The magic buffer Bicarbonate-CO2: In vivo predictive dissolution (iPD)

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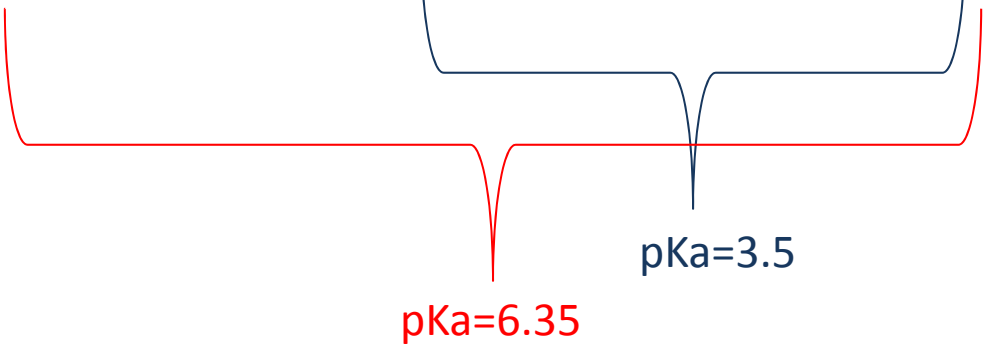
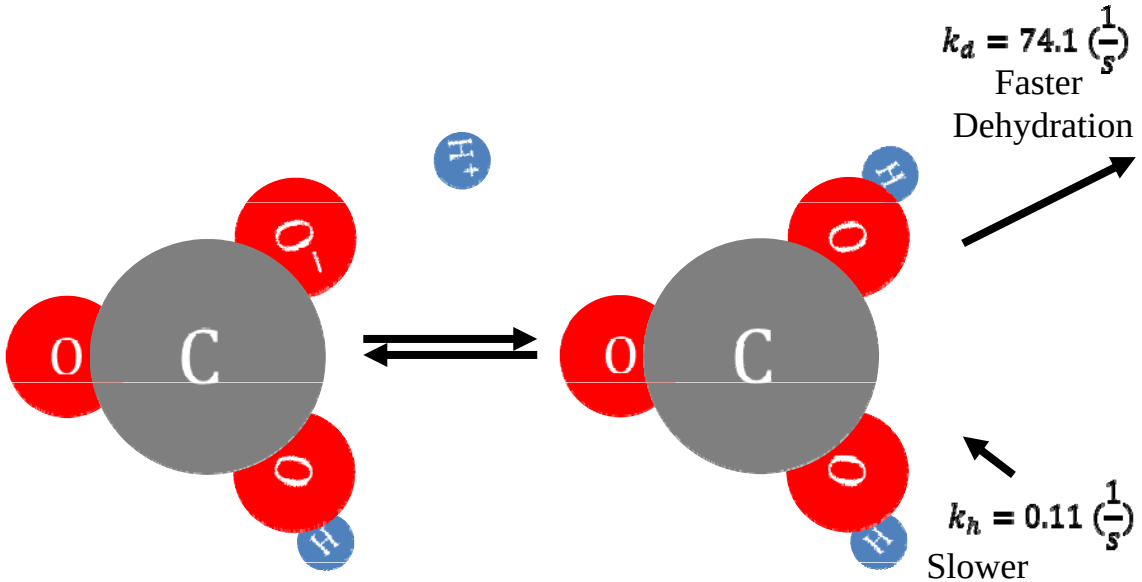
Bicarbonate

- The *in vivo* buffer
- $CO_2 + H_2O \underset{k_h}{\overset{k_d}{\rightleftharpoons}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$



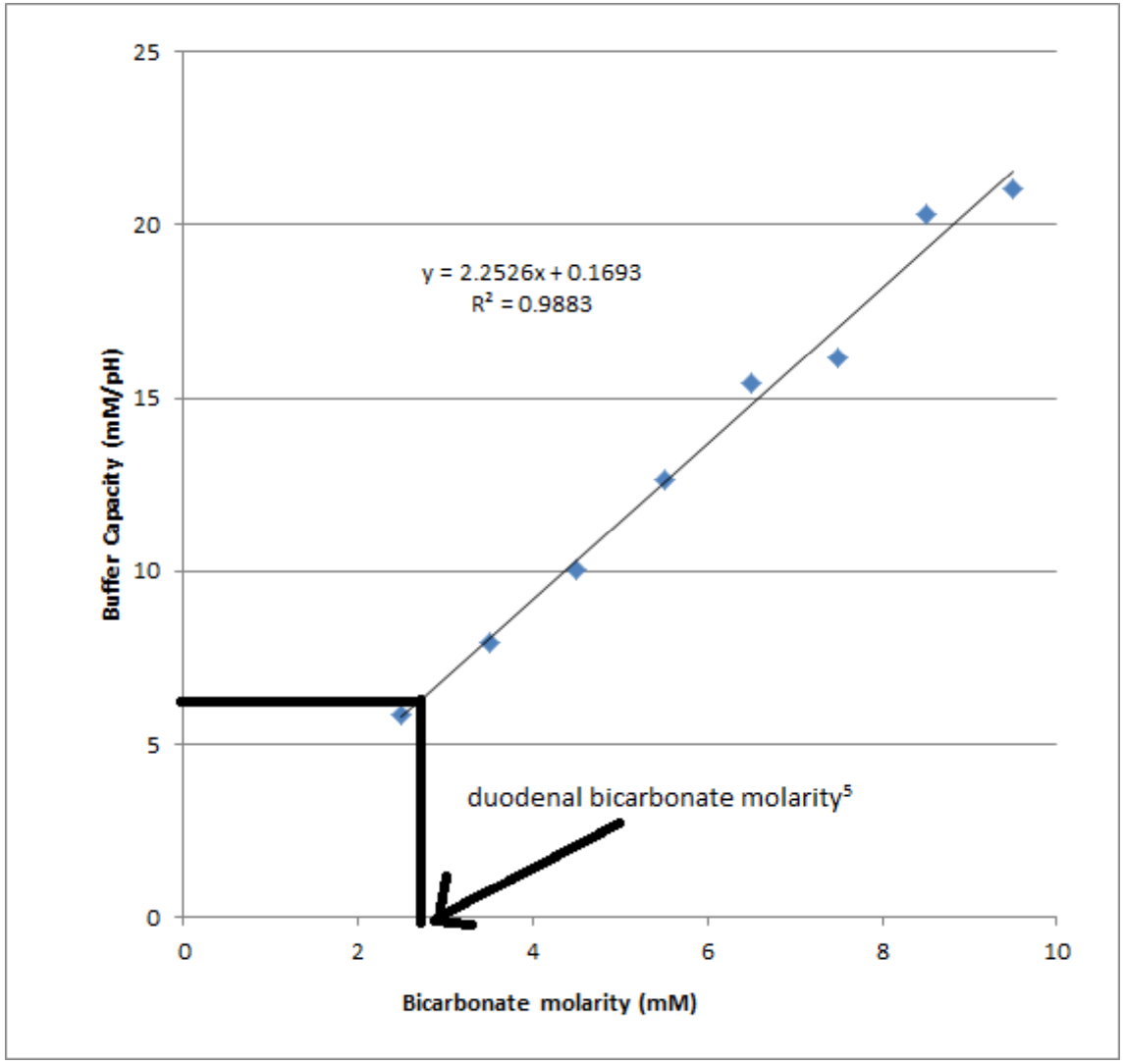
$$pKa = pKa_{H_2CO_3} + \log\left(\frac{k_d}{k_h}\right)$$

Bicarbonate

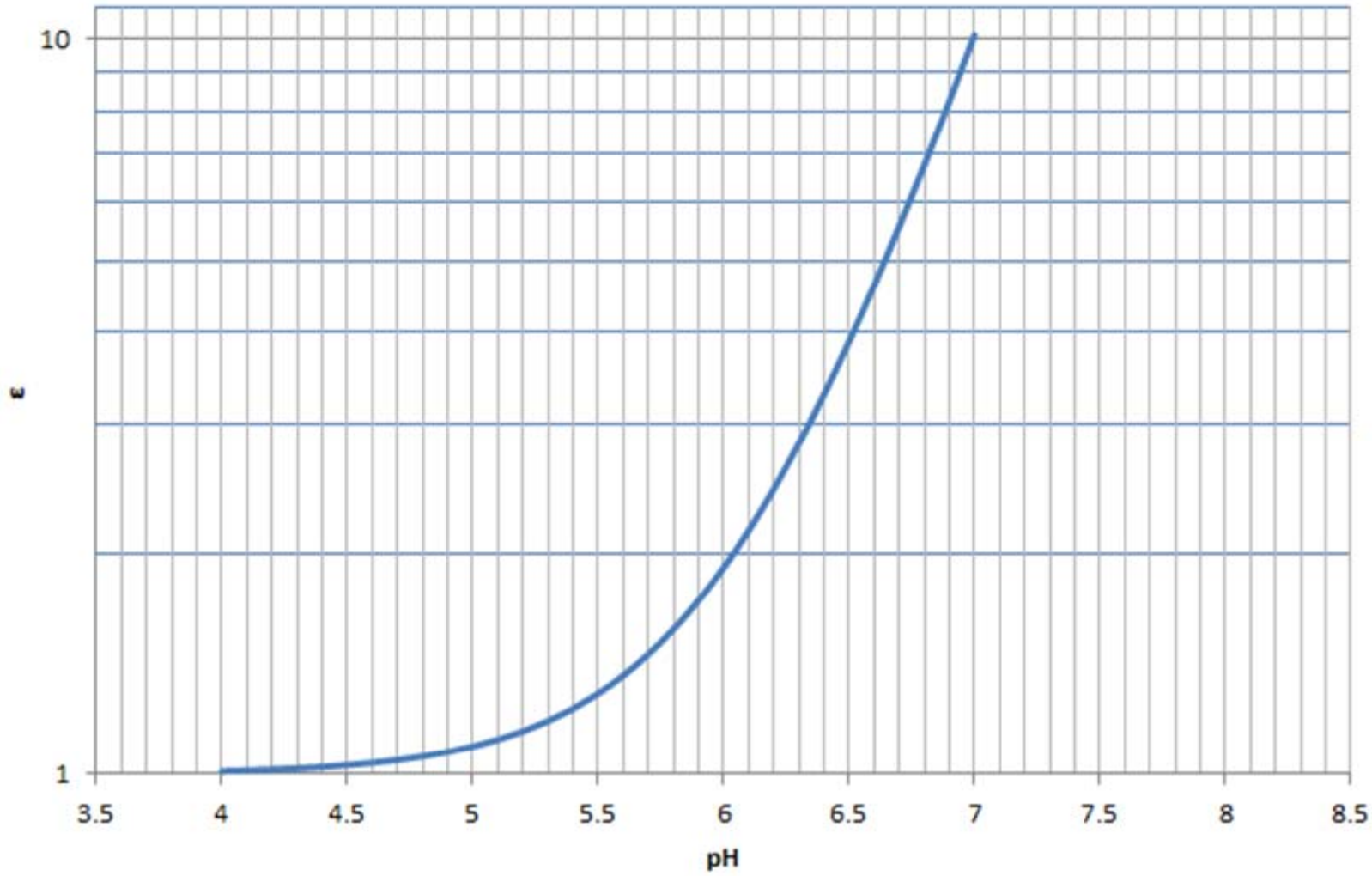


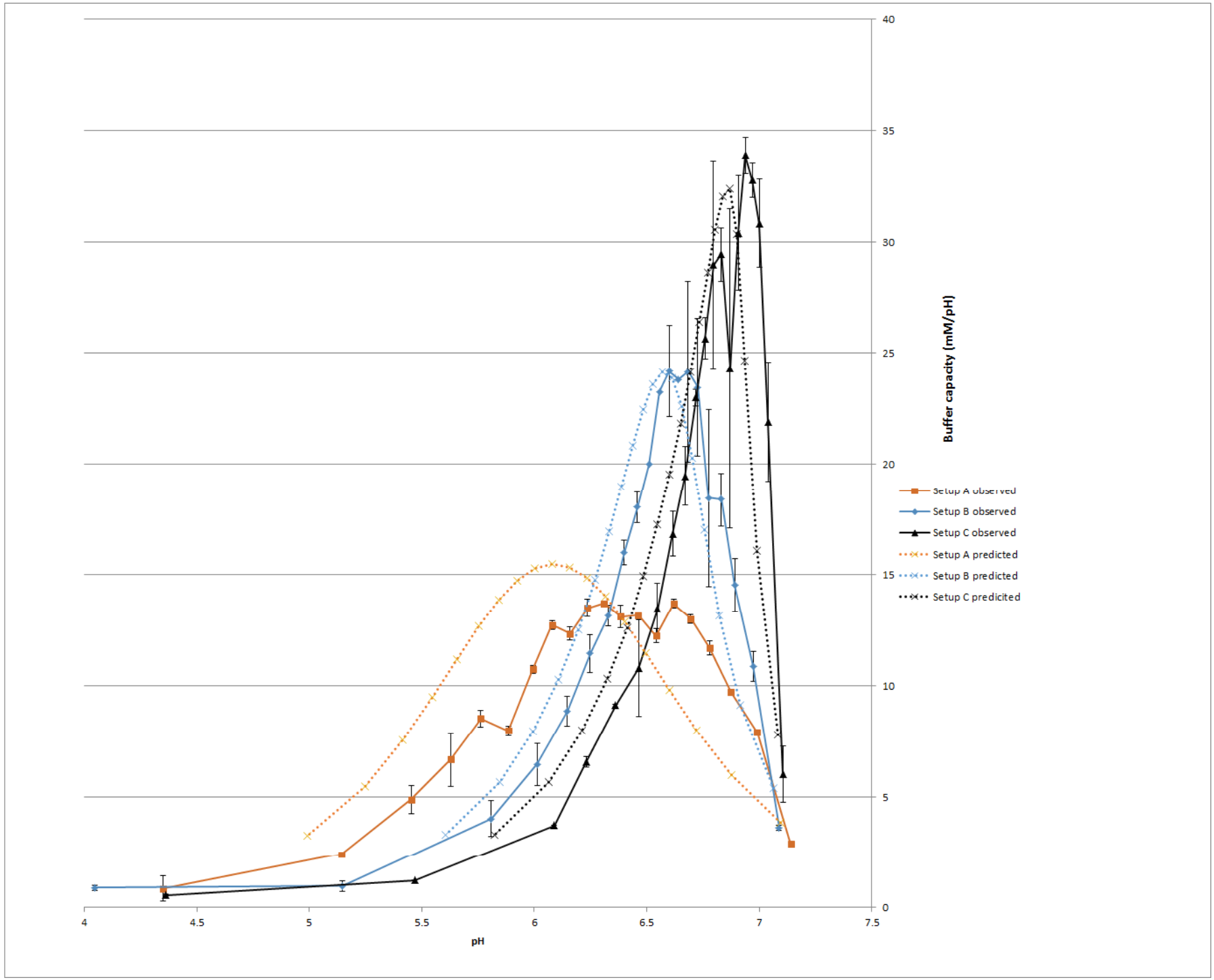
Bicarbonate + H^+ ⇌ Carbonic Acid → Carbon Dioxide + Water

- Able to effectively buffer intestinal fluid despite low molarity and wide pH range
- But nevertheless dissolution in it is slower than expected
- Effective buffer capacity=2.303[HCO_3^-]
- $\varepsilon = \beta_{op}/\beta = 1 + \frac{K_a}{[H^+]}$


25
20
15
10
5
0
0
2
4
6
8
10
y = 2.2526x + 0.1693
R² = 0.9883
Buffer Capacity (mM/pH)
Bicarbonate molarity (mM)
duodenal bicarbonate molarity[5]

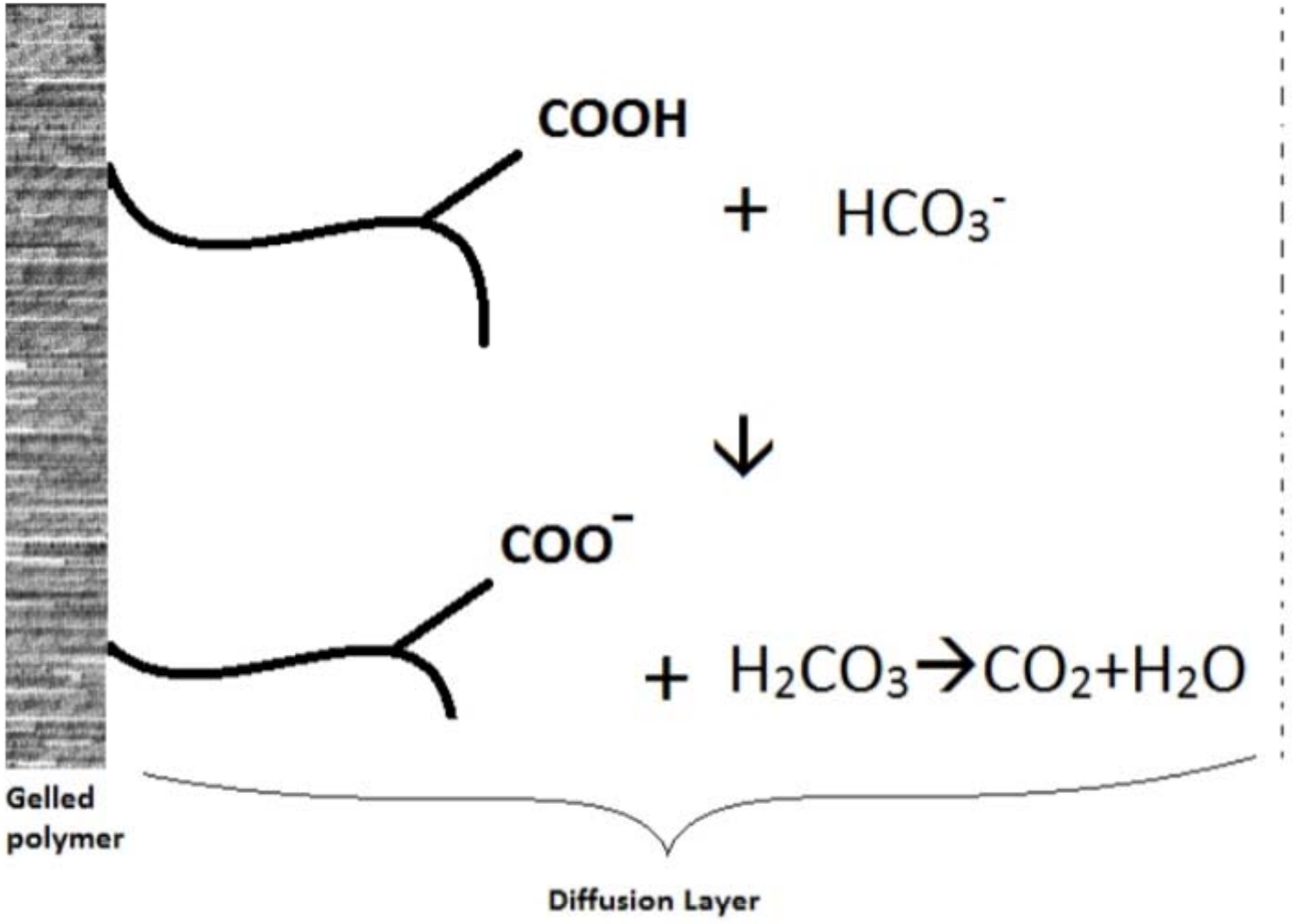
- $H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons CO_{2(aq)} + H_2O$
- $CO_{2(aq)} \rightleftharpoons CO_{2(g)}$
- Limited accumulation of conjugate acid
- Important for non-sink conditions

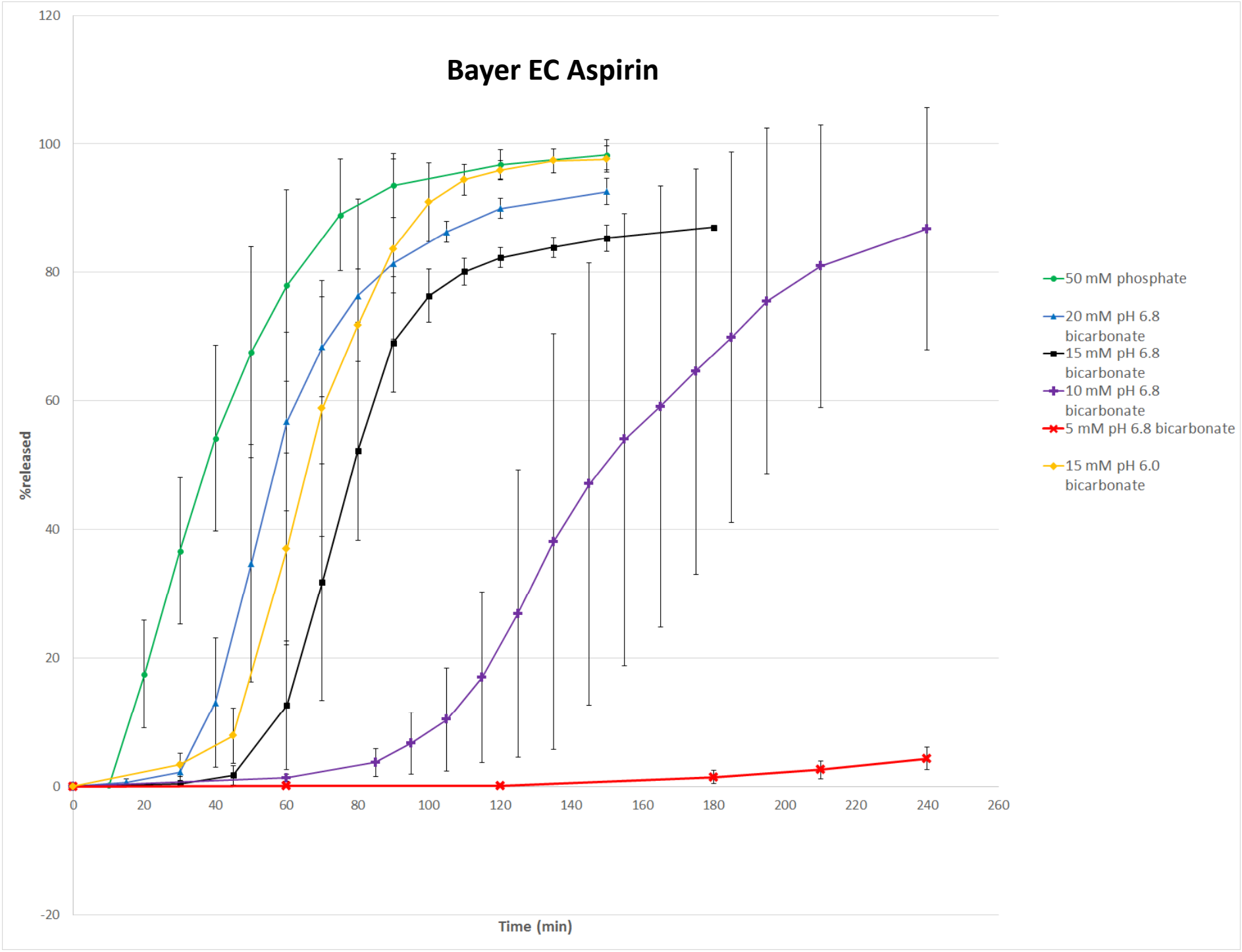

10
1
ε
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
8.5
pH

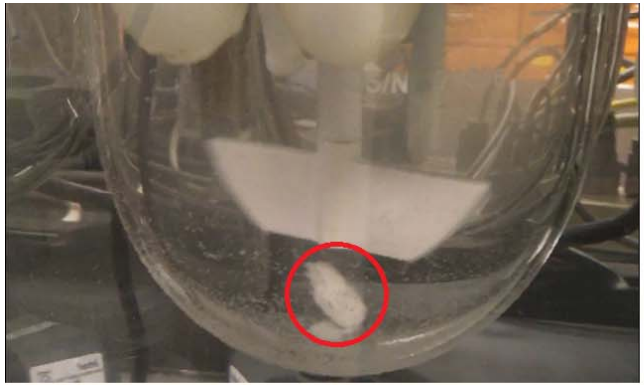
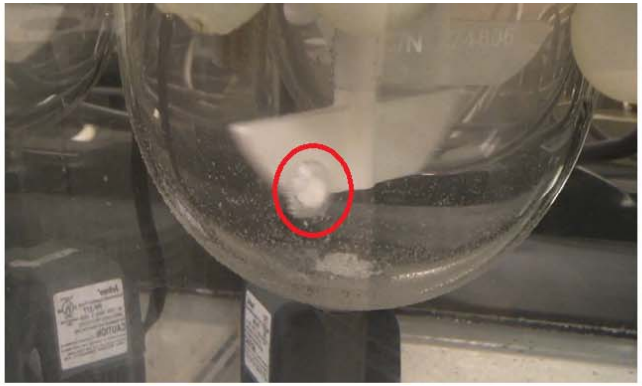
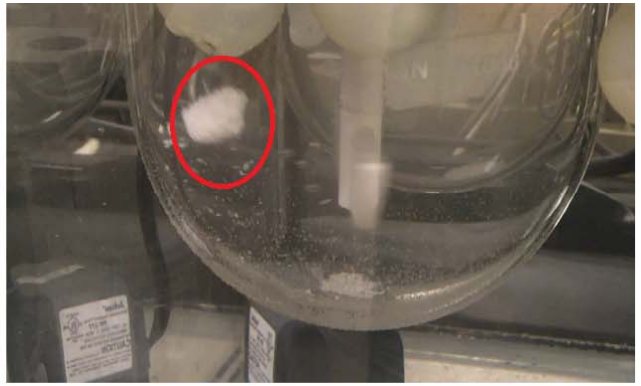

40
35
30
25
20
15
10
5
0
4
4.5
5
5.5
6
6.5
7
7.5
pH
Buffer capacity (mM/pH)
Setup A observed
Setup B observed
Setup C observed
Setup A predicted
Setup B predicted
Setup C predicited

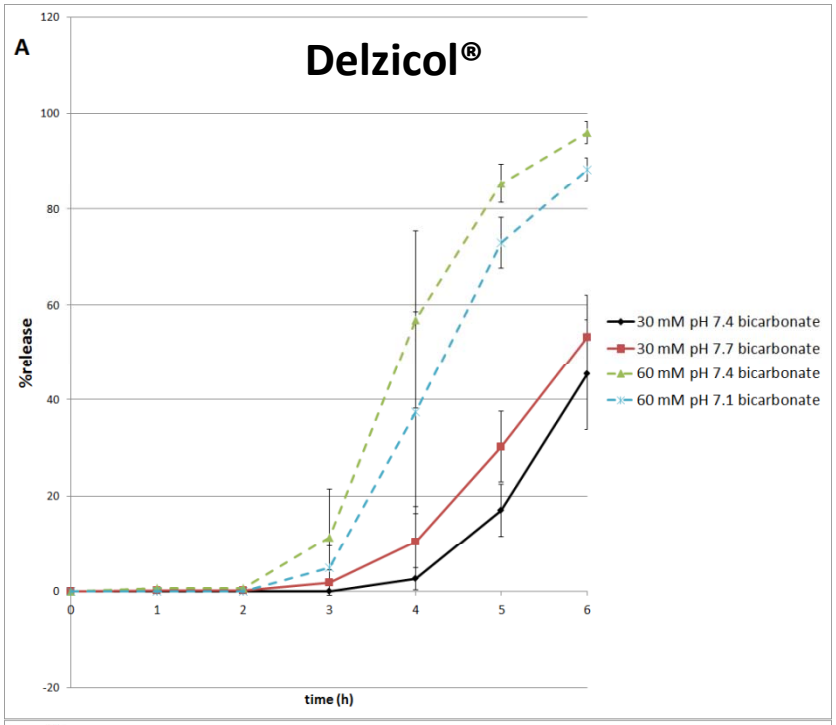
But in diffusion layer…

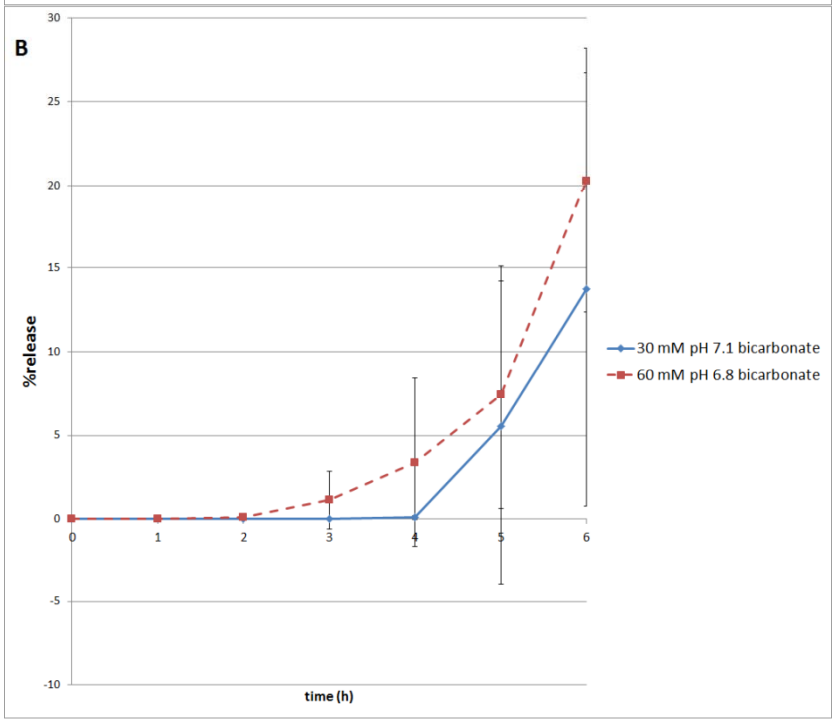
- Diffusion time ~0.6 s
- Ionization reaction time few ns-µs
- Carbonic acid dehydration time 0.013 s
- Carbon dioxide hydration time 9 s

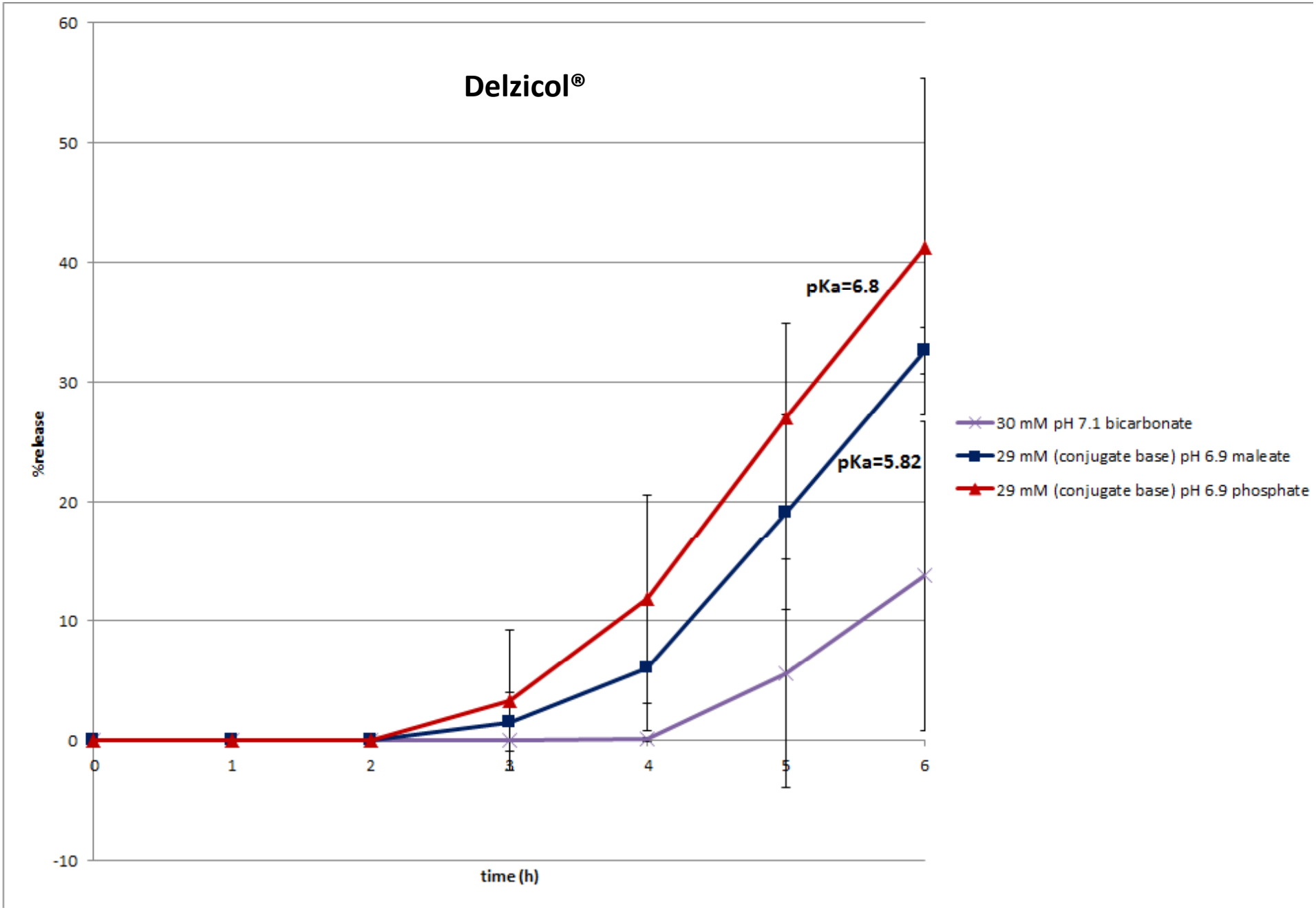

COOH
+ HCO_3^-
COO^-
+ $H_2CO_3 \rightarrow CO_2 + H_2O$
Gelled polymer
Diffusion Layer


Bayer EC Aspirin
%released
Time (min)
120
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200
220
240
260
50 mM phosphate
20 mM pH 6.8 bicarbonate
15 mM pH 6.8 bicarbonate
10 mM pH 6.8 bicarbonate
5 mM pH 6.8 bicarbonate
15 mM pH 6.0 bicarbonate


A
Delzicol®
%release
time (h)
30 mM pH 7.4 bicarbonate
30 mM pH 7.7 bicarbonate
60 mM pH 7.4 bicarbonate
60 mM pH 7.1 bicarbonate


B
%release
time (h)
30 mM pH 7.1 bicarbonate
60 mM pH 6.8 bicarbonate


Delzicol®
60
50
40
30
20
10
0
-10
%release
0
1
2
3
4
5
6
time (h)
pKa=6.8
pKa=5.82
30 mM pH 7.1 bicarbonate
29 mM (conjugate base) pH 6.9 maleate
29 mM (conjugate base) pH 6.9 phosphate

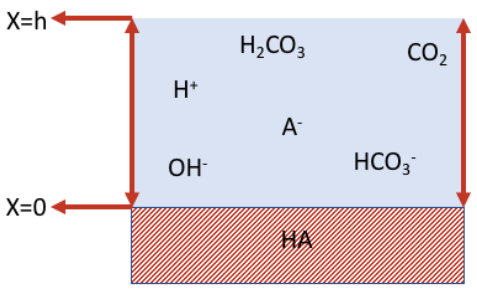
$$HA \leftrightarrow H^+ + A^-$$

$$HA + OH^- \leftrightarrow H_2O + A^-$$

$$HA + HCO_3^- \leftrightarrow H_2CO_3 + A^-$$

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3$$

$$H_2CO_3 \leftrightarrow H_2O + CO_2$$



Steady State Mass Balance

$$\frac{\partial[HA]}{\partial t} = D_{HA}\frac{\partial^2[HA]}{\partial^2 x} + \phi_1 = 0$$
$$\frac{\partial[A^-]}{\partial t} = D_{A^-}\frac{\partial^2[A^-]}{\partial^2 x} + \phi_2 = 0$$
$$\frac{\partial[H^+]}{\partial t} = D_{H^+}\frac{\partial^2[H^+]}{\partial^2 x} + \phi_3 = 0$$
$$\frac{\partial[OH^-]}{\partial t} = D_{OH^-}\frac{\partial^2[OH^-]}{\partial^2 x} + \phi_4 = 0$$
$$\frac{\partial[HCO_3^-]}{\partial t} = D_{HCO_3^-}\frac{\partial^2[HCO_3^-]}{\partial^2 x} + \phi_5 = 0$$
$$\frac{\partial[H_2CO_3]}{\partial t} = D_{H_2CO_3}\frac{\partial^2[H_2CO_3]}{\partial^2 x} + \phi_6 = 0$$
$$\frac{\partial[CO_2]}{\partial t} = D_{CO_2}\frac{\partial^2[CO_2]}{\partial^2 x} + \phi_7 = 0$$

Charge balance & electrical neutrality.

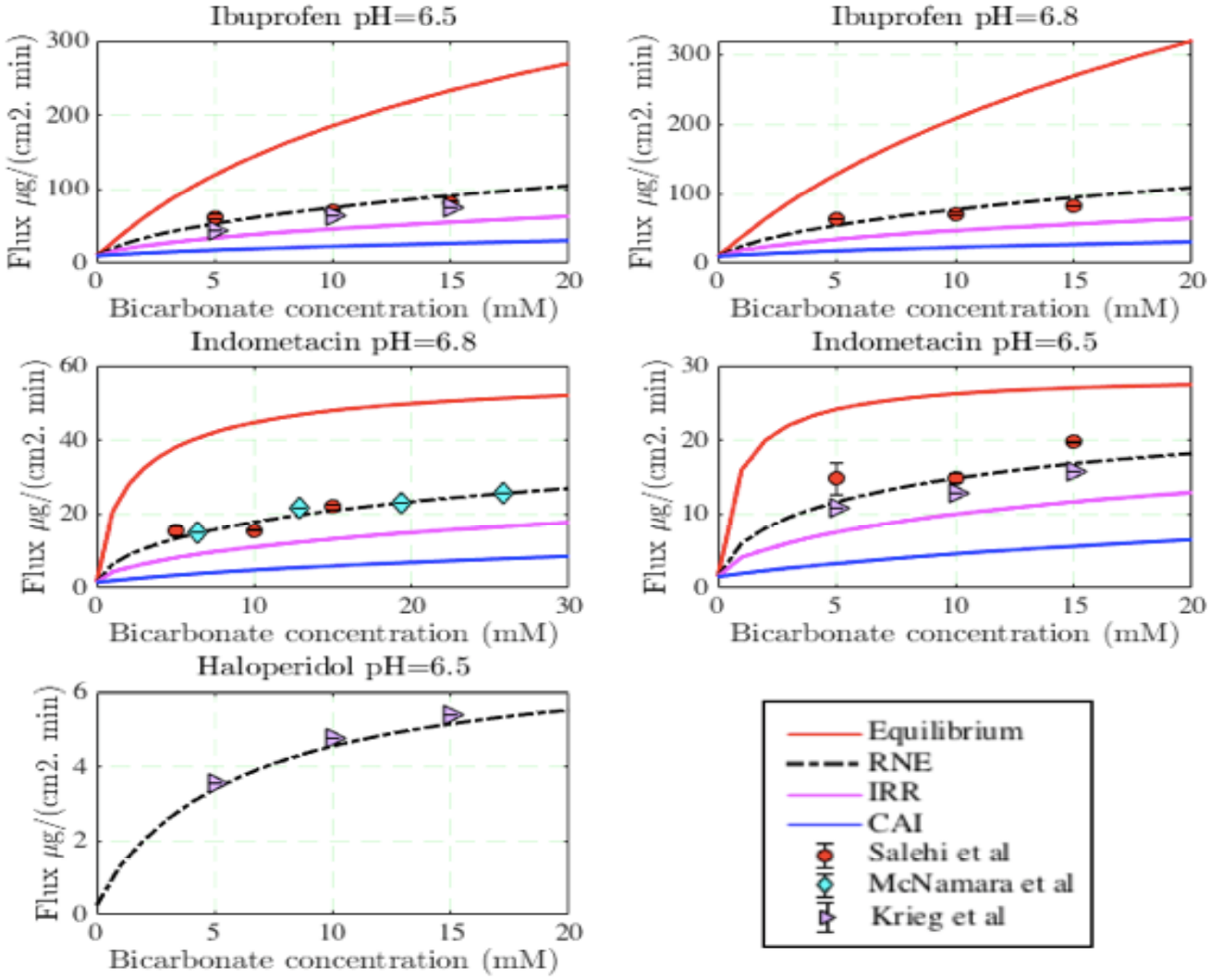
Boundary Conditions

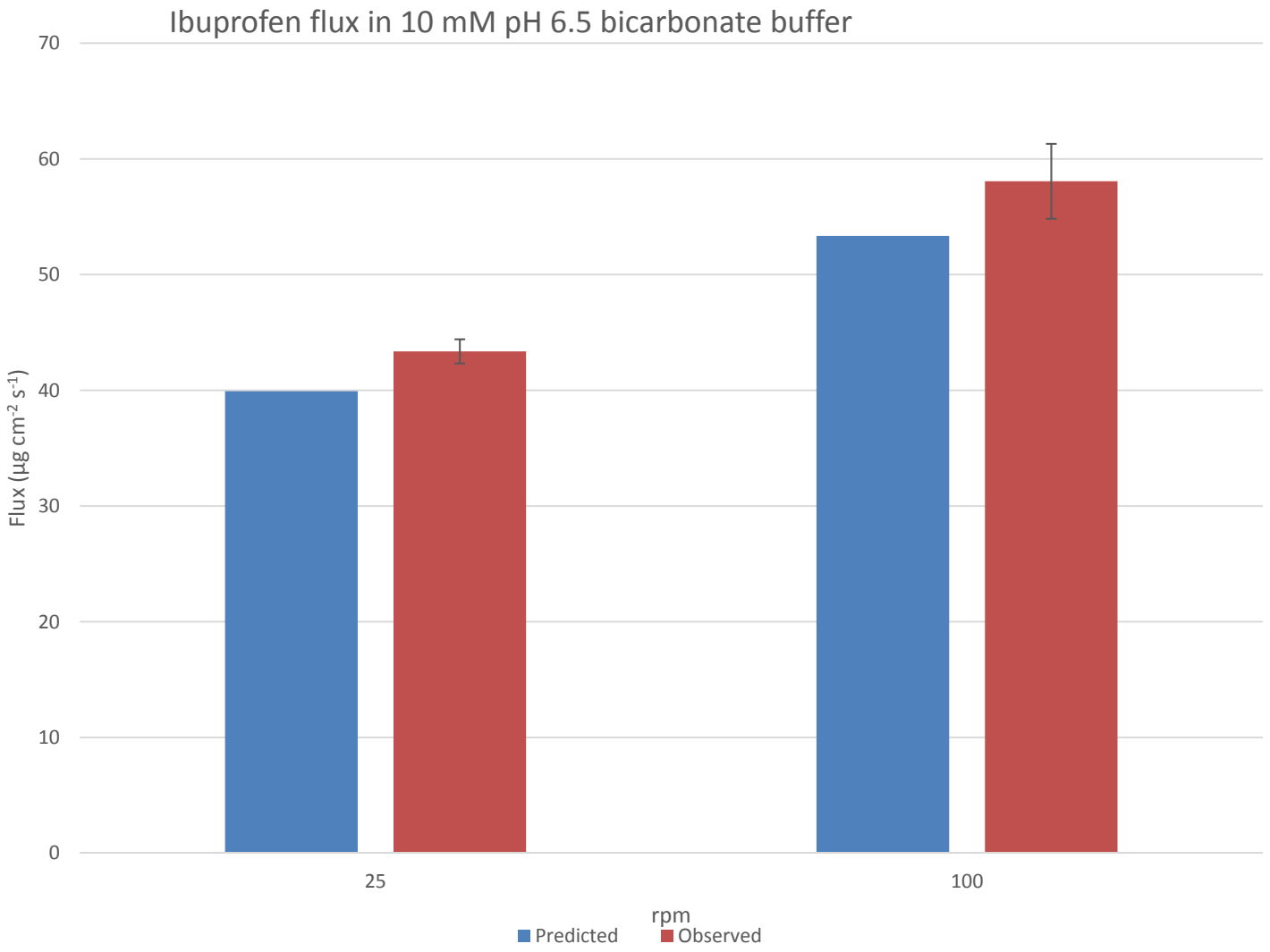
$@x = h$

$[HA] = [HA]_h$	*Known*
$[A^-] = [A^-]_h$	*Known*
$[H^+] = [H^+]_h$	*Given*
$[OH^-] = [OH^-]_h$	*Given*
$[HCO_3^-] = [HCO_3^-]_h$	*Given*
$[H_2CO_3] = [H_2CO_3]_h$	*Given*
$[CO_2] = [CO_2]_h$	*Given*

$@x = 0$

$[HA] = [HA]_0$	*Known*
$[A^-] = [A^-]_0$	*Unknown*
$[H^+] = [H^+]_0$	*Unknown*
$[OH^-] = [OH^-]_0$	*Unknown*
$[HCO_3^-] = [HCO_3^-]_0$	*Unknown*
$[H_2CO_3] = [H_2CO_3]_0$	*Unknown*
$[CO_2] = [CO_2]_0$	*Unknown*


Ibuprofen pH=6.5
Flux μg/(cm2. min)
Bicarbonate concentration (mM)
Ibuprofen pH=6.8
Flux μg/(cm2. min)
Bicarbonate concentration (mM)
Indometacin pH=6.8
Flux μg/(cm2. min)
Bicarbonate concentration (mM)
Indometacin pH=6.5
Flux μg/(cm2. min)
Bicarbonate concentration (mM)
Haloperidol pH=6.5
Flux μg/(cm2. min)
Bicarbonate concentration (mM)
Equilibrium
RNE
IRR
CAI
Salehi et al
McNamara et al
Krieg et al


Ibuprofen flux in 10 mM pH 6.5 bicarbonate buffer
70
60
50
40
30
20
10
0
Flux (µg cm-2 s-1)
25
100
rpm
Predicted
Observed

Summary

- Bicarbonate buffer is unique
- Gaseous nature of carbon dioxide and relatively slow carbon dioxide-carbonic acid equilibration
- →complex buffering action
- Difficult to simulate

Thank you