

In Vivo Predictive Dissolution: Analysis of the CO₂/Bicarbonate Buffer System

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Abstract:

Bicarbonate is the main buffer in the small intestine and it is well known that buffer properties such as pKa can affect the dissolution rate of ionizable drugs. However, bicarbonate buffer is complicated to work with experimentally. Finding a suitable substitute for bicarbonate buffer may provide a way to perform more physiologically relevant dissolution tests. The dissolution of weak acid and weak base drugs was conducted in bicarbonate and phosphate buffer using rotating disk and USP 2 dissolution methodology. Experimental results were compared to the predicted results using the film model approach of Mooney et al. based on equilibrium assumptions as well as a model accounting for the slow hydration reaction, $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3$. Assuming carbonic acid is irreversible in the dehydration direction: $\text{CO}_2 + \text{H}_2\text{O} \leftarrow \text{H}_2\text{CO}_3$, the transport analysis can accurately predict dissolution of weak acid and weak base drugs in bicarbonate buffer. The predictions show that matching the dissolution of weak acid and weak base drugs in phosphate and bicarbonate buffer is possible. The phosphate buffer concentration necessary to match physiologically relevant bicarbonate buffer (eg: 10 mM $[\text{HCO}_3^-]$, pH=6.5) is typically in the range of <1-30mM and is very dependent upon drug solubility and pKa.