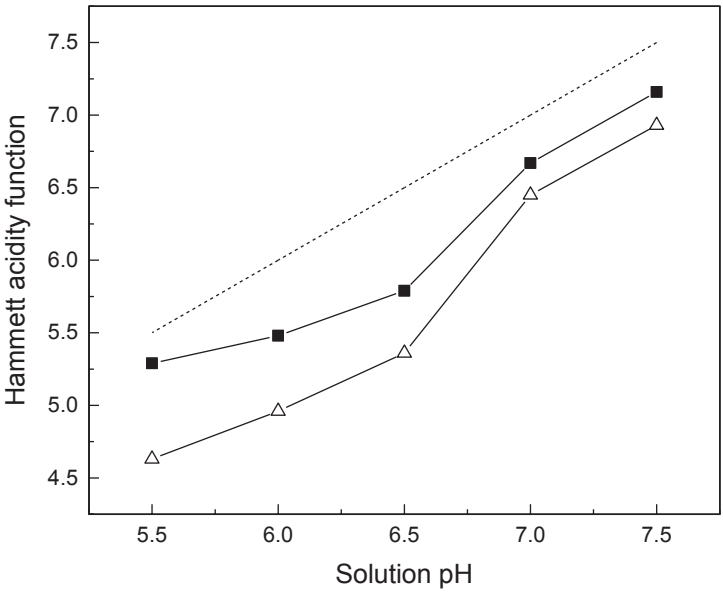

Fig. 3 Hammett acidity functions of lyophilized sucrose/buffer formulations as a function of pre-lyophilization solution pH of citrate (*solid square*) and phosphate (*triangle*) buffered systems. The *dashed line* indicates a hypothetical situation in which the Hammett functions as numerically equal to the prelyophilization solution pH. The other two lines are shown as visual aid (the figure was prepared using data reported by Chatterjee [11])

had lower H_{2-} (higher acidity) than citrate lyophiles, as shown in Fig. 3, indicative of significantly increased apparent acidity of phosphate lyophiles.

This comparison of the two buffers was extended to a system consisting of an amorphous active pharmaceutical ingredient (API) co-lyophilized with either phosphate or citrate buffer. Maximal stability in solution for this particular API was observed at pH 7, with the degradation rate increasing with lowering the solution pH. Three phosphate and four citrate formulations, each containing 200 mg/ml of the API and 20 mM buffer, were lyophilized from solutions at pH 6.6–7.35 (phosphate formulations) and 6.4–6.95 (citrate formulations). The freeze-dried formulations were X-ray amorphous and had water content below 0.5 wt.%. These samples were placed on the accelerated stability, and the concentration of degradation products measured by high-performance liquid chromatography (HPLC) after 8 months at 40 °C. The results are presented in Fig. 4 as a function of pre-lyophilization solution pH.

It can be seen that all formulations with phosphate had higher extent of degradation than citrate formulations, whereas no trend with pre-lyophilization solution pH was observed. To evaluate potential mechanism for such difference in stability, the Hammett acidity function was measured using phenol red as a probe molecule. The Hammett acidity function for phosphate- and citrate lyophiles is presented in Fig. 5 as a function of pre-lyo solution pH.