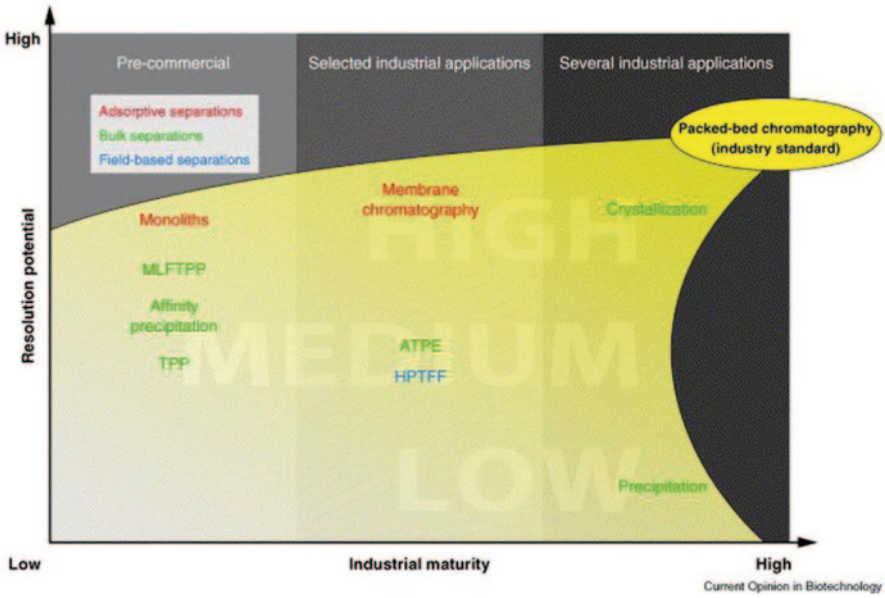

Fig. 6 A parsing of chromatography alternatives in terms of relative resolution potential and industrial maturity. Packed-bed chromatography is arguably the gold standard. *ATPE* aqueous two-phase extraction, *HPTFF* high-performance tangential flow filtration, *MLFTPP* macroaffinity ligand-facilitated three-phase partitioning, *TPP* three-phase partitioning (Adapted with permission from [43])

4. Crystalline protein suspensions offer a novel means to produce high-concentration formulations for biotherapeutics. High-concentration protein therapeutics especially mAbs, remain a formulation challenge due to high viscosity, instability due to charge interactions, and specific chemical degradation at high concentrations [39, 49, 58, 59]. Crystallization offers a formulation advantage; further, such crystalline suspensions can also be designed as sustained or controlled release formulations.

Bulk Freeze-Drying: Practical Considerations in Process Development and Scale-Up

With reference to pharmaceutical development, it becomes imperative to define the term bulk freeze-drying particularly in the context of its application and material properties. There are several possible scenarios that can be referred to as bulk freeze-drying including: (i) crystalline slurry/suspension of protein (with no lyophilization additives) being freeze-dried in trays, e.g., insulins, freeze-dried enzymes, lysozyme etc; (ii) formulated protein solutions being freeze-dried in bulk, i.e., trays;