materials of different compositions was used. Further adjustments of cooling rates by "trial and error" were done in order to achieve the same result and this indicates that the generation of the correct mass of nuclei is sensitive to the composition of the starting materials. Modelling work is much needed here to guide experimentation or trial and error would be the only solution.

3.5.4.4 Case 4 – Due to Suboptimal Hardware

As I have explained, mixing in COBC is created by the generation and cession of eddies when fluid flows through orifice baffles, propagation of oscillatory motion is achieved by the incompressibility of fluid/solvent/solvent mixtures within the COBC, while the sizes of vortices and the degrees of interactions between eddies are governed by a combination of parameters. These include baffle spacing (the distance between a pair of baffles), baffle diameter (the restriction), baffle thickness (the effective distance for eddy shedding), oscillation frequency and amplitude. In order to accommodate COBC in labs, the straight sections of baffled tubes are connected by jacketed bends, forming a serpentine shape. In Mark I of NiTech DN15 crystallisers, the baffles were not well formed within bends, leading to uneven baffle spacing, as there was a learning curve for the glass manufacturer. When the baffle spacing is larger than the optimal, eddies may be disconnected, affecting both local and overall mixing, leading to particle sedimentation. In addition, the collars that connect straight baffled tubes (or straights) and bends contained no baffle in the Mark I version; this effectively means that the baffle spacing was unintentionally doubled at the joints and consequently heavy sedimentation was seen.[16,147] Furthermore, the initial design of collars for inserting PAT probes also had some issues, *e.g.* the probe tip with respect to tube surface and the angle of probe led to some dead zones at the probe location, causing sedimentation and in some cases primary nucleation. I am glad to report that these suboptimal glassware designs have subsequently been improved from Mark II onwards, with very close to even baffle spacing at bends (Figure 3.24); with a baffle manufactured in every collar to maintain the regular baffle spacing at joints; with better design and plug-in PAT connection, and encrustation due to suboptimal hardware is no longer observed and reported.

In one case a seeded cooling crystallisation of an API was investigated in a NiTech DN15 crystalliser by a global pharmaceutical company, with appropriate seeding strategy (size and mass) and procedures and the appropriate cooling rates. Crystallisation was run for a number of hours and some build-up was observed in one straight baffled tube, which turned into encrustation gradually. We examined every aspect of the nucleation theories and practices, revisited seed preparation, seeding method and temperature, recalibrated the flow rates of the feed and the seeds, as well as the cooling rates, but the build-up and encrustation was still seen at the *same* baffled tube. After having exhausted all possible approaches, tube 3 was swapped with the last tube.