of seeds when entering the DN15 would be around about 45 °C, whereas the saturation temperature for this API was reported as 47 °C, *i.e.* the seeds were added at 2 °C supercooling. The DN15 was set up with three temperature zones, 60 to 47 °C, 47 to 30 °C, and 30 to 15 °C and the metastable zone width was unknown. During the trials, heavy encrustation took place within the first two straights of the DN15 crystalliser; the experiments were then stopped.

For seeded crystallisation in general, the amount of seed fed to a NiTech DN15 crystalliser is much smaller than that of the crystallizing solution and a smaller diameter pipe is often used. On examination, the seed pipe was clearly blocked, when no or insufficient seeds were introduced into the DN15, naturally leading to encrustation. This problem is caused by the fact that the amount of heat taken away by the surroundings is often underestimated when the diameter of the tube decreases. Table 3.8 illustrates this point. If the same heat source ($q = UA\Delta T$) from a crystallisation medium and the same heat transfer coefficient (U) are assumed in a crystallisation experiment, the temperature drop over say unit length (ΔT) has an inverse relationship to the cross sectional area (A) available for heat transfer, *e.g.* say the required temperature drop over unit length of a 15 mm diameter pipe is 5 °C, this would then become 20 °C, four times larger, when the diameter of the tube is halved from 15 to 7.5 mm (Table 3.8)! For such a large temperature change, the metastable zone was crossed, leading to spontaneous nucleation within the seed pipe, blocking the pipe. At the same time, encrustation occurred in the DN15 due to lack of seeds.

The remedies for this would come in two ways: (a) the seed pipe must thermally be insulated so that the required temperature drop is maintained; (b) the seed tank is heated up at higher temperatures so that the temperature for seeds to enter the DN15 is what one expects. The former was implemented in this particular case and the problem of encrustation was successfully resolved. During the trials, the metastable zone width for this compound was identified as 7 °C.

De facto, similar blockages happened within the feed pipes from the feed tank into the DN15 due to precisely the same reasons for some APIs with very narrow metastable zones, so the same remedies apply.

3.5.4.2 Case 2 – Due to Incorrect Seeding

A number of repeated encrustation cases happened for seeded cooling crystallisations of both pharmaceutical and speciality chemicals in NiTech DN15 crystallisers. A pharmaceutical company tested one of their APIs in a

Table 3.8 Heat transfer illustrations.

Diameter (m)	Area (m^2)	ΔT (°C)
$q = UA\Delta T$		$\Delta T = q/UA$
0.015	0.000176715	5
0.0075	4.41786×10^{-5}	20