Application of Hot Melt Extrusion technology in the development of innovative formulation containing amorphous form of active pharmaceutical ingredient

H. Kierońska, M. Kretkiewicz, K. Rogut, J. Lipner, S. Pikul, A. Krause

Pikralida sp. z o.o.; ul. Uniwersytetu Poznanskiego 10, 61-614 Poznan, Poland

Hot Melt Extrusion (HME) in pharmaceutical applications

HME is a solvent-free, continuous process of applying high temperature and pressure to melt a mix of active pharmaceutical ingredients (APIs) with polymers. The technology allows formulation of poorly soluble small molecule drugs into stable dosage forms with a high drug concentration. The proper process enables API to be mixed with the suitable thermoplastic polymer under the minimum of shear and thermal stresses and, hence, with the formation of minimal process-related API degradants. Obtaining solid molecular dispersions of APIs by forming solid solutions may improve the solubility and bioavailability of active substances with low water solubility. Moreover, the HME technique allows for masking the taste of active substances and for obtaining modified release drug forms, such as extended-release tablets or fast-disintegrating dosage forms and allows many patent circumventing pathways as well as claiming own IP.

The purpose of the project was to improve the solubility of the antidiabetic drug substance by using Hot Melt Extrusion Technique and to investigate and optimize the effects of different formulations on dissolution profile

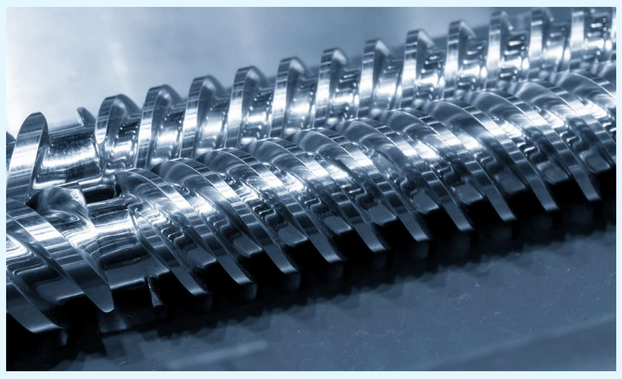
According to WHO

- Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.
- Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.
- In 2019, diabetes was the ninth leading cause of death with an estimated 1.5 million deaths directly caused by diabetes.
- Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.

Oral Diabetes Medications

The pharmacological management of diabetes (especially type 2 diabetes) has progressed exponentially in recent years, with multiple new class of drugs, new formulations and new combinations of different oral agents.

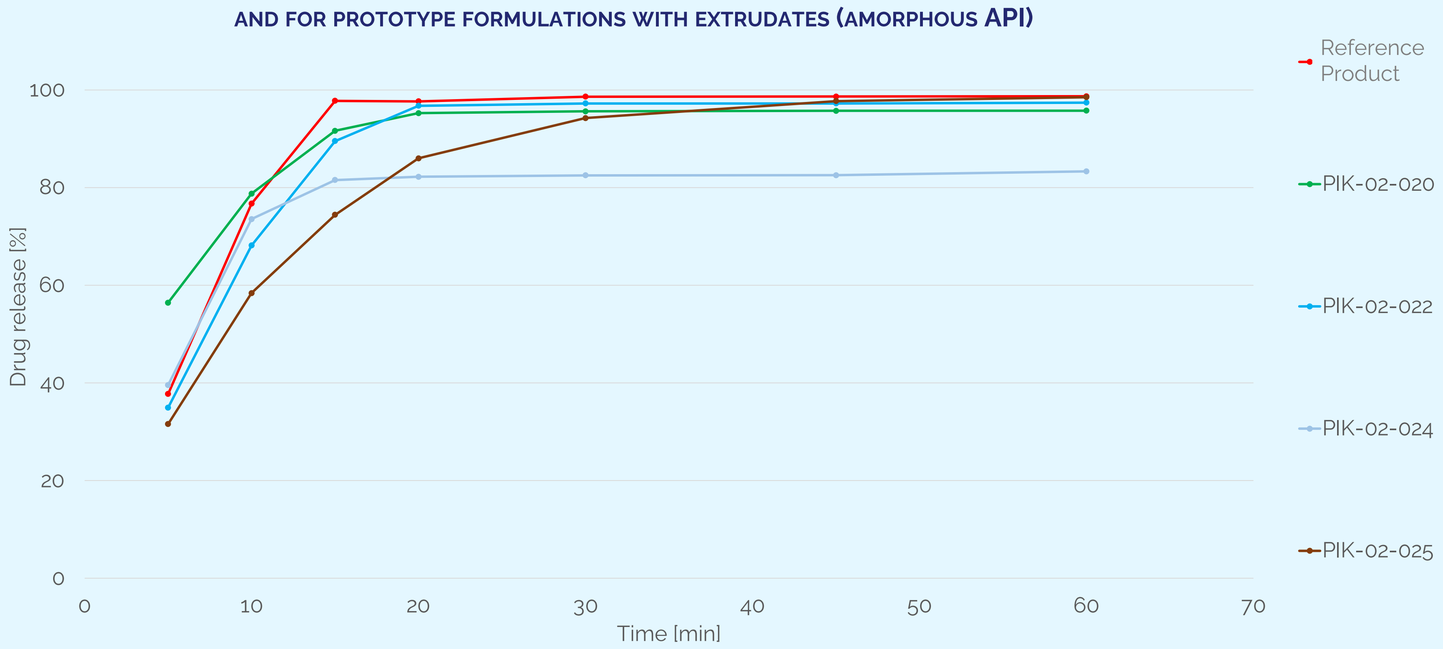
Access to these new therapies can be accelerated through the development of generic products. Therefore, the number of generic drugs is constantly increasing in recent years. Generics are cost-saving and have the same safety and efficacy profiles as their reference products.



Formulation development

- Drug absorption from the gastrointestinal tract can be limited by various factors but it is controlled by two fundamental parameters: drug solubility and permeability. The solubility of the drug substance is one of the most critical aspects to be considered during the generic development process especially for solid dosage forms.
- Differences in composition between the generic and reference medicinal product are possible, but only regarding the excipients. It has to be demonstrated during the bioavailability or bioequivalence trials that these differences in composition do not influence the therapeutic efficacy and safety and the ADME parameters (how drug is Absorbed, Distributed, Metabolized and Eliminated by the body).
- During the formulation development process, the dissolution testing is widely used as an analytical technique for evaluation of the drug release characteristics and and similarity between the generic and the reference product.

Dissolution profiles for reference product (crystalline, poorly soluble API) and for prototype formulations with extrudates (amorphous API)



Dissolution conditions

- Medium: 0.1N HCl
- Medium volume: 900 ml
- Temperature: 37±0.5˚C
- Apparatus: USP II (paddle)
- Rotation speed: 75 RPM
- Sampling timepoints: 5, 10, 15, 20, 30, 45, 60 min
- Analytical method: in house HPLC method
- Status of analytical method: validated

Project results

- A HME process for obtaining extrudate containing a stable amorphous active substance was developed.
- HME technology increased the solubility of API (crystalline substance vs extrudate).
- Four promising formulations with amorphous API obtained by HME were upscaled and manufactured.
- The dissolution profiles for reference product and for prototype formulations were analyzed and compared.
- The discriminatory power of the dissolution method (the ability of the method to detect changes in Drug Product performance) was demonstrated.
- The batch PIK-02-22 was selected for further development.
- The final lab scale batch (based on PIK-02-22 formulation) and the original product were tested under simulated fasted and fed conditions with regard to the spontaneous disintegration, dissolution and dissolution under flow-through conditions.
- Both products (the original and the generic) achieved similar results.

Summary

- The integrated in vitro methodology was implemented to study the impact of different excipients and different processing parameters.
- Application of this approach improved our ability to observe the relationship between different formulations and their in vitro parameters and assisted us in selection of the final, stable formulation.

Project no. RPWP.01.02.00-30-0047/19-00 is implemented under the Regional Operational Programme for Wielkopolskie Voivodeship 2014-2020; Priority Axis I: Innovative and Competitive Economy, Measure 1.2 Strengthening innovation potential of enterprises in of the Wielkopolskie Voivodeship.

European Funds Smart Growth · Republic of Poland · European Union European Regional Development Fund · Wielkopolska Region