

Comparison of Atomic Force Microscopy and Inverse Gas Chromatography for the Prediction of Dry Powder Inhalation Performance.

MD Jones and G Buckton

The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, UK.

Summary

The ability of the cohesive-adhesive balance approach to atomic force microscopy (AFM) and the measurement of Hansen partial solubility parameters by inverse gas chromatography (IGC) to predict the performance of carrier-based dry powder inhaler (DPI) formulations was compared. Comparison of the AFM and IGC results suggested a weak relationship between these two sets of data. Comparison of the AFM and IGC data with the *in vitro* fine particle delivery of appropriate DPI formulations revealed a previously observed pattern for the AFM measurements. However, no consistent relationship between formulation performance and the IGC data was observed. Therefore, given the weight of data available in the literature, the measurement of cohesive-adhesive balances by AFM is the more appropriate technique for the prediction of DPI performance.

Introduction

There have been a number of attempts to develop methods to predict the performance of carrier-based dry powder inhaler (DPI) formulations based on techniques examining interparticulate adhesion. The most promising have utilised colloidal probe atomic force microscopy (AFM) or inverse gas chromatography (IGC). Possibly the most useful AFM-based technique is the cohesion-adhesion balance (CAB) approach, in which the ratio between drug-drug cohesion and drug-carrier adhesion is measured. Such CAB ratios have been able to predict the performance of carrier-based DPI formulations in a number of studies¹⁻³. The majority of work using IGC to predict DPI performance has focused on the measurement of the dispersive surface energy of formulation components, from which, in theory, interparticulate adhesion can be calculated. However, a consistent relationship between surface energy and DPI performance has failed to emerge⁴⁻¹⁰. Tong *et al.* employed another IGC approach, by measuring the Hansen solubility parameters of various materials, from which the strength of the various interactions within a formulation could be calculated¹¹. This approach showed initial promise for the prediction of DPI performance.

The AFM-based CAB technique and the measurement of Hansen partial solubility parameters by IGC each have the potential to develop into useful tools for the prediction of DPI performance, but currently their relative merits are unclear. The aim of this study was, therefore, to compare these two techniques.

Methods

The AFM CAB ratios between five drugs and three carrier excipients (erythritol, lactose and mannitol) were measured. The Hansen partial solubility parameters of these materials were determined by IGC and the various cohesive and adhesive interactions between them calculated¹¹. This enabled IGC CAB ratios to be calculated. Finally, the 15 possible carrier-based DPI formulations were produced using the study materials (1:67.5 drug:carrier) and their *in vitro* fine particle fraction (FPF) quantified by aerosolisation from a *Cyclohaler* into a twin stage impinger at 60 l.min⁻¹.

Results and Discussion

The IGC CAB ratios were consistently larger than the AFM data (i.e. more cohesive). Figure 1 clearly demonstrates that when considering all the data, there was no correlation between the two sets of CAB ratios.

However, if the data for each drug are considered separately, there is evidence for some correlation, with coefficients of determination (R^2) ranging from 0.66 to 0.99. These values represent a positive relationship for four of the drugs, but for beclometasone dipropionate there was a negative relationship between the two sets of CAB ratios, i.e. as the AFM CAB ratio increased, the IGC CAB ratio decreased. It is also noteworthy that the gradient and y-intercept of the IGC CAB ratio versus AFM CAB ratio line of best fit was different for each drug, suggesting that the conversion between the two types of CAB ratio was dependent on the drug involved.

Overall, this suggests that for certain individual drugs the IGC technique employed in this study is able to produce CAB ratios that follow the same pattern as those produced by the established AFM technique. However, this was not the case for every drug and there was no apparent reason for the negative relationship between the two sets of CAB ratios in the case of beclometasone dipropionate.

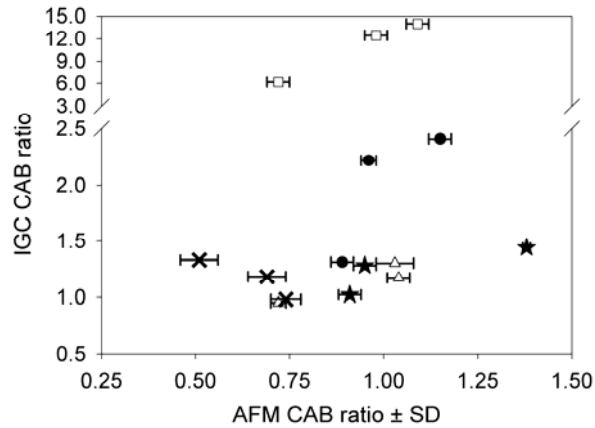


Figure 1: Comparison of IGC and AFM CAB ratios. x - beclometasone dipropionate; ★ - budesonide; △ - salbutamol sulphate; □ - terbutaline sulphate; ● - triamcinolone acetonide.

Figure 2 shows the FPF of all the carrier-based formulations tested and its relationship with the appropriate drug-carrier AFM CAB ratio. The physicochemical properties of the five drugs used in this study were not identical, especially in terms of particle size. Therefore, it is unsurprising that this figure does not show a clear overall relationship between FPF and AFM CAB ratio. However, when the data for four of the individual drugs are inspected, the previously observed relationship between these two variables becomes clearer, with slightly cohesive AFM CAB ratios being associated with the best fine particle delivery¹⁻³. Where there was no formulation with a slightly cohesive AFM CAB ratio (e.g. budesonide), extrapolation of the available data suggested that such a formulation might have produced the best fine particle delivery. The only exceptions to this pattern are the beclometasone dipropionate data, which follow the same pattern as the data for the other drugs, but translated to smaller AFM CAB ratios. This may have resulted from the use of an inappropriate beclometasone dipropionate crystal face for the AFM cohesion measurements².

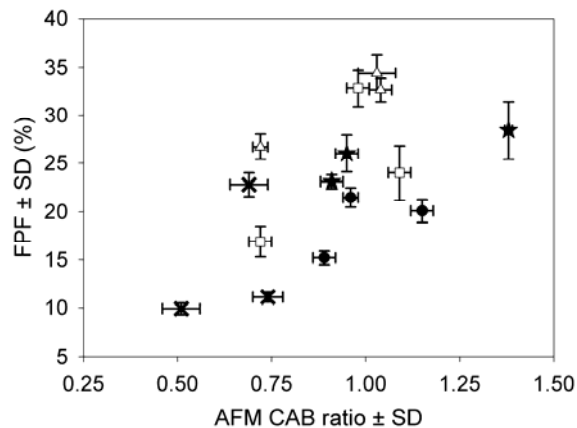


Figure 2: The relationship between FPF and AFM CAB ratio. x - beclometasone dipropionate; ★ - budesonide; △ - salbutamol sulphate; □ - terbutaline sulphate; ● - triamcinolone acetonide.

Figure 3 shows the relationship between FPF and drug-carrier interparticulate interaction strength as calculated from Hansen partial solubility parameters. Inspection of this relationship for budesonide, salbutamol sulphate, terbutaline sulphate and triamcinolone acetonide suggests that the highest fine particle delivery might be associated with a drug-carrier interparticulate interaction of ~100-115 MPa. Once again, however, the data for beclometasone dipropionate did not follow the same pattern as that observed for the drugs. As before, the reason for this is unclear. Such a relationship between FPF and drug-carrier interparticulate interaction strength might be expected given the well characterised optimum in the FPF-AFM CAB ratio relationship¹⁻³, as this implies an optimum level of drug-carrier adhesion.

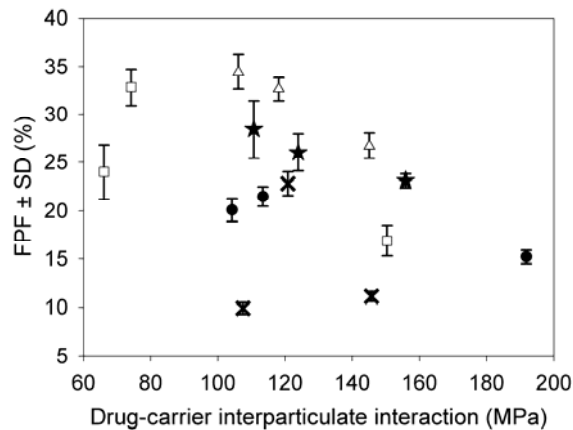


Figure 3: The relationship between FPF and drug-carrier interparticulate interaction strength as calculated from Hansen partial solubility parameters. x - beclometasone dipropionate; ★ - budesonide; △ - salbutamol sulphate; □ - terbutaline sulphate; ● - triamcinolone acetonide.

Figure 4 shows the relationship between the FPF and IGC CAB ratio. Given the inconsistent relationship between the AFM and IGC CAB ratios discussed above, it is unsurprising that Figure 4 does not reveal a consistent relationship between FPF and IGC CAB ratio. The data for beclometasone dipropionate, terbutaline sulphate and triamcinolone acetonide each suggest a different optimum IGC CAB ratio that was associated with the highest fine particle delivery. The results for budesonide and salbutamol sulphate do not suggest an optimum, although it is possible that this pattern may have been observed had there been combinations of these drugs with different carriers which resulted in higher IGC CAB ratios.

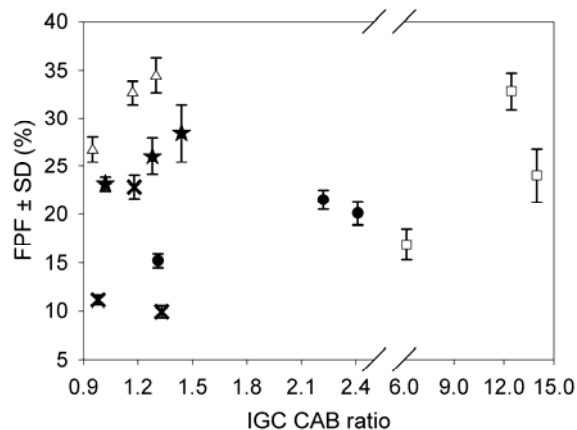


Figure 4: The relationship between FPF and IGC CAB ratio. x - beclometasone dipropionate; ★ - budesonide; △ - salbutamol sulphate; □ - terbutaline sulphate; ● - triamcinolone acetonide.

The results presented above suggest that whilst there may have been a weak relationship between the AFM and IGC data, this was not strong enough to suggest that the two techniques were measuring exactly the same phenomenon or that they could be used interchangeably. The reason for this may lie in the consideration of what each technique measures. AFM makes a direct measurement of the total adhesive force acting between the colloidal probe and the substrate. This may be made up of van der Waals', capillary and electrostatic forces¹². On the other hand, IGC measures the properties of the surfaces involved in the interaction and then seeks to calculate the strength of the resultant adhesion. Therefore, unlike AFM, IGC takes no account of capillary or electrostatic forces, although these are likely to be present in DPI formulations¹³. In addition, it was a requirement of the calculations used in this study that the IGC experiments were carried out at infinite dilution, suggesting that the solubility parameters obtained would have been biased towards the highest energy sites on the powder surfaces¹⁴. Such sites may not have been representative of all the areas involved in particle-particle adhesion, resulting in further discrepancies between the AFM and IGC data.

Conclusions

There are several studies that describe a consistent relationship between drug-carrier AFM CAB ratio and the *in vitro* performance of carrier-based DPI formulations¹⁻³. The results of this study were consistent with these previous findings. However, to date there has only been one study suggesting a relationship between drug-carrier interactions calculated from Hansen partial solubility parameters derived from IGC measurements and formulation performance¹¹. Considering this literature evidence alongside the weak, inconsistent relationships

observed in this study between AFM and IGC CAB ratios, it is reasonable to conclude that the adhesion-based technique with the most supporting evidence for the prediction of carrier-based DPI performance is the measurement of AFM CAB ratios. Using the IGC data, the drug-carrier interparticulate interactions had a more consistent relationship with FPF than the IGC CAB ratios, so this approach warrants further investigation.

The relationship between FPF and AFM CAB ratio for beclometasone dipropionate presented in this study highlights the importance of careful crystal substrate selection when applying the AFM CAB technique. It has previously been suggested that the cohesion measurement in such experiments should be made against the drug crystal face that dominated the raw drug material before milling². However, it is not known if this is always the face that dominates the resultant micronised material, so further investigation of this topic is required.

It should also be noted that there were no apparent explanations for the inconsistent behaviour of beclometasone dipropionate observed at all stages of this study. This serves to demonstrate the complexity of the many interacting variables that can affect the behaviour of DPIs and suggests that the prediction of the performance of such systems from a single type of measurement (e.g. drug-carrier adhesion) is unlikely to be successful in every case. Finally, the observation of optimum points in the relationships between drug-carrier adhesion data and fine particle delivery suggests that it is overly simplistic to expect linear relationships between these variables, as the best performance from these complex systems will be obtained as a result of achieving a balance between opposing factors.

Acknowledgements

This work was carried out whilst MDJ was the holder of a Maplethorpe Postdoctoral Fellowship of the University of London. The authors gratefully acknowledge Kostas Kostarelou and Bowen Tian (The School of Pharmacy) and Robert Price and Jag Shur (University of Bath) for access to equipment.

References

1. Jones, M.D., Harris, H., Hooton, J.C., Shur, J., King, G.S., Mathoulin, C.A., Nichol, K., Smith, T.L., Dawson, M.L., Ferrie, A.R. and Price, R. (2008). *Eur. J. Pharm. Biopharm.*, **69**(2), pp. 496-507.
2. Hooton, J.C., Jones, M.D., Harris, H., Shur, J. and Price, R. (2008). *Drug Dev. Ind. Pharm.*, **34**(9), pp. 974-983.
3. Hooton, J.C., Jones, M.D. and Price, R. (2006). *J. Pharm. Sci.*, **95**(6), pp. 1288-1297.
4. Cline, D. and Dalby, R. (2002). *Pharm. Res.*, **19**(9), pp. 1274-1277.
5. Oliveira, A.C., Buckton, G., Collins, E. and Clarke, J. (2006). *J. Pharm. Pharmacol.*, **58**(Supplement 1), p. A23.
6. Sethuraman, V.V. and Hickey, A.J. (2002). *AAPS PharmSciTech*, **3**(4), p. 28.
7. Jiang, R.G., Pan, W.S., Wang, C.L. and Liu, H. (2005). *Pharmazie*, **60**(8), pp. 632-633.
8. Thielmann, F., Naderi, M., Traini, D. and Young, P.M. (2006). *Proceedings of Respiratory Drug Delivery 10*, pp. 793-795.
9. Bernhard, F. and Steckel, H. (2005). *Proceedings of Drug Delivery to the Lungs 16*, p. 97.
10. Kumon, M., Suzuki, M., Kusai, A., Yonemochi, E. and Terada, K. (2006). *Chem. Pharm. Bull.*, **54**(11), pp. 1508-1514.
11. Tong, H.H.Y., Shekunov, B.Y., York, P. and Chow, A.H.L. (2006). *J. Pharm. Sci.*, **95**(1), pp. 228-233.
12. Podczec, F., *Particle-particle adhesion in pharmaceutical powder handling*. 1998, London: Imperial College Press.
13. Zeng, X.M., Martin, G.P. and Marriott, C., *Particulate interactions in dry powder formulations for inhalation*. 2001, London: Taylor and Francis.
14. Buckton, G. and Gill, H. (2007). *Adv. Drug Delivery Rev.*, **59**(14), pp. 1474-1479.