# Improved physical stability for co-amorphous simvastatin and glipizide combinations prepared by co-milling

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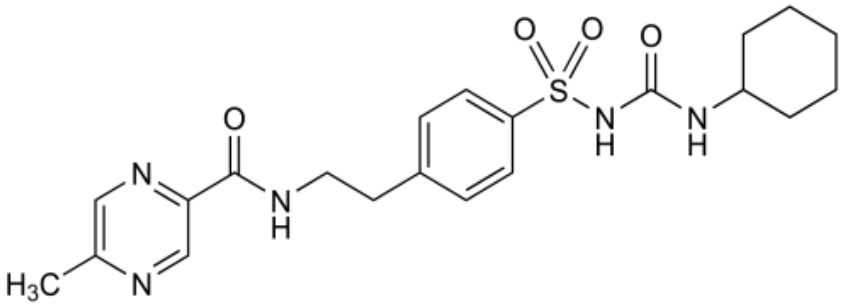
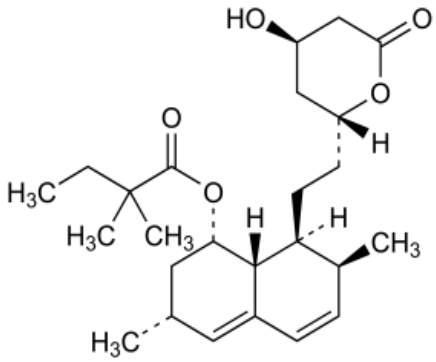
# Aim of the study

- In this study, the drug pair simvastatin-glipizide (SVS-GPZ) in different molar ratios was processed by mechanical activation (ball milling (BM) or cryomilling (CM)).
- The aim was to prepare molecularly mixed co-amorphous systems of the two drugs, which would have improved physical stability.

Glipizide

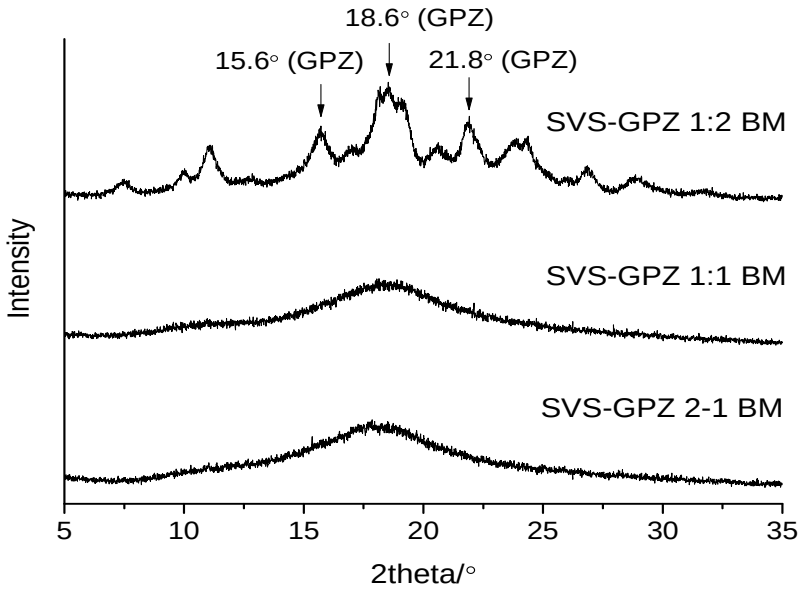


Simvastatin



# Preparation of the mixtures

- Cryomilling was able to produce co-amorphous mixtures with all SVS-GPZ ratios (2:1, 1:1 and 1:2).
- In contrast, ball milling was successful only for 2:1 and 1:1 mixtures.



# Glass transition temperature

- All co-amorphous mixtures were found to have one composition-dependent $T_g$ value between the individual $T_g$ values of the pure drugs, indicating formation of a one-phase system.
  - The higher the amount of GPZ in the mixture was, the higher was the observed $T_g$.

| Material | Observed $T_g$ [°C] | Theroretical $T_g$ [°C][1] |
|---|---|---|
| SVS | 32.6±0.2[2] | |
| GPZ | nd[3] | |
| SVS CM | 31.5±2.4 | |
| GPZ CM | 69.9±0.3 | |
| SVS-GPZ 2:1 BM | 41.1±6.2 | 42.3 |
| SVS-GPZ 1:1 BM | 46.3±6.6 | 48.4 |
| SVS-GPZ 2:1 CM | 41.5±5.1 | 42.3 |
| SVS-GPZ 1:1 CM | 46.7±5.2 | 48.4 |
| SVS-GPZ 1:2 CM | 53.6±5.3 | 54.9 |

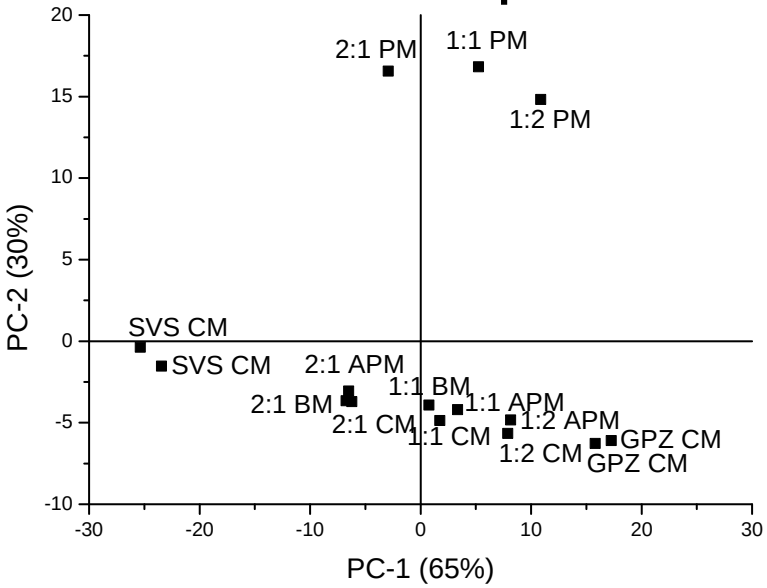
[1]Form Gordon-Taylor equation; [2]by quench cooling in DSC; [3]GPZ degraded after melting

# Interaction between SVS and GPZ

- However, the calculated Flory-Huggins interaction parameter ($\chi = 5.5 \pm 2.0$) suggested that favourable interactions were not likely between SVS and GPZ and that these two molecules might not be miscible with each other in the equilibrium state.
- This was confirmed by FTIR measurements which showed that there were no interactions between SVS and GPZ in the co-amorphous mixtures.

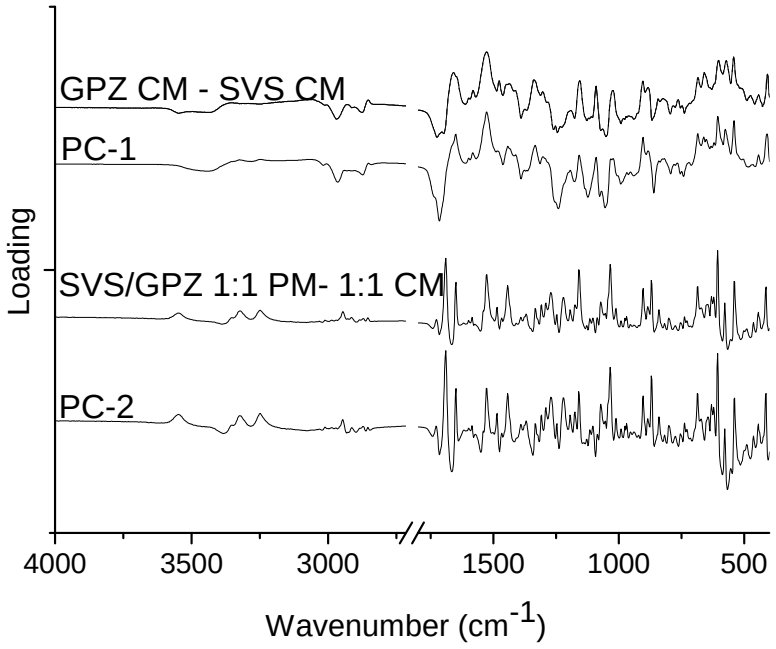
# PCA - score plot

- A PCA analysis of the IR data showed a clear difference between the crystalline mixtures and the processed (amorphous) formulations.
- SVS CM and GPZ CM form their own clusters in the score plot, with the 2:1, 1:1 and 1:2 samples (amorphous physical mixture (APM), BM, CM) placed in between, independent of the production technique.
- Thus, no interactions exist between SVS and GPZ in the co-amorphous mixtures since the PCA model classifies APMs similar to the co-amorphous mixtures.



# PCA – loading plot

- The loading plot shows that PC1 explains the difference in composition and PC2 explains the difference between crystalline and amorphous state.



# Storage stability

- For the evaluation of physical stability, the amorphous samples were stored at 4°C/0% RH, 25°C/0% RH and 25°C/60% RH.
- Stability studies revealed a higher storage stability for the co-amorphous mixtures compared to the corresponding amorphous physical mixtures.
- The stability of the co-amorphous mixtures increased as a function of increasing GPZ content.
- The most stable mixtures (1:1 and 1:2 CM) were stable for over two months at all storage conditions.

# Conclusions I

- Mechanical activation was successfully applied to obtain co-amorphous mixtures of two BCS class II drugs, simvastatin (SVS) and glipizide (GPZ).
- Increased storage stability was observed despite the lack of stabilizing interactions between SVS and GPZ.

# Conclusions II

- The most stable mixtures were stable for over two months at all storage conditions.
- The improved stability can be attributed to the formation of SVS-GPZ molecular mixture where GPZ acts as a stabilizing component (anti-plasticizer), which is beneficial for stability even in the absence of molecular interactions.

The full work has been published: Korbinian Löbmann, Clare Strachan, Holger Grohganz, Thomas Rades, Ossi Korhonen, Riikka Laitinen: Co-amorphous simvastatin and glipizide combinations show improved physical stability without evidence of intermolecular interactions. Eur J Pharm Biopharm, in press. dx.doi.org/10.1016/j.ejpb.2012.02.004