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Morphological changes observed during intrinsic dissolution rate testing of itraconazole

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The intrinsic dissolution rate (IDR) of a pure drug substance is defined as the rate at which it dissolves from a constant surface area under constant agitation whilst the pH and ionic strength of the medium are also held constant (USP 27, 2004). In an IDR test, the surface is produced by compressing a sample of the drug in a die to form a solid disc. This study of the IDR of the basic, poorly-soluble antifungal drug itraconazole, was performed using the stationary disc apparatus. Discs were prepared by compressing approximately 150 mg of itraconazole for 30 s in a 10 mm diameter die under a pressure of 1000 p.s.i. After compression, the baseplate was removed and the die containing the disc was placed into a dissolution vessel containing 500 ml of medium held at 37°C in a dissolution test apparatus stirred with a paddle at a speed of 100 rpm (Pharmatest PTW IIS, Pharmatest GmbH). Samples of medium were periodically removed for analysis of itraconazole content by HPLC. Conventional USP-based media were used such as Simulated Intestinal Fluid (SIF) and Simulated Gastric Fluid (SGF with and without surfactant) as well as non-compendial, biorelevant media such as milk and protein solution. Scanning electron microscopy was used to study the initial appearance of the disc surface prior to commencing IDR experiments as well as the changing appearance of the surface at various intervals during the tests up to 48 h (Model ISM-840, Jeol Instruments). Micrographs of freshly-compressed discs exhibited a striated surface with regular, raised ridges which arose from a roughness of the base-plate against which the drug powder had been compacted. The striations can affect the dissolution process as they tend to dissolve or erode first during the test, leading to a change in the surface area of the disc over time. Two approaches were used to try and produce a smoother baseplate surface; mechanically polishing it or covering it with aluminium foil. Micrographs showed that polishing reduced the striations whilst the aluminium foil did this even more so and consequently foil-covered plates were used routinely used for disc-production thereafter. For tests carried out in SIF, SEM revealed there was minimal change in surface morphology of the discs, which remained relatively smooth throughout the test period. For SGF, after 24 h the disc surface started to appear porous, and this became more pronounced after 48 h. However, for SGF which contained 1% w/v of the surfactant sodium dodecyl sulphate (SDS), the disc surface appeared to display a large number of villus-like protrusions. This was attributed to SDS adhering to the surface of the disc as after gently washing the disc with water it regained the original flat appearance. Itraconazole has poor aqueous solubility and a simple water wash would not be expected to dissolve the surface to any great extent, whereas SDS is readily water-soluble. The possible effect that SDS in such proximity to the dissolving surface may have on the dissolution process remains to be determined.

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