**Case Study IIa: \( K = f(x) (C_s, A) \)**

**Zinc Insulin Injectable Suspensions**

<table>
<thead>
<tr>
<th>Name</th>
<th>Solid State of Insulin</th>
<th>Average Particle Size (um)</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-Lente</td>
<td>Amorphous</td>
<td>2</td>
<td>4 - 8 fast-acting</td>
</tr>
<tr>
<td>Ultra-Lente</td>
<td>Crystal</td>
<td>25</td>
<td>10 - 14 long-acting</td>
</tr>
<tr>
<td>Lente</td>
<td>70% / 30% crys / amor</td>
<td>----</td>
<td>8 – 10 intermediate</td>
</tr>
</tbody>
</table>
Case Study IIa: $K = fx (Cs, A)$
Lente Insulin Series (SS) - Dissolution

Human Zinc Insulin Suspension in Citrate Buffer (0.026M)
Variable: Solid State

![Graph showing the absorbance over time for different insulin series (SEMILENTE, LENTE, ULTRALENTE).]
Case Study IIa: $K = f_x (Cs)$

Sensitivity to Mix of Solids, Initial

Human Zinc Insulin Dissolution Rate
as a Function of Amorphous to Crystalline Ratio
0 to 2 minutes

$Y = -0.0004X + 0.104$
$r = 0.923$
Case Study IIa: $K = fx (Cs)$
Sensitivity to Mix of Solids, Extended

Human Zinc Insulin Dissolution Rate as a Function of Amorphous to Crystalline Ratio
2 to 6 minutes

Time for Dissolution
2 to 6 minutes

$Y = .001 X + .018$
$r = .983$

AMORPHOUS / CRYSTALLINE MIXTURES
Zinc Insulin Dissolution – Mechanisms

# 1 Surface Reaction Resistance \(1/k_R\)

Schematic Representation of Ion-Complexed Protein Dissolution: Complexation Step
Zinc Insulin Dissolution – Mechanisms

#2 - Diffusional Resistance $1/k_D$

Schematic Representation of Ion-Complexed Protein Dissolution: Diffusion Step

rate of diffusion $\alpha \frac{dc}{dz}$
Case Study IIb: $K = fx(Cs)$
Zinc Insulins and Zinc Protein-Binding
(Meakin, B, Doctoral Dissertation, 1974.)

**Beef**
- High affinity: 2 zinc/hexamer $10^{13}$ M$^{-1}$/site
- Low affinity: 4 zinc/hexamer $10^{8}$ M$^{-1}$/site

**Human**
- High affinity: 2 zinc/hexamer $10^{6}$ M$^{-1}$/site
- Low affinity: 4-6 zinc/hexamer $10^{4}$ M$^{-1}$/site
Case Study IIb: \( K = f(x) (C_s) \)
Lente Insulins (Source) – Dissolution
(Prabhu, S and Meyer-Stout, PJ, Pharm Res 8:10, 1996.)
Zinc Insulin Dissolution – Ligand & Substrate

Dissolution Medium Selection
List of Ionic Species

<table>
<thead>
<tr>
<th>Ionic Species</th>
<th>Association Constants (M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acetate</td>
<td>3.3 X 10⁻²</td>
</tr>
<tr>
<td>2. Phosphate</td>
<td>2.5 X 10²</td>
</tr>
<tr>
<td>3. Citrate</td>
<td>6.9 X 10⁴</td>
</tr>
<tr>
<td>4. EDTA</td>
<td>1.0 X 10¹⁶</td>
</tr>
</tbody>
</table>
Case Study IIb: $K = f_x (C_s, D)$
Zinc-Insulin Dissolution (Complexation)
Case Study IIb: \( K = fx (Cs, D) \)
Zinc-Insulin Dissolution (Complexation)

**Human Crystalline Zinc Insulin**
**Ionic Species : Variable**

<table>
<thead>
<tr>
<th>Ionic Species</th>
<th>% Dissolved (min)</th>
<th>( t_{50%} )</th>
<th>( t_{100%} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acetate</td>
<td></td>
<td>1.5</td>
<td>40</td>
</tr>
<tr>
<td>2. Phosphate</td>
<td></td>
<td>2.5</td>
<td>20</td>
</tr>
<tr>
<td>3. Citrate</td>
<td></td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>4. EDTA</td>
<td></td>
<td>0.25</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Controlling Factor: $K = f(x) (Cs - Ct)$