# One Strategy to Address both Solubility Enhancement and Controlled Release: Polyvinyl Alcohol for Hot Melt Extrusion

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## Introduction

**The solubility and bioavailability of active pharmaceutical ingredients has become a major issue for the pharmaceutical industry. Approximately 40 % of marketed APIs and up to 90 % of APIs in development struggle with solubility [1]. Hot melt extrusion (HME) is a pharmaceutical manufacturing technology to overcome the solubility dilemma [2]. In this study, the particle size of a milled PVA:API extrudate was optimized to enable direct compression and achieve suitable galenic tablet properties. Furthermore, immediate and sustained-release kinetics were achieved by developing different tablet formulations.**

## Methods

30 % itraconazole (Selectchemie AG, Zürich, Switzerland) was mixed with 70 % polyvinyl alcohol (Parteck® MXP, MilliporeSigma, Billerica, USA) with an 87 – 89 % hydrolysis grade, MW approx. 32,000 Da using a Turbula® mixer (Bachofen AG, Muttenz, Switzerland) and extruded with a twin screw extruder (Brabender® Mini-Compounder KETSE 12/36 D, Duisburg, Germany). The extrudate was then cryo-micronized to different particle fractions (fraction 1: $D_{50}$≈ 100 µm; fraction 2: $D_{50}$≈200 µm; fraction 3: $D_{50}$≈350 µm) using an ultra-centrifugal mill (Retsch, Haan, Germany). Particle size was detected by laser diffraction with dry dispersion (Mastersizer® 2000, Malvern Instruments Ltd. UK). The obtained powder was mixed with microcrystalline cellulose (MCC, Vivapur® 102, JRS, Rosenberg, Germany), potassium carbonate, sodium chloride, magnesium stearate, highly dispersed silicon dioxide (all from MilliporeSigma), lactose (Ludipress®, BASF, Ludwigshafen, Germany) and crospovidone (Polyplasdon® XL-10, ISP Technologies INC, Wayne, US) and finally directly compressed into tablets with the Styl´one tablet press (Romaco Pharmatechnik GmbH, Karlsruhe, Germany). Galenic properties and dissolution performance were tested according to Pharmacopeia.

| | |
|---|---|
| **Viscosity (40 g/L, water, 20 °C)** | 3.4 – 4.6 mPa·s |
| **Degree of hydrolysis** | 85 – 89 % |
| **Bulk density** | 0.53±0.02 g/mL |
| **Tapped density** | 0.74±0.02 g/mL |
| **Mean particle size (laser diffraction Dv50)** | 60 – 80 µm |
| **Loss on drying (3 h, 105 °C)** | < 3 % |
| **Angle of repose** | ~ 35 ° |

**Table 1:** Material characteristics of Parteck® MXP

## Results

Compression studies with 83.5 % extrudate milled to different particle sizes and mixed with 15 % MCC, 1 % $SiO_2$ and 0.5 % magnesium stearate show satisfactory tablet hardness. Best hardness is seen for particle fraction 1, which even shows suitable tablet hardness at a 10 kN compression force (Fig. 1).

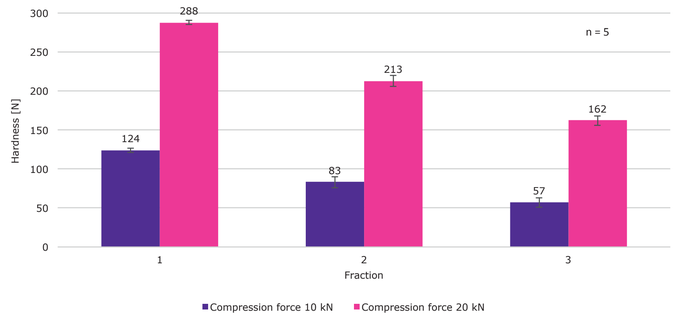



**Figure 1:** Hardness of tablets containing extrudate differing in particle size $D_{50}$: 93 µm (fraction 1), 172 µm (fraction 2), 343 µm (fraction 3).

Dissolution performance of tablets was comparable for all particle fractions (data not shown).

Tablet hardness tends to be highest for mixtures containing 15 % MCC. A lower (10 %) or higher (20 %) amount of MCC leads to a decrease of tablet hardness by trend (Fig. 2).

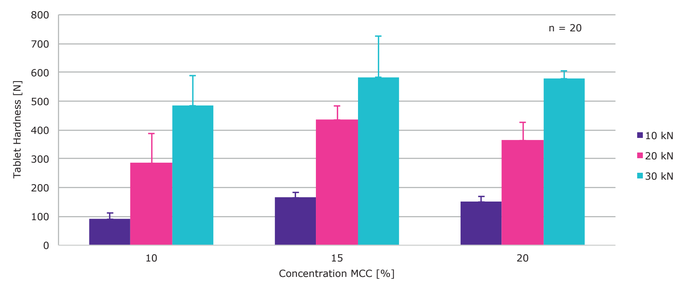



**Figure 2:** Hardness of tablets containing extrudate and different amounts of MCC, compressed at different compression forces

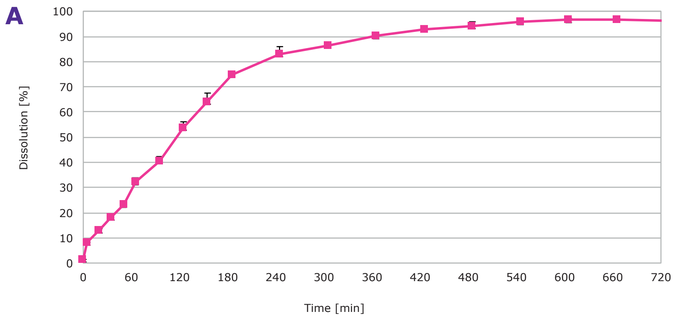
The dissolution performance of the compressed extrudate with 15 % MCC is shown in Fig. 3 A.

The API is slowly released from the formulated tablet over 9 hours. An enhanced performance is seen in comparison to the crystalline drug and, furthermore, sustained release is achieved by compressing the extrudate with MCC.

Further tablet formulation development is done with the extrudate having optimal particle size in order to achieve a targeted API release. Table 2 shows the evaluated tablet compositions. Formulations are developed containing up to 70 % of the extrudate.

| | Tablet 1 | Tablet 2 | Tablet 3 | Tablet 4 |
|---|---|---|---|---|
| **Extrudate (%)** | 50.00 | 50.00 | 60.00 | 70.00 |
| **Microcrystalline cellulose (%)** | 10.00 | 10.00 | 10.00 | 14.50 |
| **$K_2CO_3$ (%)** | – | 14.75 | 10.00 | 5.00 |
| **NaCl (%)** | 14.75 | – | – | – |
| **Magnesium stearate (%)** | 0.50 | 0.50 | 0.50 | 0.50 |
| **Lactose (%)** | 16.25 | 16.25 | 11.00 | – |
| **Silica (%)** | 1.00 | 1.00 | 1.00 | – |
| **Crospovidone (%)** | 7.50 | 7.50 | 7.50 | 10.00 |

**Table 2:** Composition of developed tablet formulations (1000 mg oval-shaped tablets, length 19 mm)



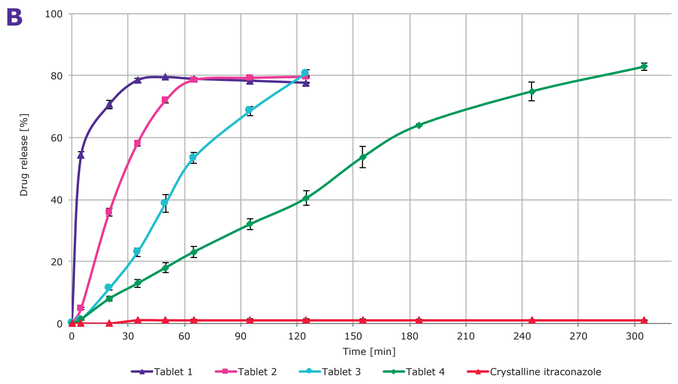




**Figure 3:** Dissolution of directly compressed tablets with itraconazole.
A: Sustained-release profile of a tablet containing 83.5 % extrudate, 1 % $SiO_2$, 0.5 % magnesium stearate and 15 % MCC. B: Immediate-release profile of tablets with salts and lactose added (see Table 2). Dissolution medium: 900 mL SGF, 37 °C, 75 rpm, n=3

All formulations show good tablet hardnesses even at low compression force (Table 3).

| | Tablet 1 | Tablet 2 | Tablet 3 | Tablet 4 |
|---|---|---|---|---|
| **Compressed force (kN)** | 10 | 10 | 10 | 10 |
| **Hardness (N)** | 138±5 | 118±17 | 100±6 | 236±10 |

**Table 3:** Tablet hardness and required compression force for the different formulations

The dissolution profiles of the different formulations show significantly different release curves. A very fast API release is achieved with formulation 1, including NaCl as a component. Formulation 2 shows a slower release compared to formulation 1 which includes $K_2CO_3$ instead of NaCl. The release time is further prolonged by reducing the salt quantity (formulation 4). Increasing the incorporated extrudate content leads also to a slower release of the API even though the amount of the disintegrant crospovidone is increased.

The presence of inorganic salts allows for sufficient moisture ingress into the tablet and rapid hydration of the entire tablet might lead to a faster API release compared to tablets with higher extrudate and lower salt amount as described for other polymers [3].

## Summary

**This study evaluates the optimal particle size of a PVA-based hot-melt extrudate for tablet formulation development. MCC is evaluated as a binder. Tablets consisting of high amount of PVA extrudate combined with MCC show sustained dissolution performance. However, the release kinetics can be easily shifted from sustained to immediate release through addition of salt and other suitable excipients. All tablets, regardless of formulation or extrudate content, demonstrated good tablet hardness, ease in the tableting process, and significant increase in the solubility of the API.**

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The typical technical data above serve to generally characterize the excipient. These values are not meant as specifications and they do not have binding character. The product specification is available separately at: www.emdmillipore.com

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