In recent years, a number of authors have described the development of methodology to assess in-vitro dissolution of the respirable fraction of inhaled products. The respirable dose is typically captured either using a filter or modified stage within a cascade impactor. Dissolution measurement is carried out using flow-through, diffusion cell or paddle apparatus. None of these methods can be regarded as standard; and each has strengths and limitations. In-vitro dissolution testing has obvious application in the development of modified release inhaler products, where a link to in-vivo performance has been demonstrated. The significance of dissolution for in-vivo performance of conventional inhalant products has yet to be established. The small size of respirable particles is likely to enable rapid dissolution. Nevertheless, dissolution may be a factor limiting in-vivo absorption of very poorly soluble molecules, representing a potential obstacle to development of such drugs.

The methodology described here differs from that previously published in the combination of approaches used for dose collection and dissolution measurement. The dose is collected using a filter inserted above stage 3 of the NGI, an approach described previously by Davies & Feddah and by Riley et al. This approach was preferred to the alternative published approach of capturing particles on the impactation stages (as described by Son et al1 and Arora et al6) as it allows dissolution assessment on the entire fine particle dose as a single fraction and disperses the dose over a greater surface area. A stainless steel filter is used in preference to glass fibre used by previous authors, as this was found to be more compatible with the selected paddle dissolution apparatus. A ‘paddle over disk’ dissolution set-up was found to be more practicable and robust than the flow-through approach described by previous authors.

Using the above approach, a dissolution method has been developed for a drug in a dry powder inhaler formulation. This drug has very low aqueous solubility (<0.1 µg/ml). A surfactant-containing medium was therefore used to maintain sink conditions and achieve a measurable dissolution rate. The use of a surfactant in the medium has a degree of bio-relevance, since high surfactant levels are known to be present in the lungs. These modify surface tension of the lung tissues to aid with breathing and may play a part in absorption of hydrophobic drugs.

The capability of the method has been demonstrated by application to formulations containing in vivo API size, representing a potential obstacle to development of such drugs.

Experimental

Fine Particle Dose Collection

A stainless steel filter was placed above the stage 3 nozzles in the body of the NGI (Fig. 1(a)). Two actuations of the per dry powder inhaler device were performed at 60 Lpm to give a measurable drug loading on the filter.

Dissolution Testing

After FPD capture the filter was removed from the NGI body and placed into one of the vessels of a USP 2 dissolution bath (Fig. 1(b)) containing 400ml of dissolution medium: 20 mM piperazine-1,4-bis(2-ethanesulfonic acid) (PIPES) buffer pH 6.8 containing 134 mM sodium chloride and 5 mM sodium dodecyl sulfate (SDS). The bath temperature was set to 37°C and the paddle speed 50 rpm. An automated fraction collector was used to take samples at periodic time intervals up to 16h. The resulting solutions were analysed by UPLC.

References