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Application of Microscopy in Pharmaceutical Development from Discovery to Manufacture Process Scale-up

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Microscopic analysis has been widely used for the identification, and investigation of pharmaceutical materials. It enables detailed observations and measurement of the microstructures and the interaction between active pharmaceutical ingredient (API) and inert excipients. SEM/ESEM/EDX can be used as a PAT tool in a multi disciplinary fashion to achieve real time release in pharmaceutical manufacture. Several applications of microscopic analysis will be presented as case studies as described below.

1. Use of microscopic aspect ratio to control powder flow characteristic for active pharmaceutical ingredient: Acceptance criteria for API particle size distribution are often required by worldwide regulatory authorities especially for insoluble drugs. However API morphology (round vs needle shape), though critical to manufacturability of the finished product is not usually controlled. The development of an aspect ratio specification using microscopic image analysis is described which help downstream process control and content uniformity of solid dosage form manufacture (Fig 1).

2. Use of SEM to select excipient for ordered mixing of low dose formulations: Ordered mixing is defined as the adsorption of small drug particles onto the surface of large excipients to effect content uniformity of low dose drugs. Dissociation of drug from the excipient is not critical for oral dosage forms but is of paramount importance for dry powder inhalation (DPI). Physical properties of excipients have been shown to significantly affect ordered mixing (Table 1), especially the surface structure of excipients (Fig 2), which plays a key role in surface adsorption. A case study in modulating the mixing energy input to effect adhesion and release of API from excipient will be described for a DPI formulation development

3. Use of SEM to control coating levels upon process scale-up: Coating is a usual technique in sustained-released formulation to delay or slow down the release of API over an extended period of time to reduce the number of doses over a day, a week or a month. By measuring the coating thickness required from small scale batch that exhibit required release profile, we can establish a correlation between the film thickness, film quality and dissolution profile. When the coating process is not performing such as spray drying, the film becomes rugged leading to a faster dissolution. Upon scale up the coating efficiency may change and the film thickness could be a more precise control than weight gain. Lastly real time SEM monitoring can ensure consistence from batch to batch to improve overall coating process control.

In summary, microscopic analysis is a useful tool in pharmaceutical development and manufacture controls in order to improve the quality of pharmaceutical products.

Table 1. Ordered mixing improves blend uniformity

Lactose	Blend content uniformity (%)	Comments
Lactose 1	97.1	Ordered mixing
Lactose 2	87.9	No ordered mixing

Figure 1. Compound with long aspect ratio.

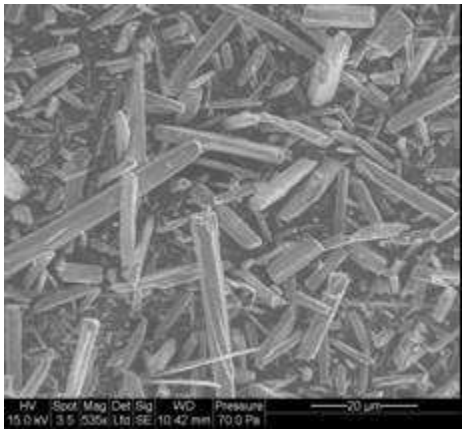
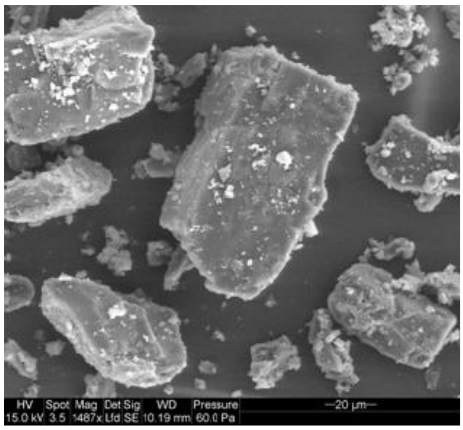


Figure 2. Surface property of lactose which facilitates ordered mixing.



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