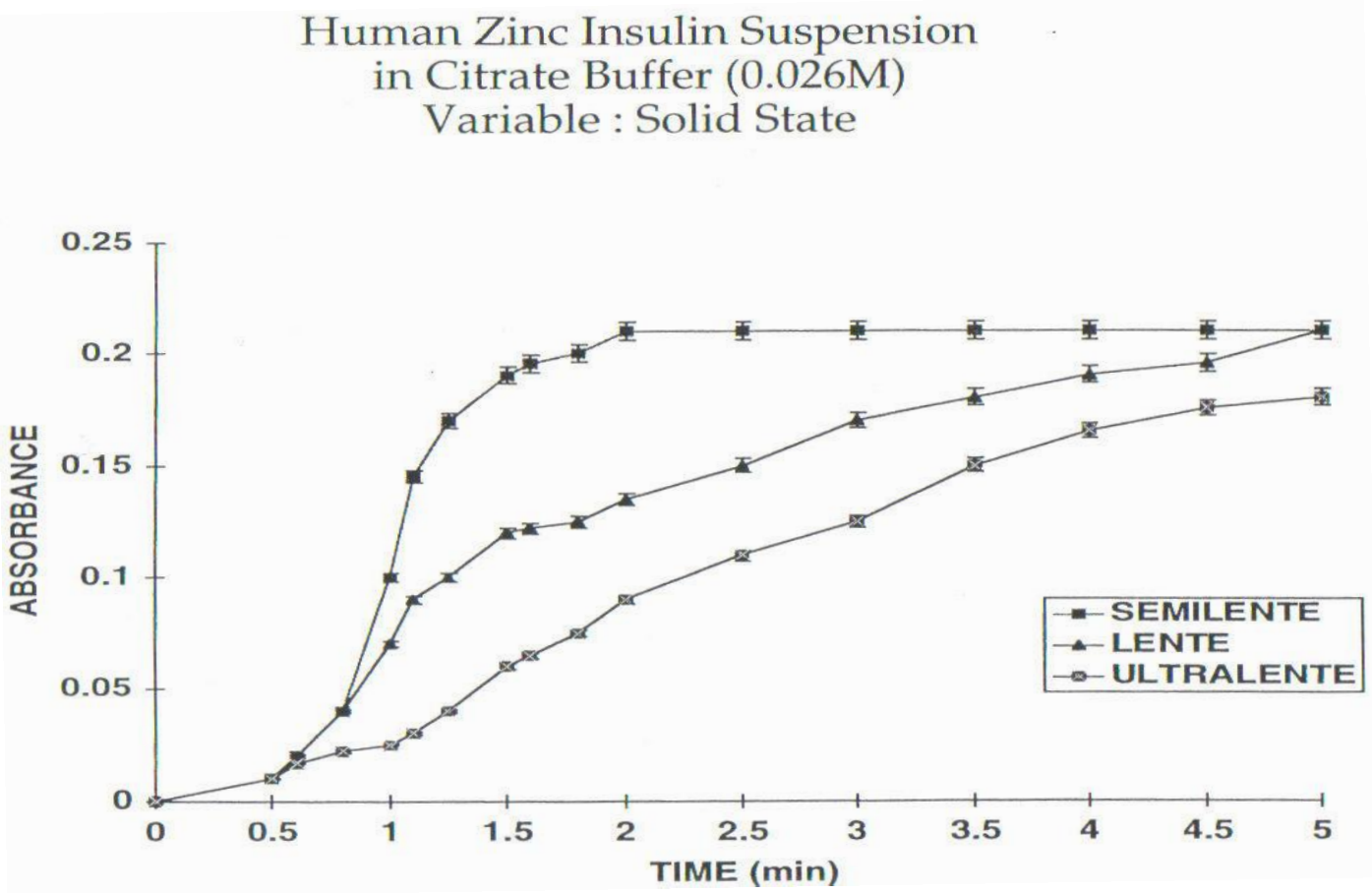
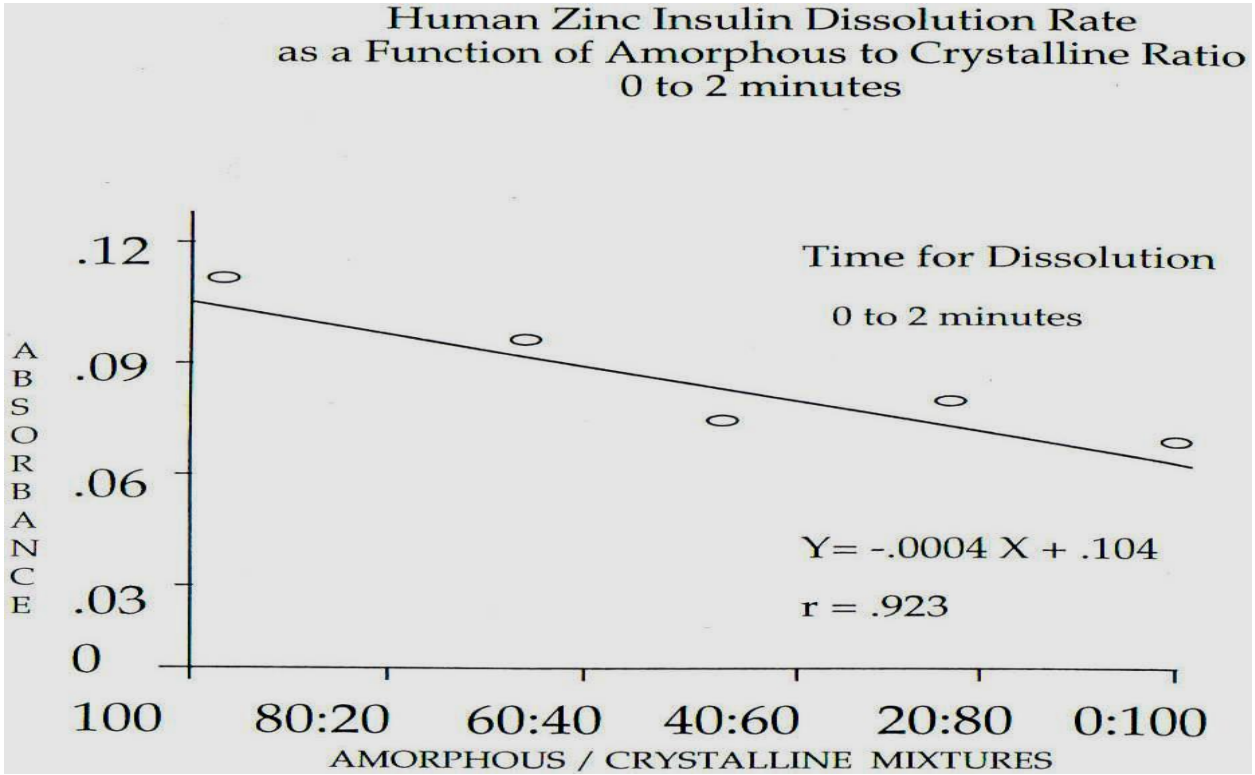
Case Study IIa: K = fx (Cs, A)
Zinc Insulin Injectable Suspensions

Name	Solid State of Insulin	Average Particle Size (um)	Duration of Action (hours)
Semi-Lente	Amorphous	2	4 - 8 fast-acting
Ultra-Lente	Crystal	25	10 -14 long-acting
Lente	70% / 30% crys / amor	----	8 –10 intermediate

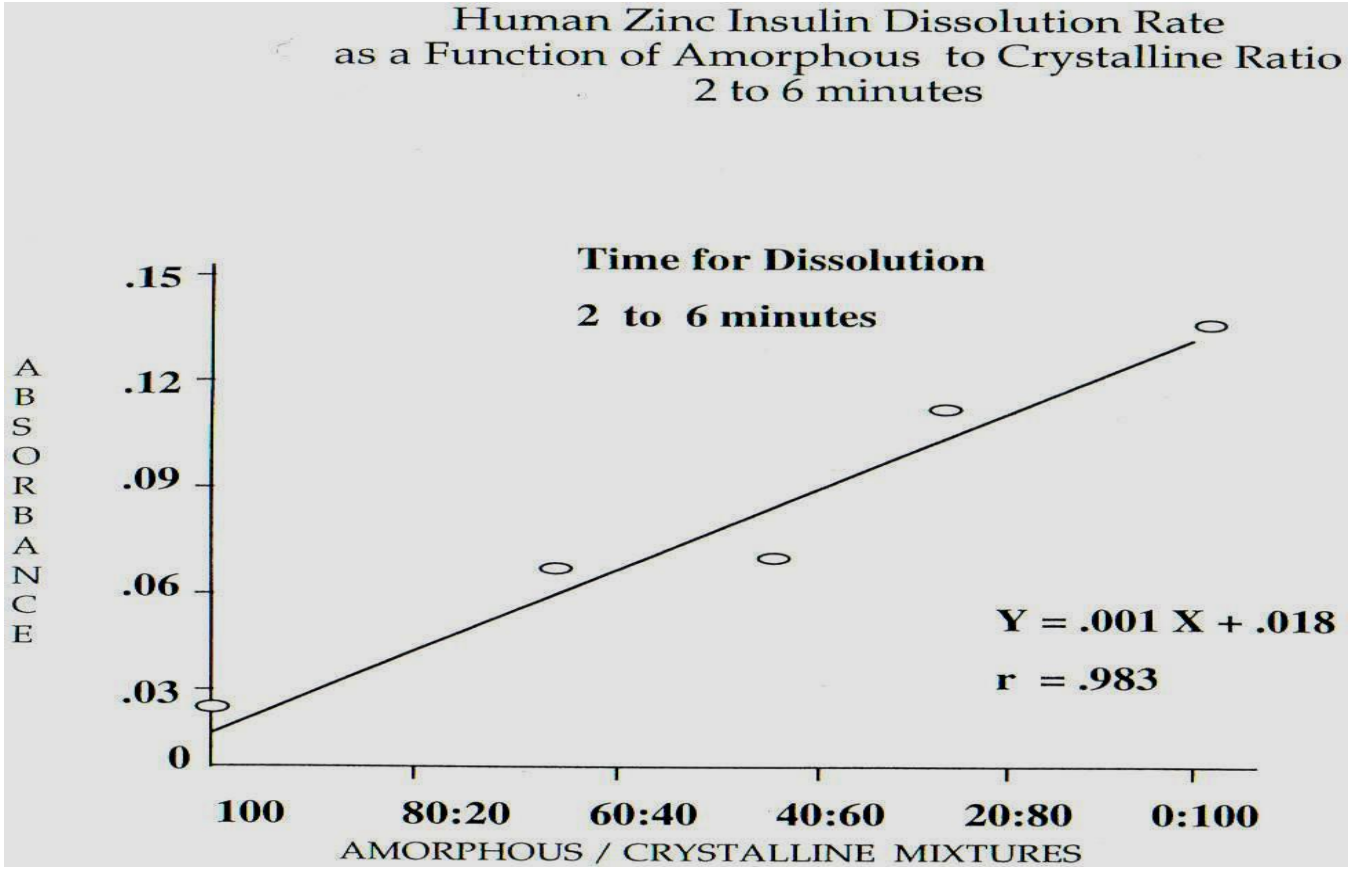
Case Study IIa: K = fx (Cs, A)
Lente Insulin Series (SS) - Dissolution



Case Study IIa: K = fx (Cs) Sensitivity to Mix of Solids, Initial

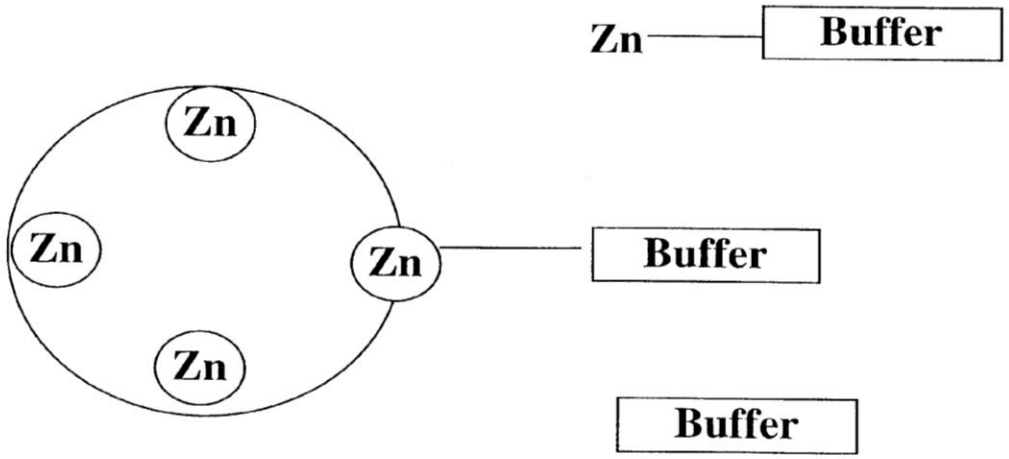


Case Study IIa: K = fx (Cs)
Sensitivity to Mix of Solids, Extended

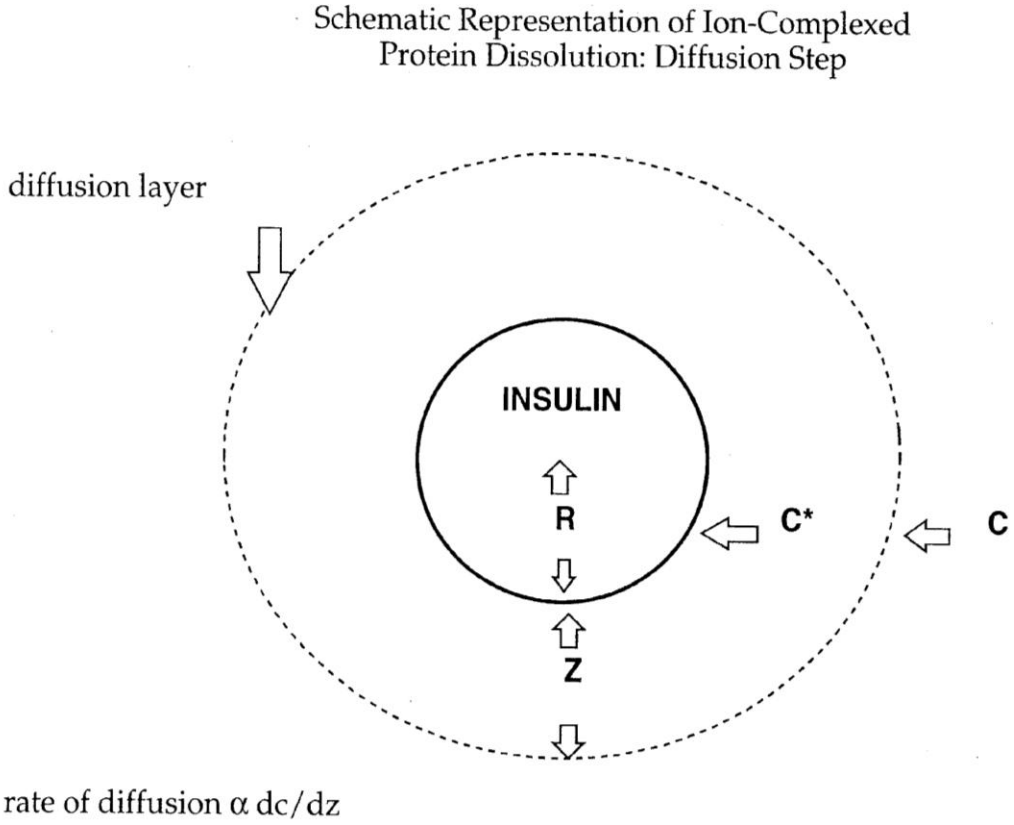


Zinc Insulin Dissolution – Mechanisms # 1 Surface Reaction Resistance $1/k_R$

Schematic Representation of Ion-Complexed Protein Dissolution: Complexation Step



Zinc Insulin Dissolution – Mechanisms #2 - Diffusional Resistance $1/k_D$



Case Study IIb: K = fx (Cs)
Zinc Insulins and Zinc Protein-Binding
(Meakin, B, Doctoral Dissertation, 1974.)

Beef

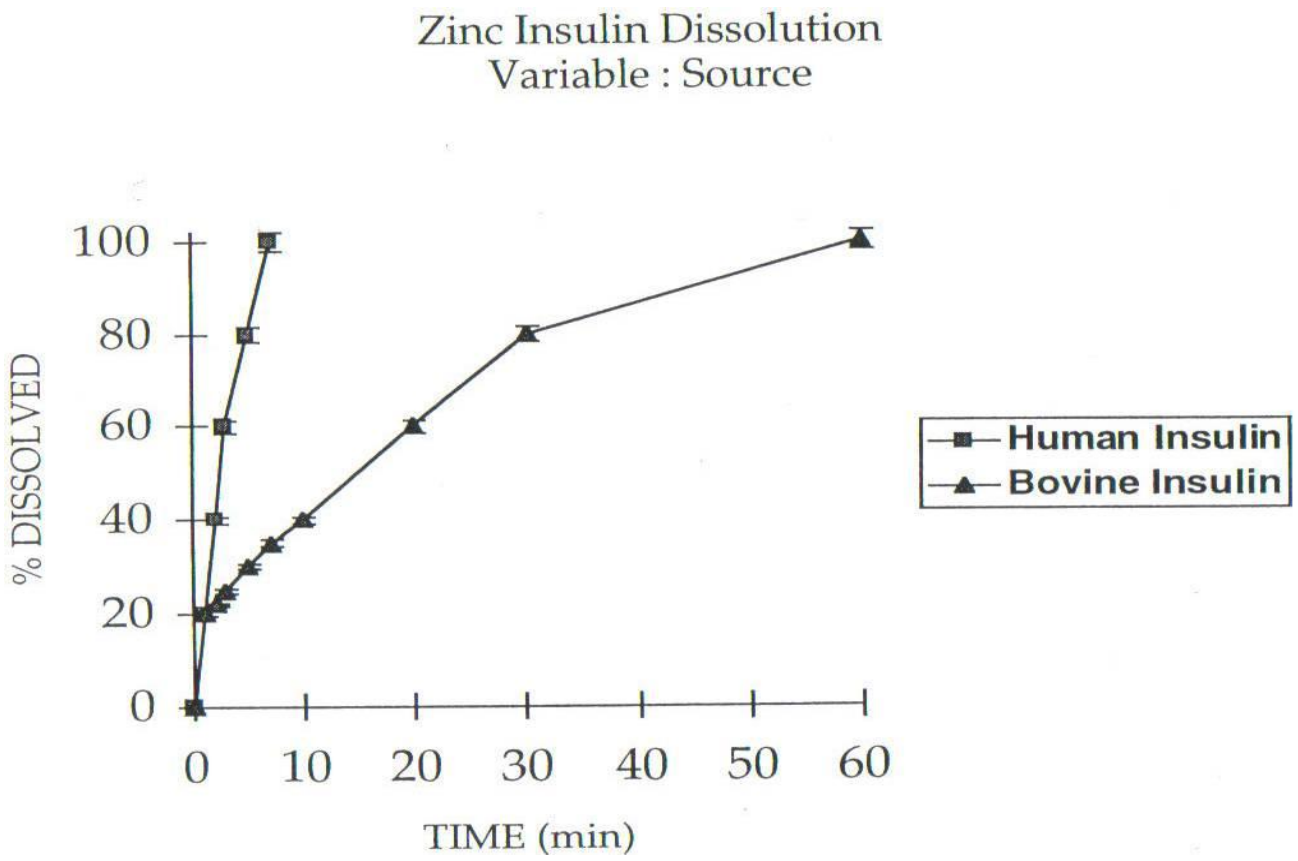
- High affinity: 2 zinc/hexamer 10^{13} M^{-1}/site
- Low affinity: 4 zinc/hexamer 10^{8} M^{-1}/site

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 = fx (Cs)
Lente Insulins (Source) – Dissolution

(Prabhu, S and Meyer-Stout, PJ, Pharm Res 8:10, 1996.)

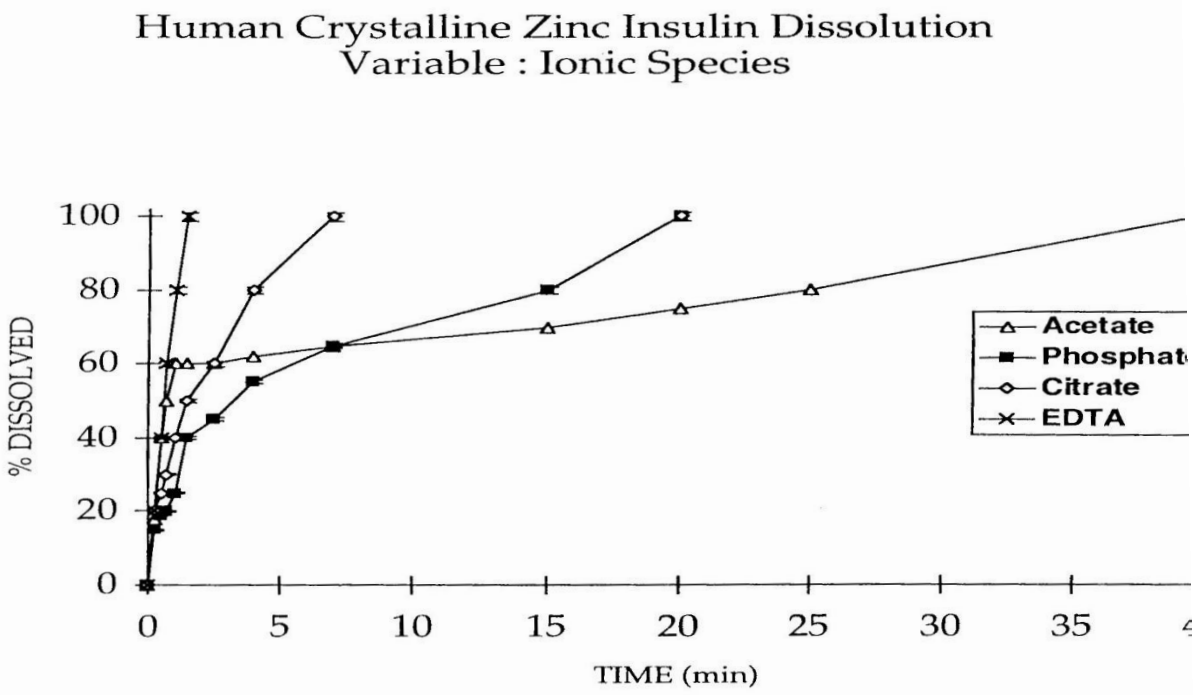


Zinc Insulin Dissolution – Ligand & Substrate

Dissolution Medium Selection
List of Ionic Species

	Ionic Species	Association Constants (M^{-1})
1.	Acetate	3.3×10^{-2}
2.	Phosphate	2.5×10^{2}
3.	Citrate	6.9×10^{4}
4.	EDTA	1.0×10^{16}

Case Study IIb: K = fx (Cs, D)
Zinc-Insulin Dissolution(Complexation)



Case Study IIb: K = fx (Cs, D) Zinc-Insulin Dissolution(Complexation)

Human Crystalline Zinc Insulin
Ionic Species : Variable

Ionic Species	% Dissolved (min)	
	$t_{50\%}$	$t_{100\%}$
1. Acetate	1.5	40
2. Phosphate	2.5	20
3. Citrate	1.5	7.5
4. EDTA	0.25	2.0

Controlling Factor: K = fx (Cs – Ct)