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Monitoring phase transformations in formulations

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The disproportionation of pioglitazone hydrochloride in intact tablets was mapped by transmission-mode synchrotron X-ray diffractometry (SXRD; Argonne National Laboratories). Tablet mapping was performed in situ at the beamline using a custom-built temperature and humidity controlled setup. Presence of basic excipients (magnesium stearate or croscarmellose sodium) caused disproportionation, yielding the crystalline free base. The disproportionation reaction, influenced by sorbed water and microenvironmental acidity, was initiated at the tablet surface and progressed toward the core. The transformation was solution-mediated, and the spatial heterogeneity in disproportionation could be explained by the migration of sorbed water. SXRD also revealed spatial heterogeneity in mannitol phase composition in intact 'unperturbed'lyophilized cakes. When lyophilized alone, mannitol appeared to crystallize completely, predominantly as the delta anhydrous polymorph. On the other hand, a second non-crystallizing component influenced the crystallization behavior of mannitol and there was pronounced intra vial heterogeneity in mannitol phase composition. Vertical mapping of 'as is'lyophiles using SXRD revealed the formation of mannitol hemihydrate and spatial heterogeneity in its distribution across the depth of the lyophile. Such intra vial heterogeneity can have a pronounced "local" effect and hence serious implications on the stability of lyophilized formulations. Processing conditions for lyophilization (annealing at different temperatures) and formulation composition influenced the formation and distribution of mannitol hemihydrate in the final lyophile.

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