Structure – Mechanics Study of Cocrystals to Optimize Tablet Size

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Purpose: The tableting performance of high dose and poorly compressible drug molecules may be improved by co-crystallization. Improved compressibility can help to reduce the overall compact size, by substantially decreasing the quantities of excipients otherwise required. These smaller size compacts may improve patient compliance, packaging, and storage. High dose metformin used in the treatment of type-2 diabetes mellitus was chosen for the present study. It is hypothesized that a small sized compact of metformin can be produced with metformin-salicylate cocrystal due to improved compactability.

Materials and Methods:

Metformin salicylate cocrystal were prepared as per a reported method [(1)]. These cocrystal were characterized by DSC, TGA, PXRD, and FTIR. A previously published DM^3 approach [(2)] was used to investigate the impact of the fundamental molecular and macroscopic properties and manufacturing parameters on tableting performance, and to reduce tablet size for better patient compliance. Structural properties of the crystals including d-spacing and attachment energies were calculated from the metformin salicylate cocrystal crystal structure (REFCODE GEVJUO) [(1)] using Material Studio®. Macroscopic compaction properties were evaluated with a compaction simulator by keeping same constant volume that of parent cocrystal components. This is important because response of punch movement is the function of solid volume in the die and not its weight [(3)].

Results and Discussion:

DSC confirmed cocrystal formation with a melting point of 147.8 ± 0.5°C which is consistent with the reported melting point 148.0°C (± 0.5°C) [(1)]. The PXRD confirmed that the characteristic peaks at 22.4°, 26.8°, 29.8°, and 30.2° 2θ were consistent with the calculated pattern from the single crystal structure. Particle density of metformin salicylate was significantly higher (P= 0.002) than metformin and lower than (P= 0.02) sodium salicylate. Similar particle size ranges (d_{50} = 45 µm) were chosen for Metformin salicylate cocrystal, metformin HCl, and sodium salicylate to avoid any impact of particle size on the compaction behavior. The preliminary study of compaction showed that metformin and sodium salicylate physical mixture compressed at 21.68 MPa resulted in tablet capping, while metformin salicylate cocrystal tablets were intact. Further studies will include "*in-die*" Heckle parameters and the work parameter [(3)] using Prestester compaction simulator. Finally, all experimental data will be evaluated qualitatively and quantitively using multivariate techniques including PCA and PLS to identify critical material and manufacturing parameters required to optimize tablet size with acceptable strength.

Conclusions:

Preliminary results showed that metformin salicylate cocrystals have better compression characteristics than physical mixtures of metformin HCl and sodium salicylate. These promising preliminary data indicate that it might be possible to reduce tablet size with acceptable strength of high does and poorly compressible metformin HCl due to improved compactability.

References:

1) Pérez-Fernández, R., Fresno, N., Goya, P., Elguero, J., Menéndez-Taboada, L., García-Granda, S., Marco, C., 2013. Structure and Thermodynamical Properties of Metformin Salicylate. Crystal Growth & Design 13, 1780–1785.

2) Haware, R.V., Kancharla, J.P., Udupa, A.K., Staton, S., Gupta, M.R., Al-Achi, A., Stagner, W.C., 2015. Physico-Mechanical Properties of Coprocessed Excipient MicroceLac® 100 by DM(3) Approach. Pharm. Res. 32, 3618–3635.

3) Haware, R.V., Tho, I. and Bauer-Brandl, A., 2009. Application of multivariate methods to compression behavior evaluation of directly compressible materials. European Journal of Pharmaceutics and Biopharmaceutics, 72(1), pp.148-155.