British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1118

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 13th APS International PharmSci 2022

Assessment of Prediction Models for Punch Sticking in Tablet Formulations

Edward Rhodes[a,b]*, Jeremy R. Everett[b], Paul Whiteside[a], Deborah Kraus[a], Michael Cram[a], Neil Dawson[a]

[a]*Pfizer UK R&D Ltd, Sandwich, Kent, CT13 9NJ* [b]*University of Greenwich, Chatham Maritime, Kent, ME4 4TB*

ARTICLE INFO

Received: 16/06/2022
Accepted: 07/07/2022
Published: 04/11/2022

*Corresponding author.
Tel.: 01304 640 052
Fax: 01304 640 052
E-mail:
edward.rhodes@pfizer.com

KEYWORDS: Punch Sticking; Predictive modelling; Formulation development; Tabletting; Raman microscopy

Acronyms: Active Pharmaceutical Ingredient (API), Near Infrared (NIR), Principal component analysis (PCA), Scanning electron microscopy energy dispersive X-ray spectroscopy (SEM-EDX).

SUMMARY

Punch sticking is a common tablet compression manufacturing issue experienced during late-stage large-scale manufacturing. Prediction of punch sticking propensity and identification of the sticking component is important for early-stage formulation development. Application of novel predictive capabilities offers early-stage sticking propensity assessment. 16 API compounds were utilised to assess punch sticking prediction using removable punch tip tooling. API descriptors were tested for sticking correlation using multivariate analysis. NIR imaging, SEM-EDX and Raman microscopy were used to examine the material adhered to the punch tips. Predictive modelling using linear and non-linear equations proved inaccurate in punch sticking mass prediction. PCA analysis identified sticking correlated physical descriptors and provided a dataset and method for further descriptor studies. Raman microscopy was identified as a suitable technique for chemical identification of punch sticking material, which offers insight towards a mechanistic understanding.

INTRODUCTION

Punch sticking is a common issue in tablet manufacturing and is defined as the adherence of material to tablet tooling. Typically experienced at late-stage large-scale manufacturing, prediction of punch sticking likelihood and sticking component is an important area for early-stage formulation development. Paul et al, 2017 identified a mathematical model for describing the punch sticking kinetics of a wide-range of compounds and proposed API sticking mechanisms using UV-VIS spectroscopy. Building upon this work, the Hill equation was developed into an internal Pfizer modelling tool for sticking mass prediction. In this study we aim to assess the predictive applications of mathematical modelling, predictive descriptors, and adherence identification of API formulations.

MATERIALS AND METHODS

Sixteen APIs were assessed using removable punch tip tooling on a Korsch XP-1 at 50 rpm with compacts at solid fraction of 0.85 (Blend composition = 10% API, 89.75% micro-crystalline cellulose and 0.25% magnesium stearate). Linear and non-linear models were applied using Microsoft Excel with numerical solver optimisation. Correlation of molecular and physical descriptors was assessed by multivariate PCA analysis using SIMCA v.14. Adhered material was analysed using NIR (Sapphire) and SEM-EDX (Carl Zeiss EvoMA15). A confocal Raman microscope (WITec alpha500R, 785 nm laser) was used to collect spectra with a spectral window of 1800 - 100 cm^{-1} at a spectral resolution of ~ 4 cm^{-1}.

https://doi.org/10.5920/bjpharm.1118

RESULTS AND DISCUSSION

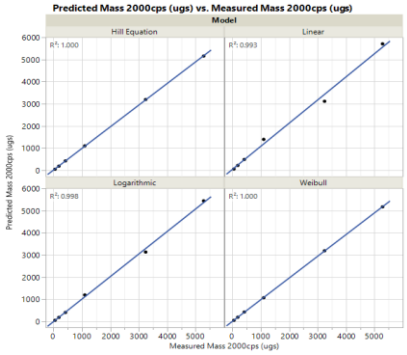

Fig. 1. *Correlation of actual mass vs predicted masses, full 2000 compressions fitting.*

The 16 API compounds showed a range of sticking propensity (Low to Very High) at 100 compressions. Six compounds were selected and run to 2000 compressions to assess predictive capabilities. Non-linear Hill and Weibull equations fitted most compounds with high correlation using full data plot. Mass predictions were shown to be inaccurate using model fitting and extrapolation with inaccurate prediction evident at low compressions with some improvement in accuracy seen with increased compression numbers.

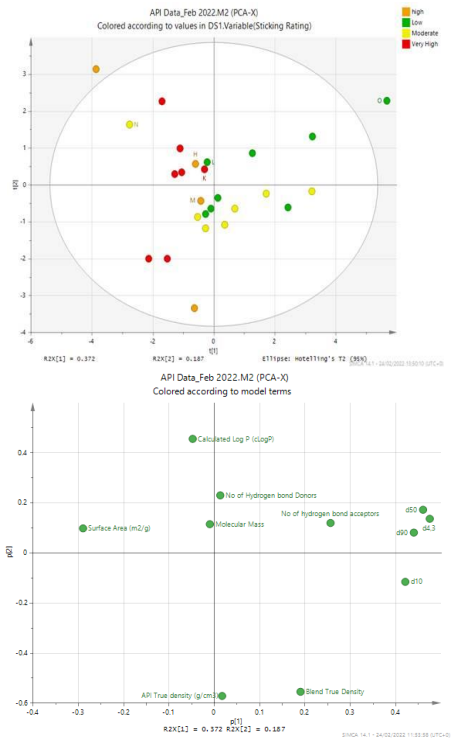

Fig. 2. *Multivariate PCA analysis loading and score plots.*

API descriptor sticking correlation was assessed by PCA analysis using physical properties (surface area, particle size and true density). Molecular descriptors (Lipinski rule of 5) were also included. Surface area, particle size and hydrogen bond acceptors showed correlation to sticking propensity. Future investigation into further molecular descriptors (*e.g.*, crystal structure descriptors) is of interest.

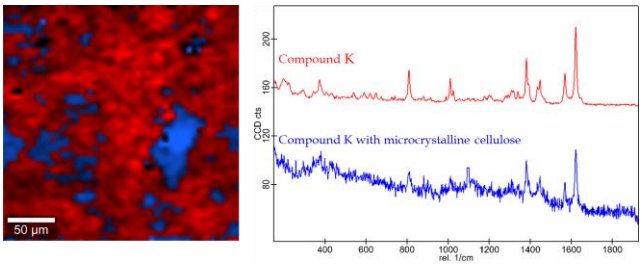

Fig. 3. *Raman microscopy of Compound K punch tip: chemical map (left) and corresponding Raman spectra (right).*

Raman microscopy confirmed API as the major sticking component for each of the high-sticking formulations. NIR and SEM-EDX imaging were largely unsuccessful due to interference from the metal punch tips and a lack of chemical specificity, respectively.

CONCLUSIONS

Linear and non-linear equations were shown to be inaccurate due to the unpredictive nature of high sticking compounds and present the need for extended compression runs to improve confidence in mass prediction of punch sticking. PCA was able to identify sticking correlated physical descriptors and provided a dataset and method for further descriptor correlation studies with next steps focusing on API crystal structure descriptors and sticking relation. Raman microscopy was used successfully to provide chemical identification of the adhered material, aiding mechanistic understanding and further investigations into three-dimensional imaging of adhered material and layering mechanisms.

REFERENCES

Paul, S., Taylor, L.J., Murphy, B., Krzyzaniak, J, Dawson, N, Mullarney, M.P., Meenan, P, Sun, C.C., 2017. Mechanism and Kinetics of Punch Sticking of Pharmaceuticals, Journal of Pharmaceutical Sciences, Volume 106