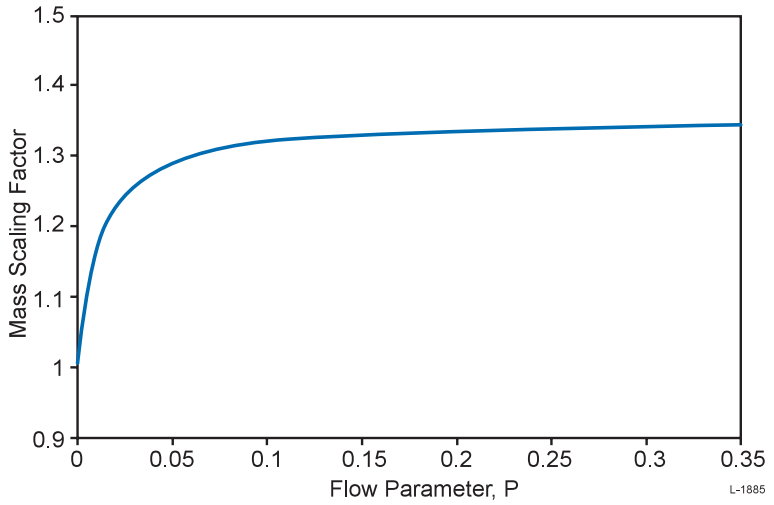

Fig. 18 Mass flow rate scaling factor as a function of the flow parameter

process monitoring during manufacturing operations, here, we make an attempt to evaluate applicability of this technique during freeze-drying cycle development. As has been previously mentioned, generation of primary drying design space for cycle development utilizes the vial heat transfer coefficient (K_v) and product mass transfer resistance (R_p) data. It has been shown by Schneid et al. [17] and Kuu et al. [20], that estimation of these parameters is achievable using TDLAS mass flow rate in conjunction with heat and mass transfer mathematical models.

While one aspect of primary drying, design space generation, focuses on screening shelf temperature and chamber pressure conditions that yield acceptable product temperature, estimation of choked flow conditions for a small-scale lyophilizer is another important aspect of the design space generation. Shelf temperature and pressure conditions that generate sublimation rate causing choked flow in the lyophilizer sets the boundary in the design space [21]. TDLAS-derived sublimation rate measurements can be rapidly applied to estimate the limits of choke flow conditions.

Another application of the TDLAS-derived sublimation rate is an estimation of residual moisture content in the product. Lyophilized formulation stability is sensitive to the presence of residual water left in the formulation after completion of secondary drying. In general, formulations are lyophilized to contain $<1\%$ w/w moisture content. However, for some formulations [54, 55], it has been shown that long-term stability is optimum at 1–3 % w/w moisture content. Schneid et al. [18] devised a technique to use TDLAS-derived sublimation rate to estimate residual moisture in 2 % BSA/5 % sucrose formulation. The technique involved a two-step process. In step 1, an "anchor point" was estimated which was essentially residual moisture content in the vials at the beginning of secondary drying process. In step 2, using this "anchor point," the total amount of water required to get to a predeter-