

# Investigating Blend Uniformity of API/Excipient Mixtures via Surface Energy Distribution Measurements

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## Purpose

The powder blending process is often identified as a challenging operation in solid dosage form manufacturing. On one hand, inadequate blending leads to poor active ingredient/excipient mixing. On the other hand, excessive blending could potentially deleteriously affect the drug content uniformity the final product. Mixing behavior is complex and can be affected by various chemical and physical properties of the solid materials like density, particle size, particle shape, and surface energy. When large difference in these material properties exists between the active components and excipients, poor mixing effects can occur. In this study, the surface energy values of a model active pharmaceutical ingredient (API), excipient, various physical mixtures of the two, and final capsule blend have been measured and their effects on blend uniformity investigated.

## Methods

Paracetamol and lactose were used as model API and excipient, respectively. Blends at 4% drug substance loading were taken from a full scale commercial blending process. In addition, blends taken from capsules after filling were obtained. For comparison purposes, physical mixtures and fully segregated blends were made at identical paracetamol/lactose were produced. The fully segregated sample column was produced by loading lactose first, followed by paracetamol, such that only minor mixing occurred at the interface. Inverse Gas Chromatography (IGC) was then used to measure the surface energy distributions of pure components and all physical and 'real' blends. IGC has been used previously to study the anisotropic nature of pharmaceutical materials [1-3]. BET surface areas of the pure materials and different blends were also obtained using standard nitrogen sorption methods. Finally, an HPLC method was used to determine content uniformity of the final capsule material.

## Results

Total surface energy distributions for the pure paracetamol and lactose samples indicated that paracetamol was higher in surface energy and had a broader distribution (values ranged between 25 and 60 mJ/m<sup>2</sup>). Lactose was lower in energy and more uniform (values between 37 and 50 mJ/m<sup>2</sup>). Mixing conditions had a significant effect on the blend surface energy values. The fully segregated mixture had the highest average surface energy, supporting poor mixing. The physical mixture and mixture taken from the capsules had intermediate average surface energy values. The blended mixture from the full scale commercial blending process has the lowest average surface energy, indicating the most uniform blend of high energy API and low energy excipient. These results are highlighted in Figure 1 where total surface energy distributions are shown for the individual components and different blends.

## Conclusion

Blends from different processes could be distinguished based on their surface energy distribution. Increased blending energy during processing produced final blends with narrower energy distributions due to the more uniform distribution of the drug substance. Surface energy values have a potential for indicating final blend uniformity and likelihood for powder demixing.

## REFERENCES:

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Total Surface Energy Distribution

