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On the use of self-assembled monolayers as supports for pharmaceutical crystallisation

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The discovery of new polymorphs and the control of crystal properties, *e.g.*, shape, size, number, are of utmost importance in the field of pharmaceutical crystallisation. Heterogenous nucleation represents a useful tool to direct the crystallisation pathway. Surfaces have been widely studied to induce nucleation, but a deep understanding of the action of heterogeneous nucleants is compromised by the joint effects of surface chemistry and topography.

In this work, we present the use of surfaces with sub-nm roughness to isolate the effect of surface chemistry on the crystallisation of pharmaceuticals and proteins. Self-assembled monolayers (SAMs) exposing different groups (thiols, amines, methacrylates) have been prepared on glass coverslips. The batch crystallisation of a model small molecule, *e.g.*, aspirin, was studied. Depending on the surface chemistry, it was possible to induce nucleation in less than 100 hours or inhibit nucleation for more than 1500 hours. These pieces of evidence suggest that the interplay between surface and drug interactions influenced nucleation kinetics. In particular, the acid surface tension of SAMs was related to the nucleation ability of the SAM.

As a step further, we also studied the crystallisation of complex macromolecules, *i.e.*, proteins, on SAMs. Depending on the width of the metastability zone of the protein of interest, the action of SAMs was more or less important. For example, it was possible to strongly induce the nucleation of lysozyme on thiol-terminated SAMs. Conversely, proteinase K crystallisation turned out to be unaffected by the presence of SAMs.

The results of this study highlight the central role of surface-drug interaction for the design of effective heteronucleants.