

continuous crystallizers (*e.g.*, draft tube baffle (DTB) crystallizer,<sup>56,76</sup> OBC,<sup>52</sup> static mixers<sup>32,77,78</sup>). Another PI approach within the space domain controls the crystallization in confined spaces using the principle of miniaturizing the crystallization environment.

### 7.3.1 Structure

It is a well-known fact that the crystallization kinetics (*e.g.*, level of supersaturation) is greatly influenced by the hydrodynamic conditions caused through rather vigorous, turbulent mixing because it controls heat and mass transfer. Thus, spatial randomness needs to be avoided by providing structure.<sup>7</sup> For instance, mixing plays a decisive role in reactive crystallization/precipitation or often also in antisolvent crystallizations where locally very high supersaturation levels can be generated rapidly with temporal and spatial gradients. Consequently, the micromixing needs to be faster than the crystallization kinetics to prevent non-uniform and unpredictable CQAs (CSD, morphology, and purity).<sup>55,56,79–81</sup> The intrinsic multiphase nature of crystallization processes (keeping crystals well suspended while mixing liquid streams) complicates this topic. Large density differences between solid and liquid phases may cause suspension density gradients in the axial direction of a stirred tank (*e.g.*, MSMPR)<sup>82–85</sup> or different RTD of the solid phase compared to the liquid phase (*e.g.*, PFC).<sup>44,86,87</sup> Thus, strong mixing is required to overcome the gravitational settling of the crystals for ideal homogeneous suspensions within continuous crystallizers aimed at preventing classifying product removal and ensuring that all crystals have the same processing history (RTD) to achieve uniform product CQAs.<sup>22,88</sup> On this account, the complex process mixing needs to be distinguished based on different scales: (i) macromixing, which refers to the overall mixing performance of the crystallizer described by the RTD that sets a general environment for micromixing and indirectly influences the distribution of supersaturation, (ii) mesomixing, which refers to the disintegration of large eddies that forms a direct environment for micromixing, and (iii) micromixing, which refers to the mixing on the molecular level and is the fastest of the three length scales of mixing (Figure 7.4).<sup>56,57,79,81,88,89</sup> For extended discussion of these and other mixing topics the interested reader is referred to specialist literature.<sup>55–57,79,90,91</sup>

In general, the concepts of intensifying mixing encompasses various designs of structures that can be applied either at the entrance or within the continuous crystallizer to generate rapid mixing as well as to eliminate local regions of uncontrolled supersaturation or back mixing (*e.g.*, in PFC). In addition, the focus of this section is on PI using passive structures and not for instance impellers.

Confined impinging jet (CIJ) mixers,<sup>78,92</sup> T-mixers,<sup>93</sup> Y-mixers,<sup>30,94–96</sup> mixing elbows,<sup>20,97</sup> and vortex-type mixers (*e.g.*, Roughton<sup>80,95,98,99</sup> and Multi-Inlet Vortex Mixer<sup>100</sup>) are non-helical shaped static mixers applied for PI in continuous crystallization processes. These type of static mixers are typically