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Physical characterization of drugs and excipients

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To make products of a uniform quality it is necessary to have good control over the materials. This is especially, but not exclusively, true for inhalation dosage forms, unstable materials (e.g. proteins) and powders with poor aqueous solubilities. Changes in physical form include size, habit, polymorphism, solvates and degree of crystallinity, which cause changes in surface area, rate of solution, surface energy, tendency to acquire and hold electrostatic charge, compressibility and others. Whilst some physical changes are easy to measure, others remain difficult to assess with confidence. For example it can be very hard to detect the presence of small amounts of amorphous material in a powder. There has been a growing realisation that amorphous forms are of increasing importance in pharmaceutical products. The desire may be to remove all the amorphous material in order to maintain physical stability, or conversely to use the amorphous form in order to stabilise protein drugs. A problem is that the amorphous state is complex and relatively difficult to study. In this presentation gravimetric vapour sorption, isothermal microcalorimetry and near infra-red spectroscopy will be described as suitable techniques by which to probe the amorphous state. It will be shown that it is possible to understand much about sugars and microcrystalline cellulose by the use of these techniques. Lactose exists in the amorphous form, as crystalline alpha and beta anhydrates and as the alpha monohydrate. As the different forms are required in different dosage forms (e.g. partially amorphous for direct compression, but 100% crystalline for inhalation), it is important to study inter-conversion. Our work on spray drying lactose solutions and suspensions under various conditions, has revealed an extremely complex series of events relating to morphological inter-conversions. These include rapid and extreme changes between the alpha and beta form, as well as the formation of a collapsed glassy state which can hold substantial amounts of water and which is not readily dried. Trehalose can exist as the amorphous form and as a crystalline dihydrate, raffinose exists as an amorphous form and as multiple hydrates up to the pentahydrate. Raffinose is curious as it converts directly from the hydrate to the amorphous state as a consequence of drying (whilst retaining the outer appearance (habit) of the crystalline form) (Saleki-Gerhardt et al, 1995). The conditions under which these sugars convert between different forms have been investigated through studies with near IR, isothermal microcalorimetry and gravimetric water sorption. We now have a good understanding of the properties of these carbohydrates. Microcrystalline cellulose has a complex physical form and there is a history of differences in functionality between certain suppliers. This makes it valuable to have techniques with which to probe the physical form, to ensure that the material will be of suitable quality. We have studied microcrystalline cellulose (Emcocel), and silicified microcrystalline cellulose (Prosolv SMCC) before and after wet granulation. The analytical techniques find differences in wet granulated Emcocel, which is the only sample which shows a decrease in compactability. Wet granulated SMCC remains essentially the same as the starting material. With NIR spectroscopy it was also possible to differentiate between Emcocel and SMCC. In conclusion, by use of multiple techniques it is possible to develop a detailed understanding of the physical form of materials, which in turn will allow an improved chance of manufacturing dosage forms with optimum properties.

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