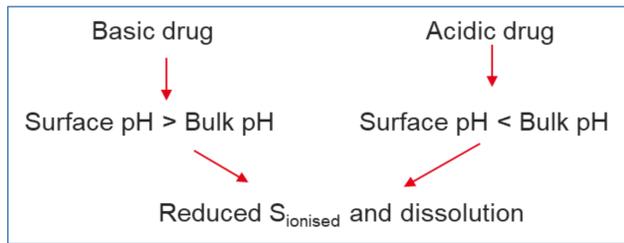


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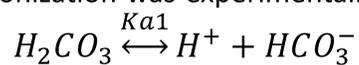
## Background

The microenvironment pH at the dissolving particle surface, rather than the bulk pH, guides the pH-dependent solubility of the drug at the particle surface.

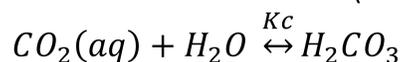


Buffers of sufficient capacity neutralize the increased or decreased hydrogen ions in the diffusion layer, thereby making the surface pH equal to bulk pH. However, this capacity to neutralize differs from buffer to buffer, and in the mechanistic surface pH model, this depends both on the concentration and  $pK_a$  of the buffer.

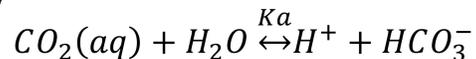
Bicarbonate buffer is the weakest among the commonly used buffers and the  $pK_a$  of carbonic acid ionization was experimentally determined to be 3.55 at 35°C.



However, carbonic acid is formed by hydration of dissolved carbon dioxide by water and the reaction rate constant for this step ( $K_c$ ) is  $10^6 - 10^{10}$  times slower than the carbonic acid ionization constant ( $K_{a1}$ ).



Therefore the hydration reaction is the rate limiting step and the overall reaction is given by



where  $K_a$  is the overall equilibrium reaction rate constant and the value of  $pK_a$  was determined to be 6.05 [1].

If the reaction between  $CO_2$  and  $H_2O$  is instantaneous, the  $pK_a$  of bicarbonate buffer would be 3.55, and if it is slow, the effective  $pK_a$  of bicarbonate buffer would be 6.05. In addition, the effective  $pK_a$  within the diffusion layer might be different from the bulk because the time the molecule spends in the diffusion layer (rapid dissolution) may be less than the reaction time; this could lead to different calculated dissolution flux rates than experimentally observed values [1]. In this work, we predict the effective  $pK_a$  of bicarbonate buffer using which we can recover observed dissolution rates.

## Methods

Intrinsic disk dissolution rates/flux values are calculated using the Levich equation using surface solubility calculated using the mechanistic surface pH model originally implemented in Simcyp V14. The model is verified by predicting the intrinsic dissolution rates measured in the presence of phosphate buffer for three acidic and one basic drugs (Figure 1).

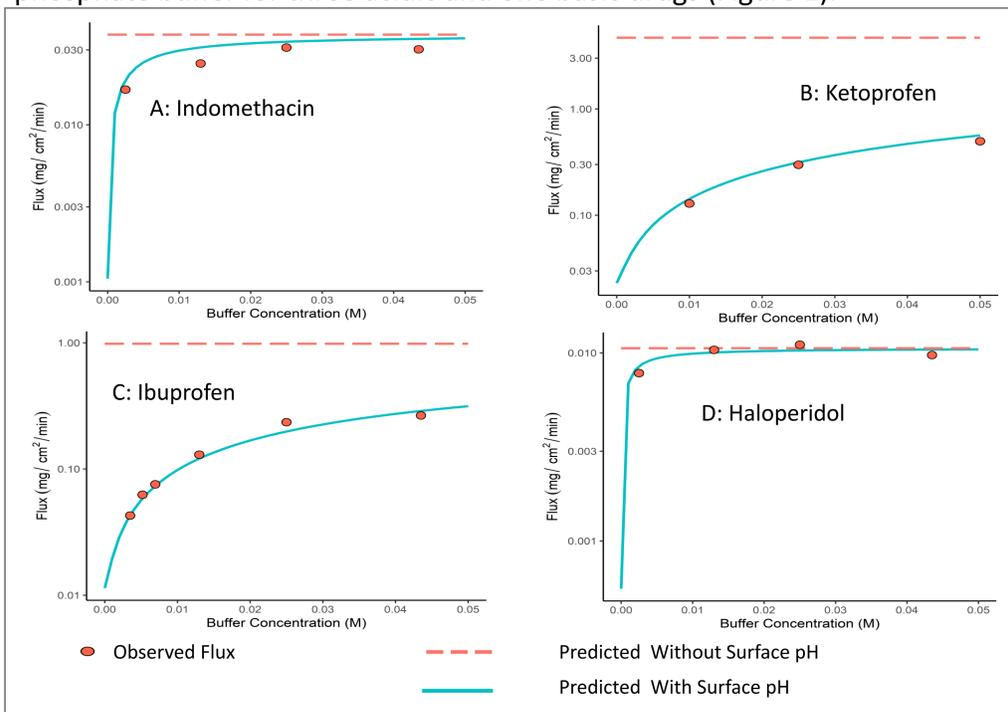


Figure 1. Observed [2] and predicted flux using of three acid drugs and a basic drug at different phosphate buffer concentrations.

The apparent  $pK_a$  of bicarbonate buffer in the mechanistic surface pH model was changed iteratively to match the observed Intrinsic dissolution rate in the presence of different concentrations of bicarbonate buffer.

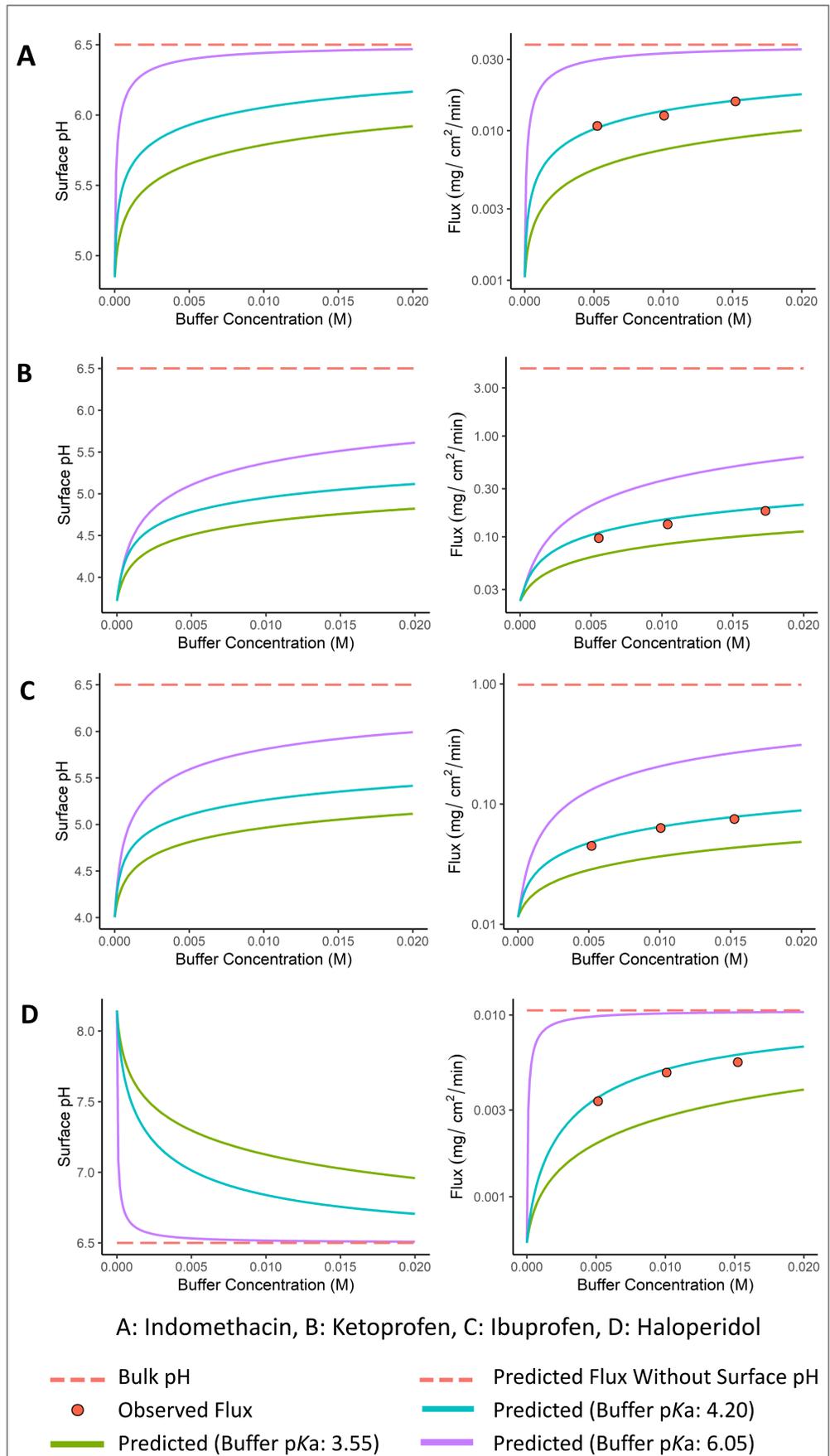


Figure 2. Observed [2] and predicted flux, using different buffer  $pK_a$  values, and their corresponding surface pH values for three acidic drugs and a basic drug at different bicarbonate buffer concentrations.

## Results and Conclusions

As observed for all four drugs, when 6.05 is used as the  $pK_a$ , the flux rates are higher and surface pH is closer to bulk pH - this is due to the high buffer capacity. When 3.55 is used as  $pK_a$ , the flux is slower than observed due to very low buffer capacity. However, when an effective  $pK_a$  of 4.2 is used, the observed data can be explained well.

## References

- Krieg, B.J., et al., Journal of pharmaceutical sciences, 2014. **103**(11): p. 3473-3490.
- Krieg, B.J., et al., Journal of pharmaceutical sciences, 2015. **104**(9) : p. 2894-2904.

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