sectional planes

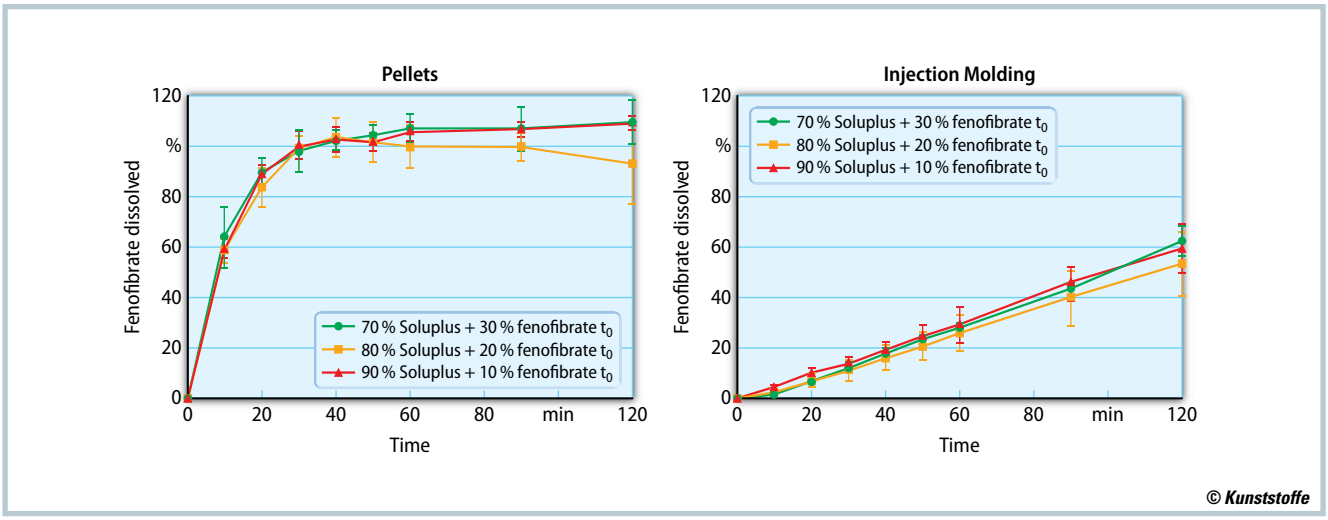

Fig. 6. Release profiles of compounded micro pellets (left) and injection molded tablets (right), each with 10, 20 and 30 % fenofibrate API loading: The degree of sustained release attained by the injection molded product is often desirable in therapy (test results: RCPE – Research Center Pharmaceutical Engineering, Graz, Austria)

4 mm across the tablet thickness) at the end of the injection process can be seen as a measure of the homogeneity of the API distribution (**Fig. 5**). The value of an equivalent distribution over all four cross-sectional planes is expressed by S_e and has a limit value of 2.5. The closer the values of S in the cross-sectional planes are to the limit S_e, the more uniformly the API is distributed within the cross-sectional planes. The S-values for the cases under consideration lie in a good range between 1 and 2. The values in the inner cross-sectional planes tend to tail away somewhat. This may be explained by the flow conditions and the filling pattern of the cavities.

Trials Complement the Simulation Results

A further primary aim of the study was to verify the results of the flow simulation under real injection molding conditions. The first step consisted in using compounded micro-pellets loaded with 10 to 30 % API and approximately 1 mm in diameter (development step I in **Fig. 1**).

In development step II, the compounding is omitted. Instead, an API mixed with polymer powder (premix) is dosed directly via a side feeder (manufacturer: Movacolor BV, Snee, The Netherlands) into the feed zone of the reciprocating-screw plasticizing unit. Melting and mixing of the polymer-API system takes place at temperatures of between 150 and 180 °C, i. e. lower than in the case of thermoplastic injection molding.

It did not prove possible to reproduce all the factors at the desired level of detail in the simulation. For this reason, trials were used as a complement for the simulation and to aid with the evaluation.

Implementation of development step II (single-injection molding pro- »

cess with in-line compounding) is creating new challenges with regard to:

- Moisture absorption of the material before and during the dosing process,
- Metering of the powder – if necessary processing with starve feeding of the screw channels,
- Complete, homogeneous melting of the powder mixture during dosing,
- Demolding problems due to the sticky consistency of the polymer-API composite on the mold cavities and in the gate area.

It has since proved possible to produce tablets from Soluplus pellets and API powder in a single-step process (**Title figure**).

Analytical View: Release Profiles Provide Information

The therapeutic effect depends critically on the release profile, which can be studied as a function of API loading (**Fig. 6**). For this, in the present case, pre-compounded micro-pellets with a varied API content of between 10 and 30 % were used to injection mold the tablets.

To facilitate comparison of the release profiles for compounded pellets and injection molded tablets, the two batches were each dissolved in acid (with a pH value similar to the conditions in the stomach). Subsequent chromatographic separation of the API release essentially yielded the following findings:

- The API loading has almost no influence on API release response. This applies both to the merely compounded micro-pellets and to the injection molded tablets.
- On account of their larger specific surface area, micro-pellets lead to much faster release.
- Injection molded tablets can effectively sustain API release; this is often required for therapeutic dosing. In addition, injection molded tablets are less likely to fracture than pressed powder tablets. One reason for this is the greater degree of compaction that occurs during shaping.

The development partners have already developed mold and injection molding machine concepts under economic aspects aimed at translating these research results into pharmaceutical mass production (output of 200,000 tablets per hour). In this connection, they studied injection molds with full hot runner systems and 128 cavities.

Conclusion

The results of the research show that injection molding holds plenty of potential for increasing efficiency and quality in the manufacture of pharmaceutical dosage forms. The method makes it possible, e.g., to produce tablets that offer sustained-release of the API and a reduced risk of breakage. ■