

### 10.3.3 Transition from Batch to Continuous Crystallisation

Although there are limited studies on continuous protein crystallisation (Table 10.4), the existing studies of batch protein crystallisation prove that it is technically feasible, since the batch operation of a crystalliser can be converted into the continuous mode with relative ease. Five experimental studies have been reported so far: four conducted the crystallisation of lysozyme in a tubular crystalliser,<sup>113,115–117</sup> whereas the remaining one performed the crystallisation of lysozyme and mAb01 in a mixed-suspension, mixed-product-removal (MSMPR) crystalliser with tubular bypass.<sup>118</sup> The four simulation studies constructed the models for the size and shape distribution of lysozyme protein in MSMPR and plug flow crystallisers, as well as the corresponding control schemes.<sup>110,119–121</sup>

The two early studies of continuous protein crystallisation focused on the crystal growth behaviour under flow conditions instead of the crystallisation process itself.<sup>115,116</sup> One of the more recent experimental studies investigated the crystallisation of lysozyme under slug flow in a tubular crystalliser and achieved a decent yield of 68%.<sup>113</sup> The supersaturation was manipulated through temperature to control the nucleation and growth of lysozyme crystals. The tubular crystalliser was separated into three segments for temperature control, where the first segment was designed for nucleation and the remaining two were for the growth of crystals. Although the liquid flow was laminar, the introduction of air bubbles ensured sufficient mixing along the crystalliser, preventing the deposition of crystals on the inner wall of the crystalliser and achieving a narrow size distribution of protein crystals. The continuous crystallisation of lysozyme was also demonstrated in an oscillatory flow crystalliser,<sup>117</sup> which will be discussed in detail in the next section.

In another recent experimental study, lysozyme and mAb01 were crystallised separately in an MSMPR crystalliser with the high yield of 93% in both cases.<sup>118</sup> Unlike the conventional configuration, the MSMPR crystalliser in this study was unjacketed and its cooling was provided by the cooled liquid flowing out from a tubular bypass. The advantage of such a configuration

**Table 10.4** Summary of published studies on continuous protein crystallisation.

Protein	Crystalliser		Nature of study	Reference
	Category	Type		
Lysozyme	Stirred tank	MSMPR	Experimental	118
			Modelling	110, 119 and 120
	Tubular	Direct flow	Experimental	113, 115 and 116
Antibody (mAb01)	Stirred tank	MSMPR	Modelling	121
			Experimental	117
			Experimental	118