Issues Related to the Formulation and Delivery of Pharmaceutical Proteins

Pretoria16 August

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Delivery of Proteins

Welcome to the kingdom of the needle?

- Are we stuck to the needle?

Formulation: from raw material to final dosage form

Points to consider

- Route of administration
- Dose (conc. and volume)
- Temperature of storage
- Container and closure
- Exposure to light
- Exposure to air
- Compatibility of excipients
- Compatibility of pH
- Adsorption during delivery
- Shear sensitivity

Formulation principles

Wang, Int. J. Pharmaceutics

Functionality of excipients; they act as:

- Stabilizers
- Bulking agents
- Surfactants
- Isotonicity modifiers
- pH/buffering agents
- Preservatives

Points to consider

Liquid versus freeze dried form

- Stability
- Costs of goods - Revenues of finished product
- Storage of finished product
- Convenience end user

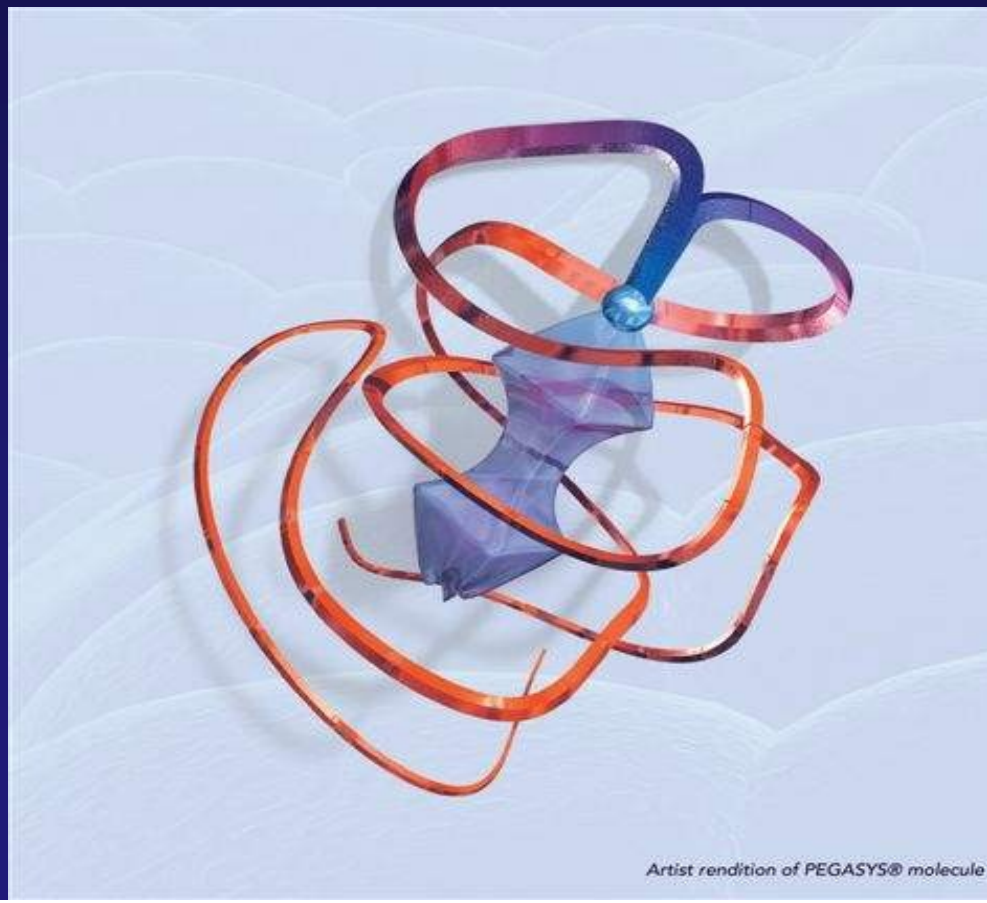
Wei Wang*
International Journal of Pharmaceutics 203 (2000) 1–60
Lyophilization and development of solid protein pharmaceuticals

Why Parenteral *Depot* Formulations?

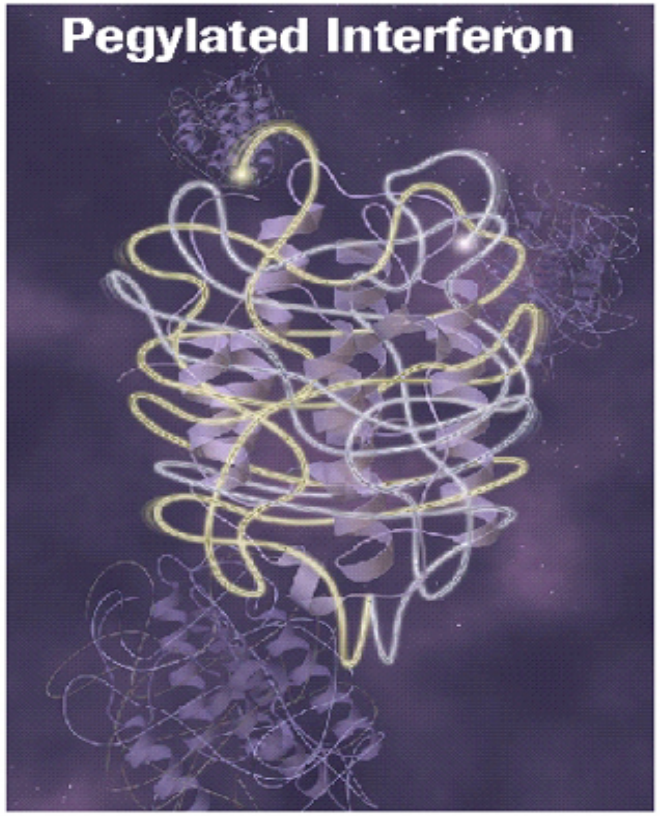
- Elimination half-life time is short
- Controlled release is required
- Site directed delivery is required (drug targeting)

PEGylated proteins

- PEG-Interferon alfa
- PEG-G-CSF
- ……



Strategies for improved protein delivery



http://www.roche.com/pages/facets/10/pegasyse.htm

Aranesp™ is an erythropoiesis stimulating protein closely related to erythropoietin that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp™ is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3.[1]

Table 2. Comparison of pharmacokinetic parameters for intravenous darbepoetin alfa and recombinant human erythropoietin*

Parameter	Darbepoetin alfa (n = 11)	rHu-EPO (n = 10)
Terminal half-life (hr)	25.3 ± 2.2	8.5 ± 2.4
Clearance (mL/h per kg)	1.6 ± 0.3	4.0 ± 0.3
$AUC_{(0-96\ h)}$ (ng·h per mL)	291.0 ± 7.6	131.9 ± 8.3
V_d (mL/kg)	52.4 ± 2.0	48.7 ± 2.1

*Adapted from reference 8. Results are given as mean ± standard error of the mean. rHu-EPO indicates recombinant human erythropoietin; AUC, area under the serum concentration–time curve; V_d, volume of distribution at steady state.

Darbepoetin alfa (Aranesp)

JOHN POWELL, RPH, BCOP, AND CHERYLE GURK-TURNER, RPH

Modified Release Systems for Pharmaceutical Proteins

- Solid Complexes (insulin)(hours): ……
- Polymer solutions/hydrogels (days): Atrix, Macromed
- Microspheres from biodegradable polymers (0-1 month….)

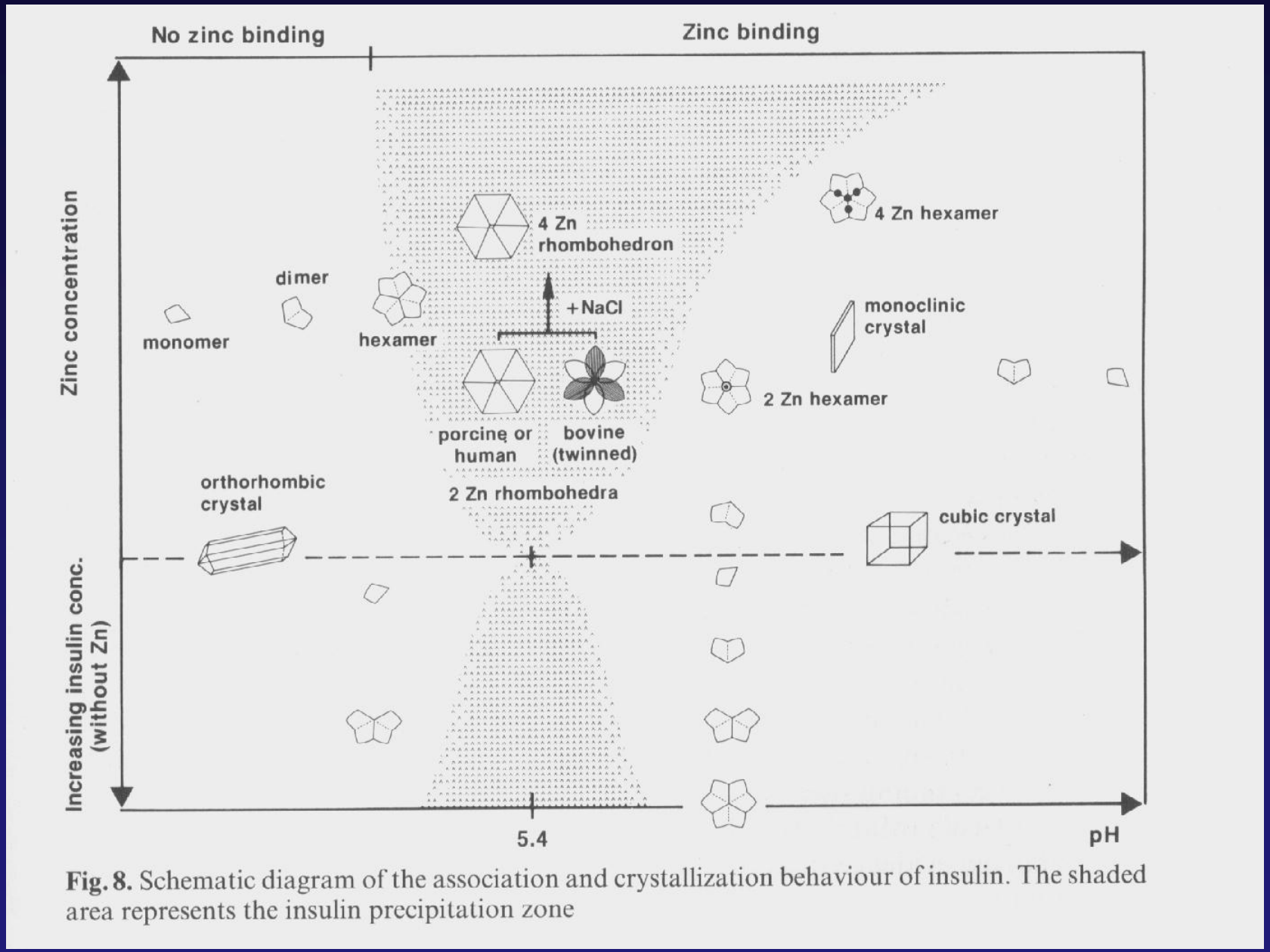


Fig. 8. Schematic diagram of the association and crystallization behaviour of insulin. The shaded area represents the insulin precipitation zone

Brange, 198

Liquid/solid state hydrogels

SABER™ Delivery System

Sucrose Acetate IsoButyrate Extended Release

- High Viscosity Liquid (example SAIB)
- Hydrophobic
- Viscosity Drops with Addition of Solvent
- Biocompatible
- Biodegradable
- Established safety profile
- Strong patent position
- Low cost manufacturing
- Applications:
  - **Parenteral depot**

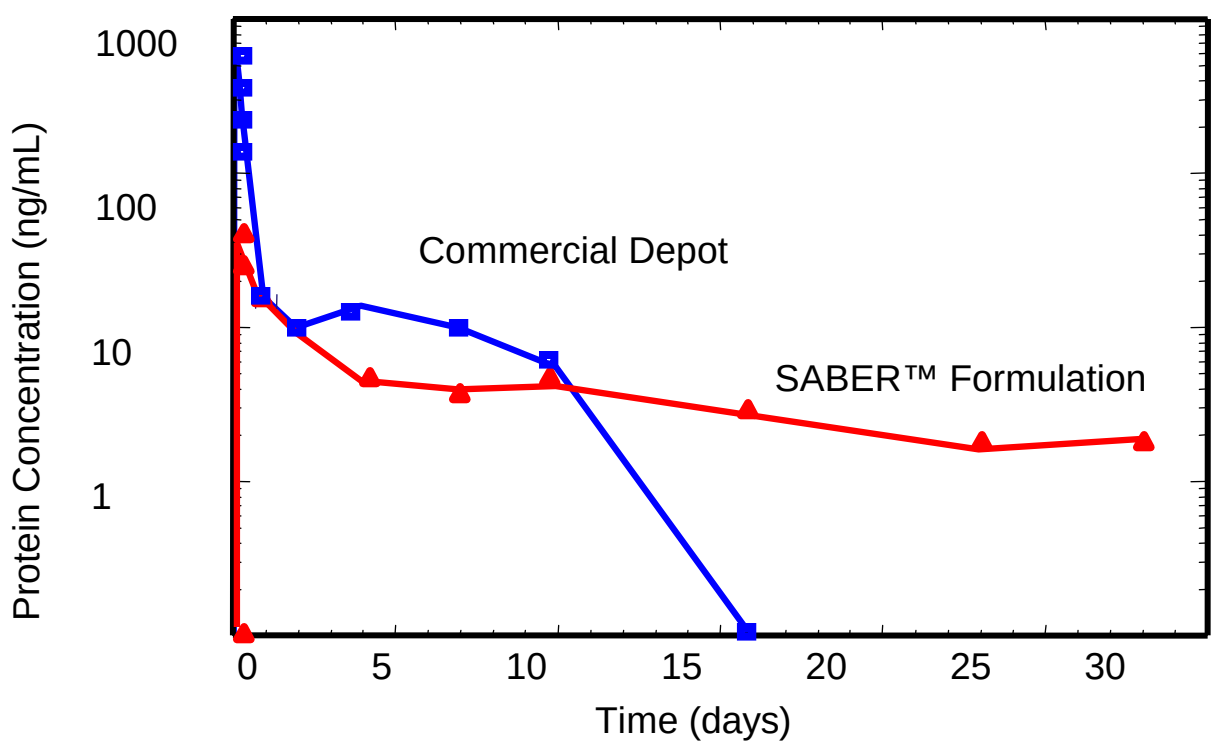

SAIB Only


85/15 SAIB:Ethanol

DURECT

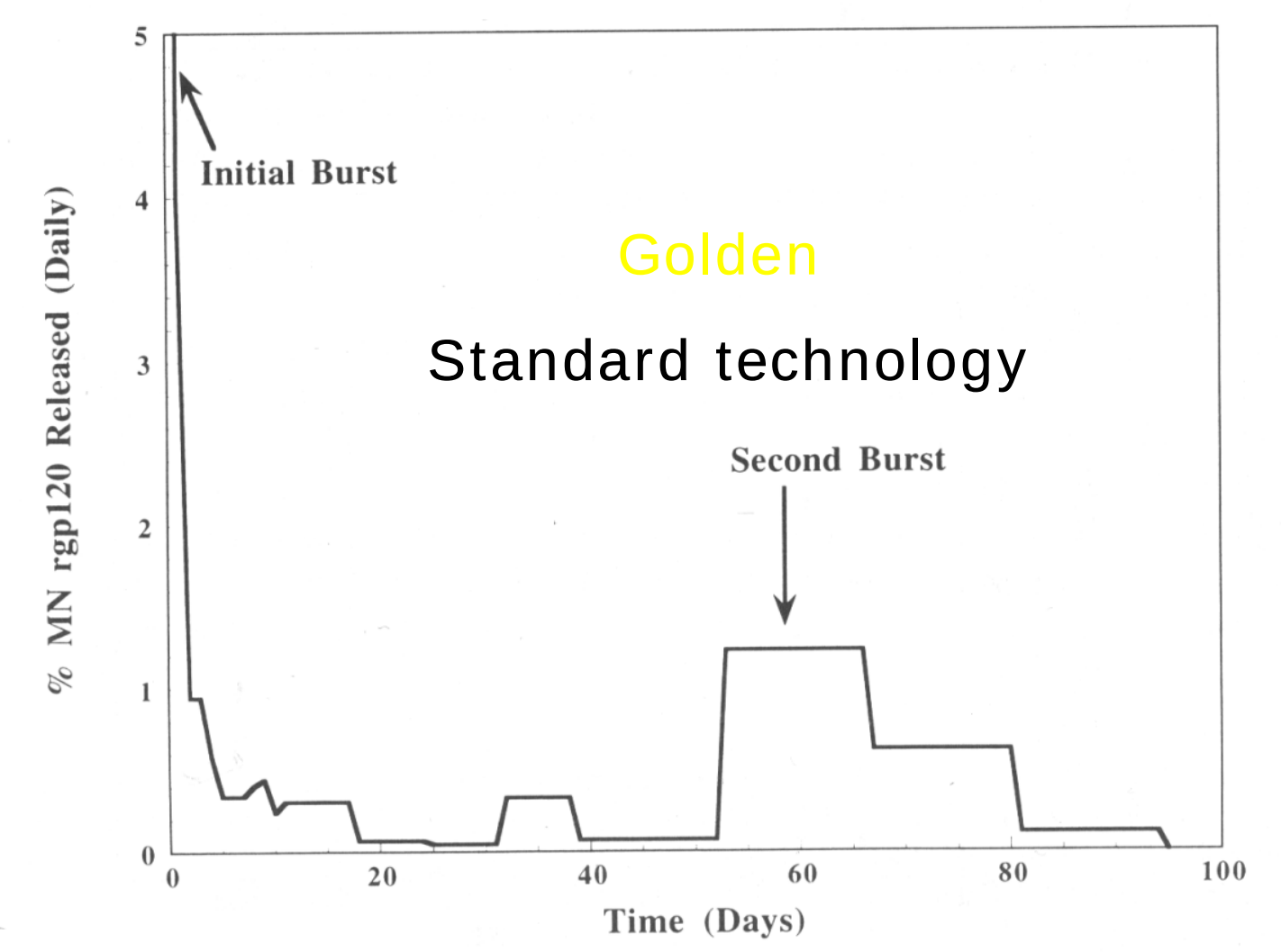
www.artrixlabs.com

In Vivo Protein Pharmacokinetics



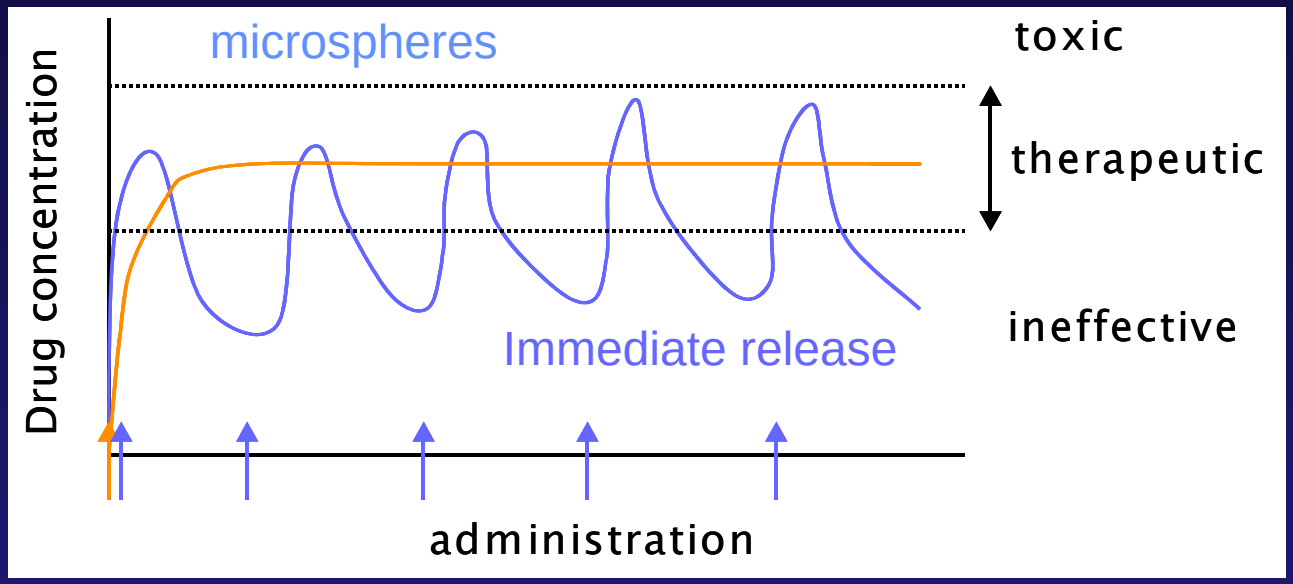
>10x reduction in injection volume
>10x reduction in "burst"

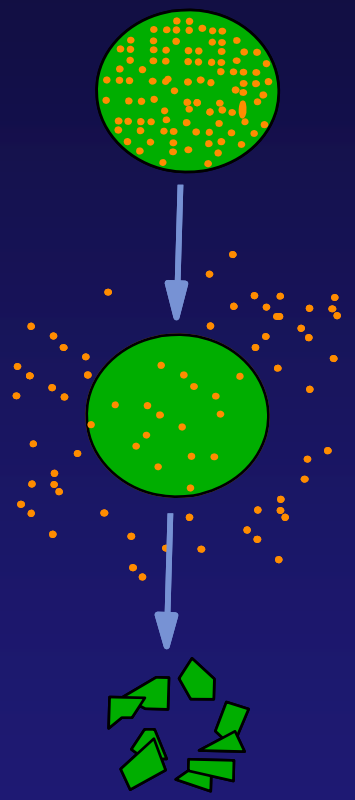
In vitro release of MN rgp120 from PLGA microspheres



From Cleland, 1997

Strategies for improved protein delivery



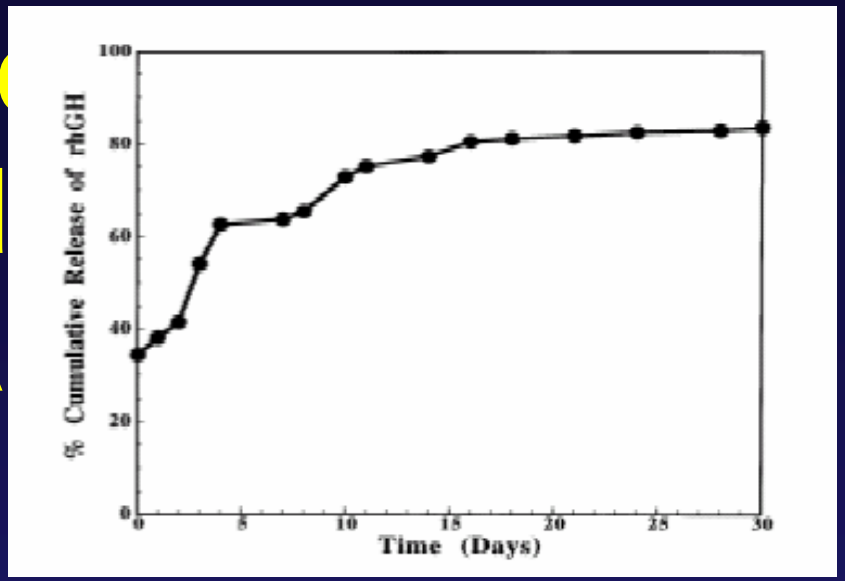


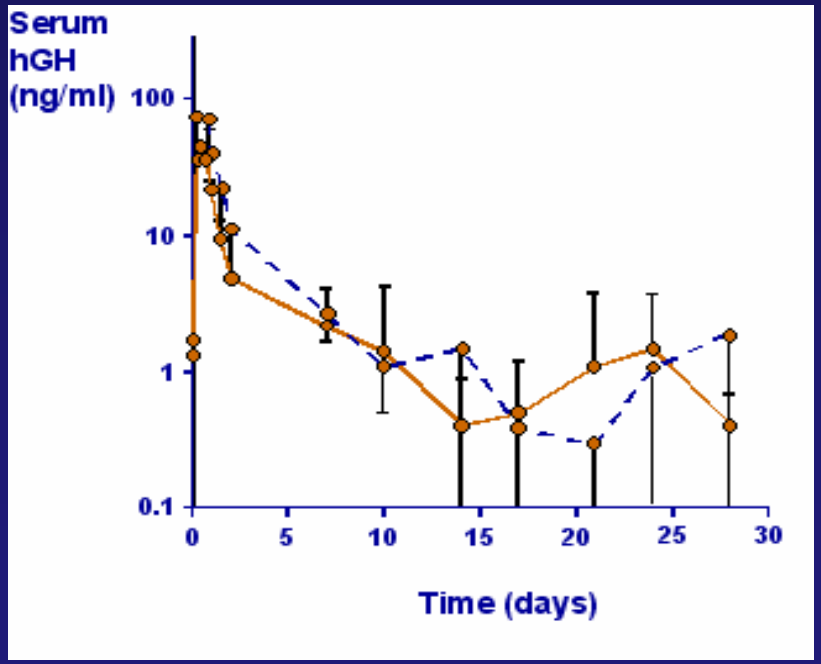
Approved microsphere products

- Lupron Depot, Trelstar Depot, Sandostatin LAR
- All based on PLGA

Biodegradable p
injectable d

- Most systems are based on PLGA
  - Drawbacks
    - Hydrophobic
    - Acid degradation products
    - Use of organic solvents
  - Consequences
    - Protein stability problems
    - Limited control over release kinetics
  - Strong need for improved protein delivery systems





Degradation…….

In vitro Release of rhGH from PLGA microspheres (research stage) during 30 days. Composition of the released protein

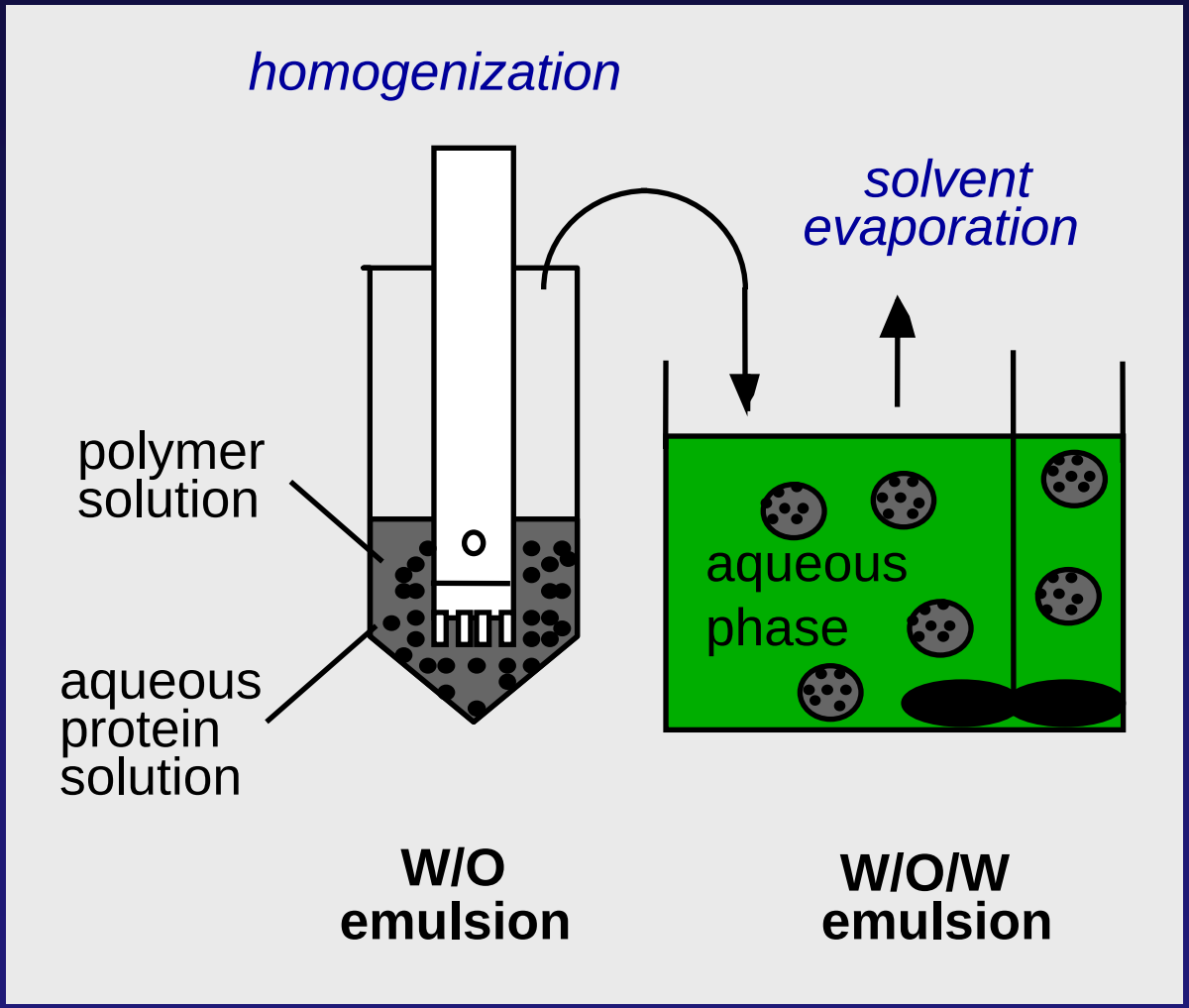
- Monomer 74%; Dimer 26%
- Non-oxidixed 82%
- Non-deamidated 35%

Cleland, Pharmaceutical Research

✚PolyActive™

- Implants in over 20,000 patients (as of 2003)
- Device Master File present

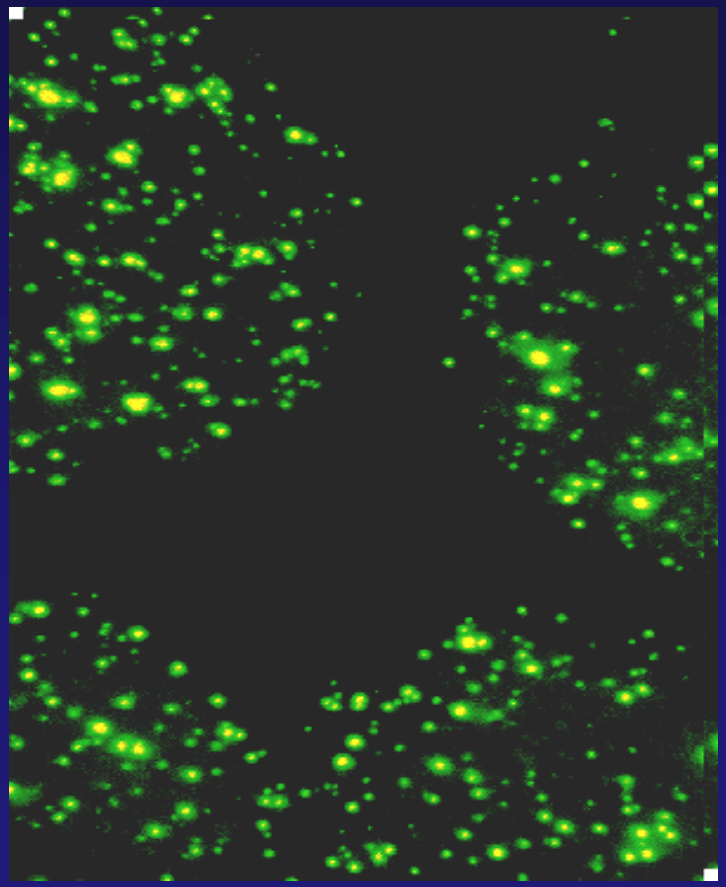
PolyActive™ Microspheres – Protein Incorporation



- Lab scale: 1-5 g
- Scaled-up to 50 –100 g
- Similar to well-established MS processes
- MS characteristics controlled by e.g. polymer type & concentration, stirring speed, aqueous phase.

PolyActive™ Microspheres Morphology

Distribution of FITC labeled lysozyme

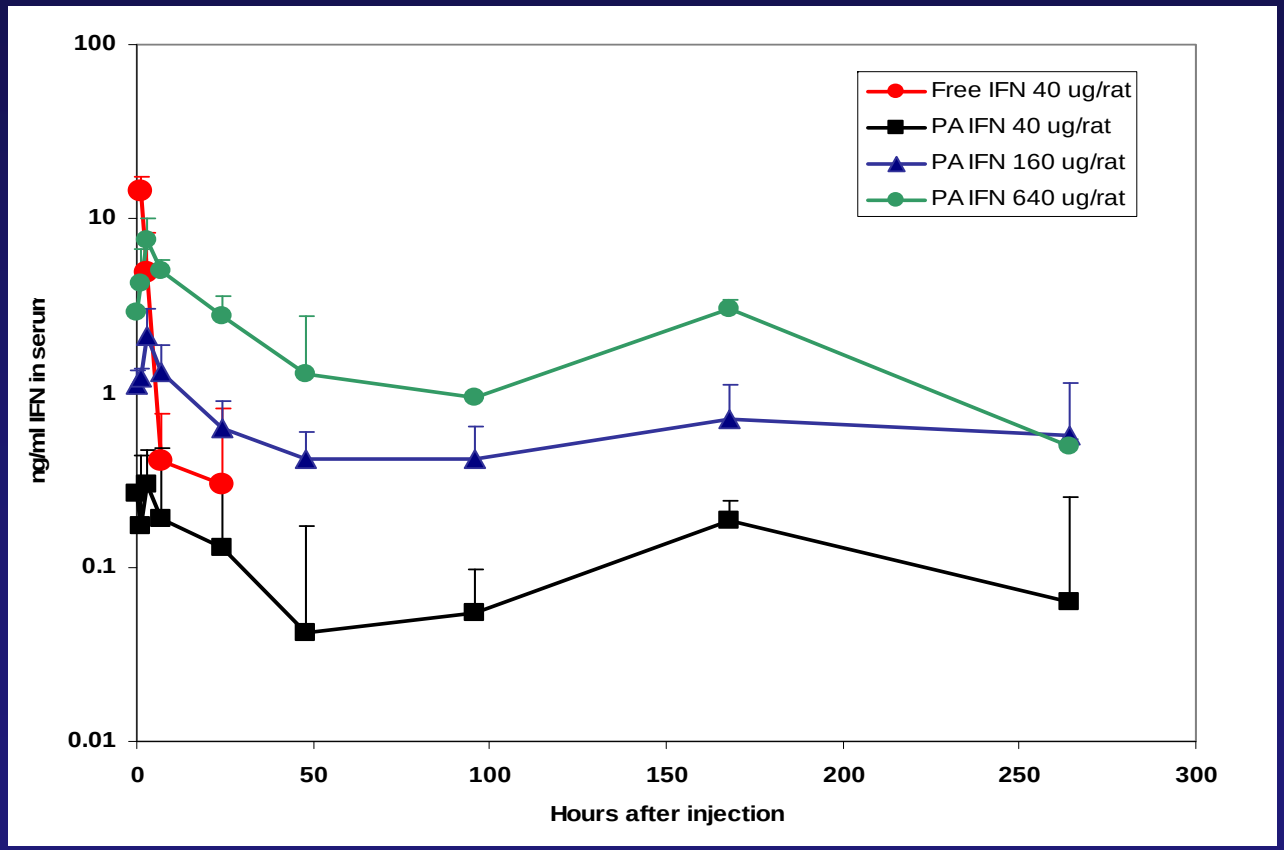


25 - 75 µm

In vivo release from PolyActive™ microspheres

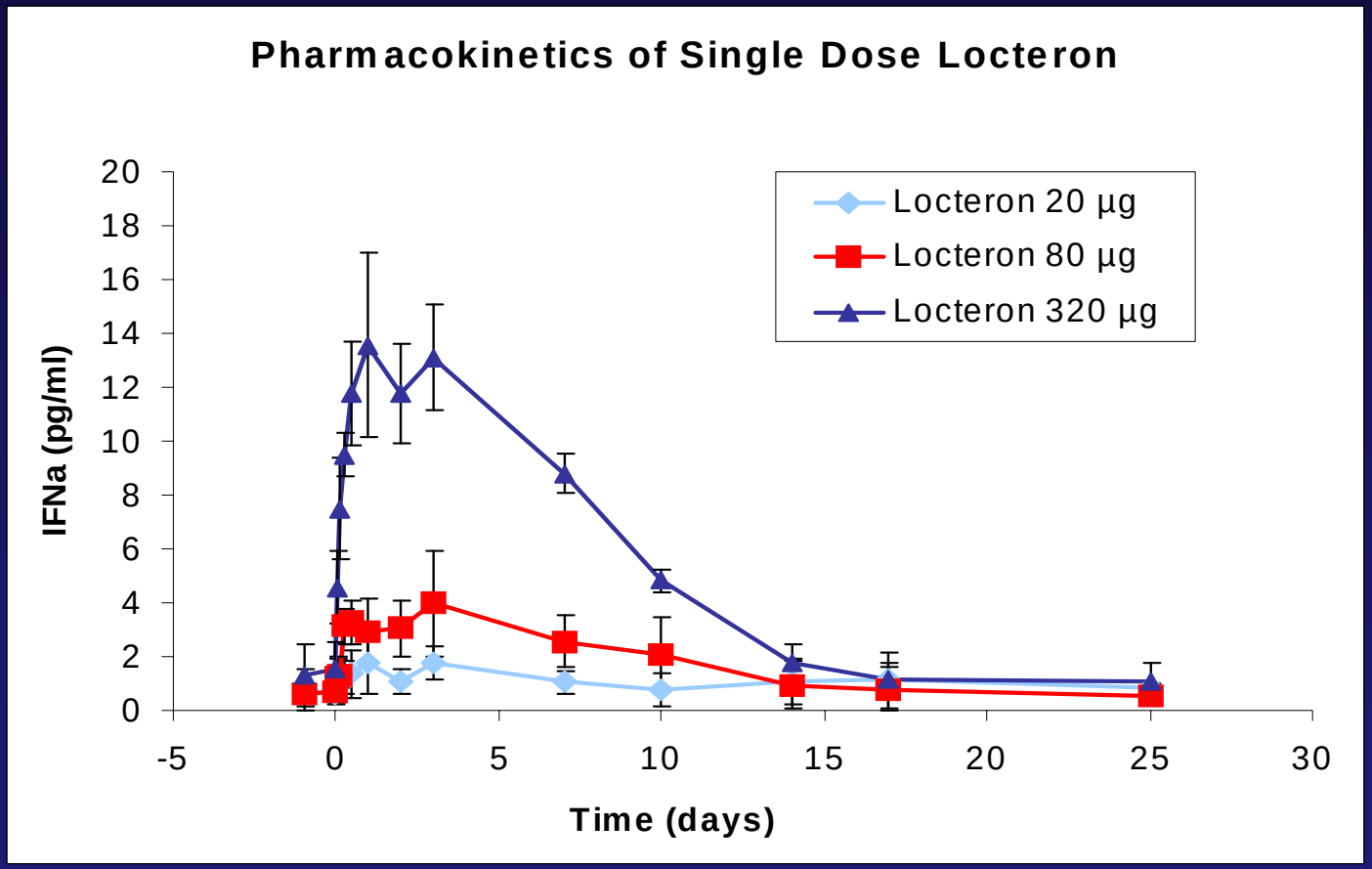
Release of IFN from PolyActive™ microspheres, SC injected in rats

Alfa-interferon

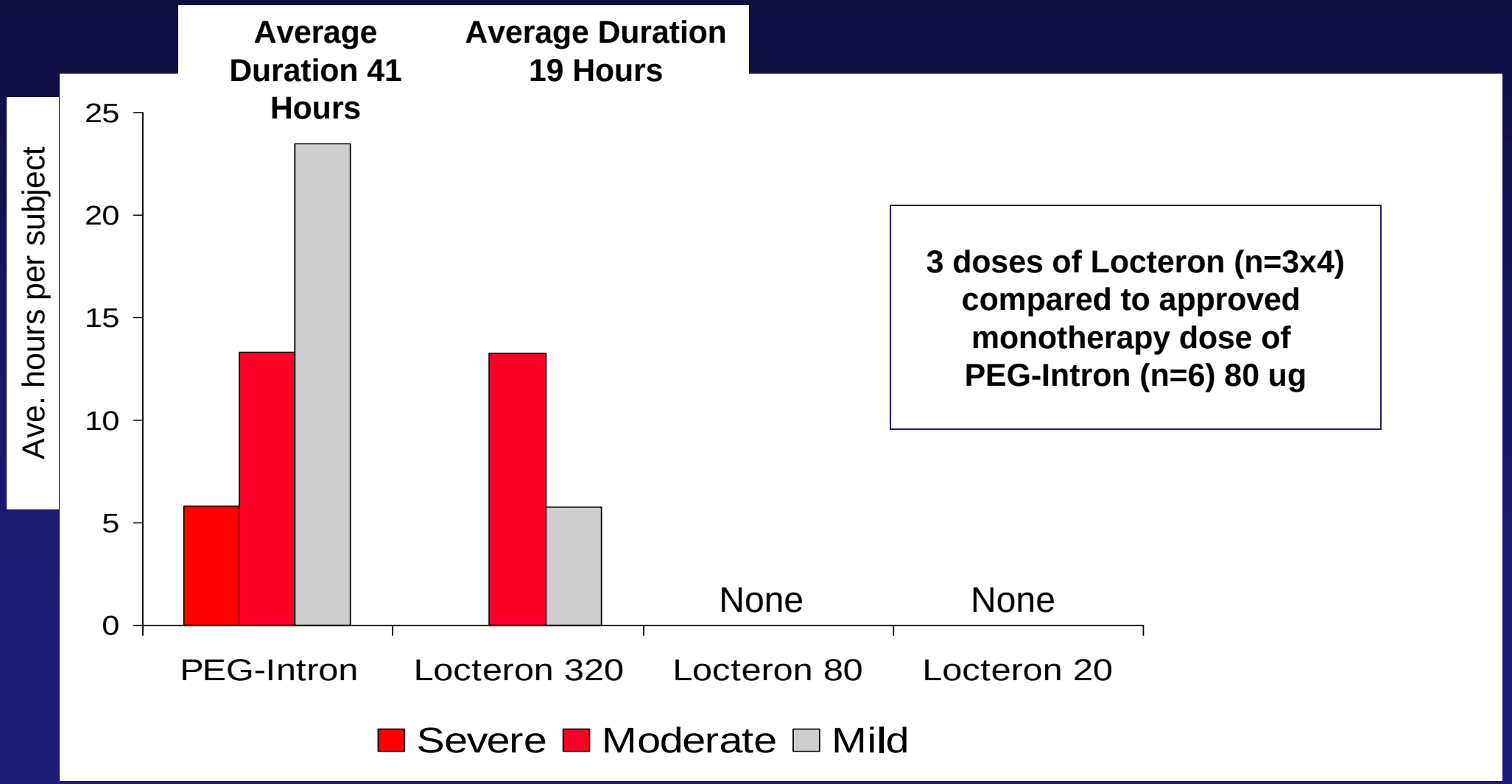


Pharm. Res 2005

Pharmacokinetics, safety and biomarkers in man after administration of LocteronTM, alfa-interferon MS, a once every 2 weeks controlled release formulation of IFNa2b (Q4, 2005)



Reduced flu-like symptoms in Locteron (alfa-interferon) groups



Conclusion re Locteron™

- Less side effects
- Dosing interval increased

- Efficacy?

Phase II clinical study started Jan 2007

First results published of 12 weeks treatment on July 26 2007

Log 4+ viral reduction (360 and 480 microgram) with microsphere delivered interferon alfa

Dextran-Based Hydrogel: *Alternative* to PLGA technology

Wim Hennink et al./UU/OctoPlus

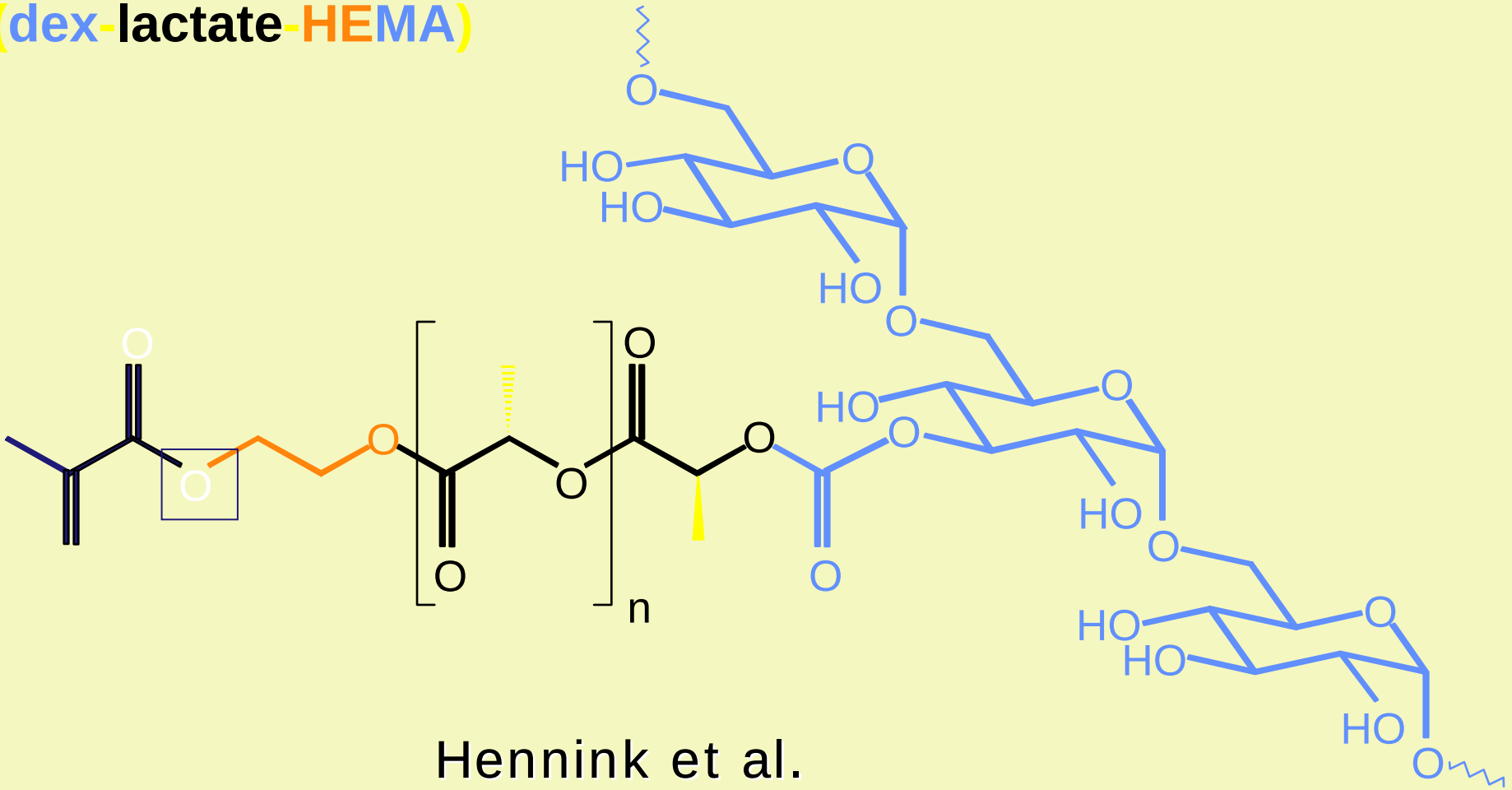
Why?

- **dextran: non-toxic; used as plasma expander**
- **hydrogel:**
  - **network of hydrophilic polymers**
  - **good compatibility with protein**
  - **possibilities to manipulate the release:**
    - **cross-link density of the hydrogel**
    - **degradation characteristics of the hydrogel**

Derivatized Dextran

Dextran-oligolactate-HydroxyEthyl Methacrylate

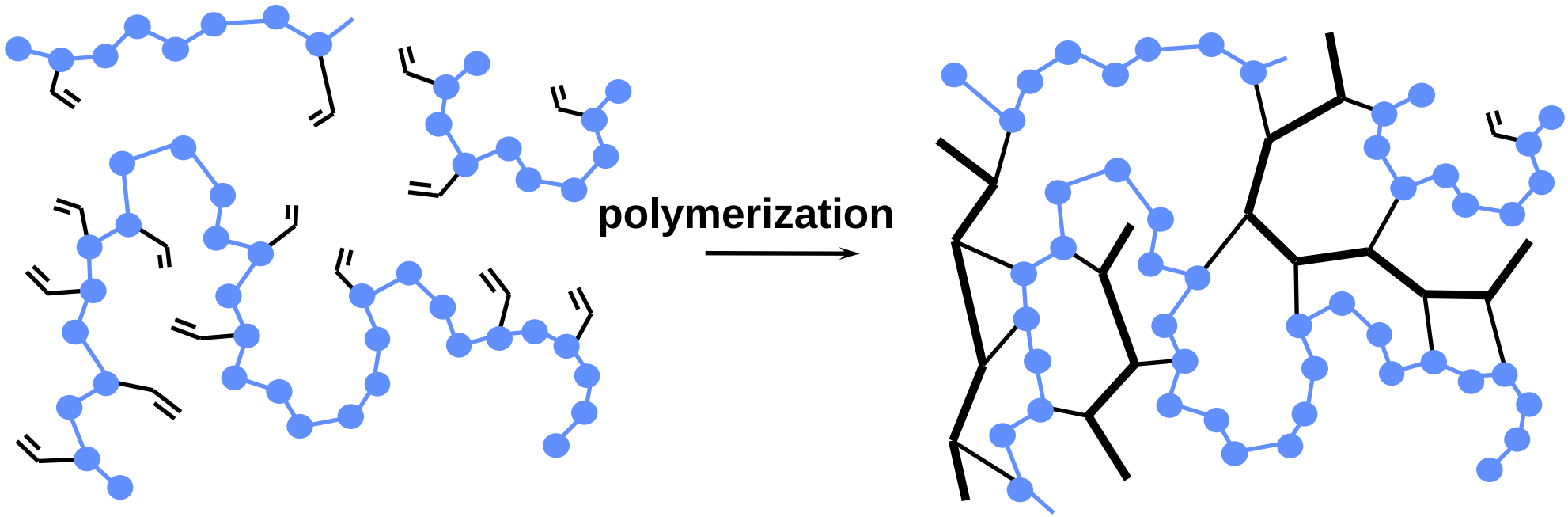
(dex-lactate-HEMA)



Hennink et al.

Dextran Hydrogel

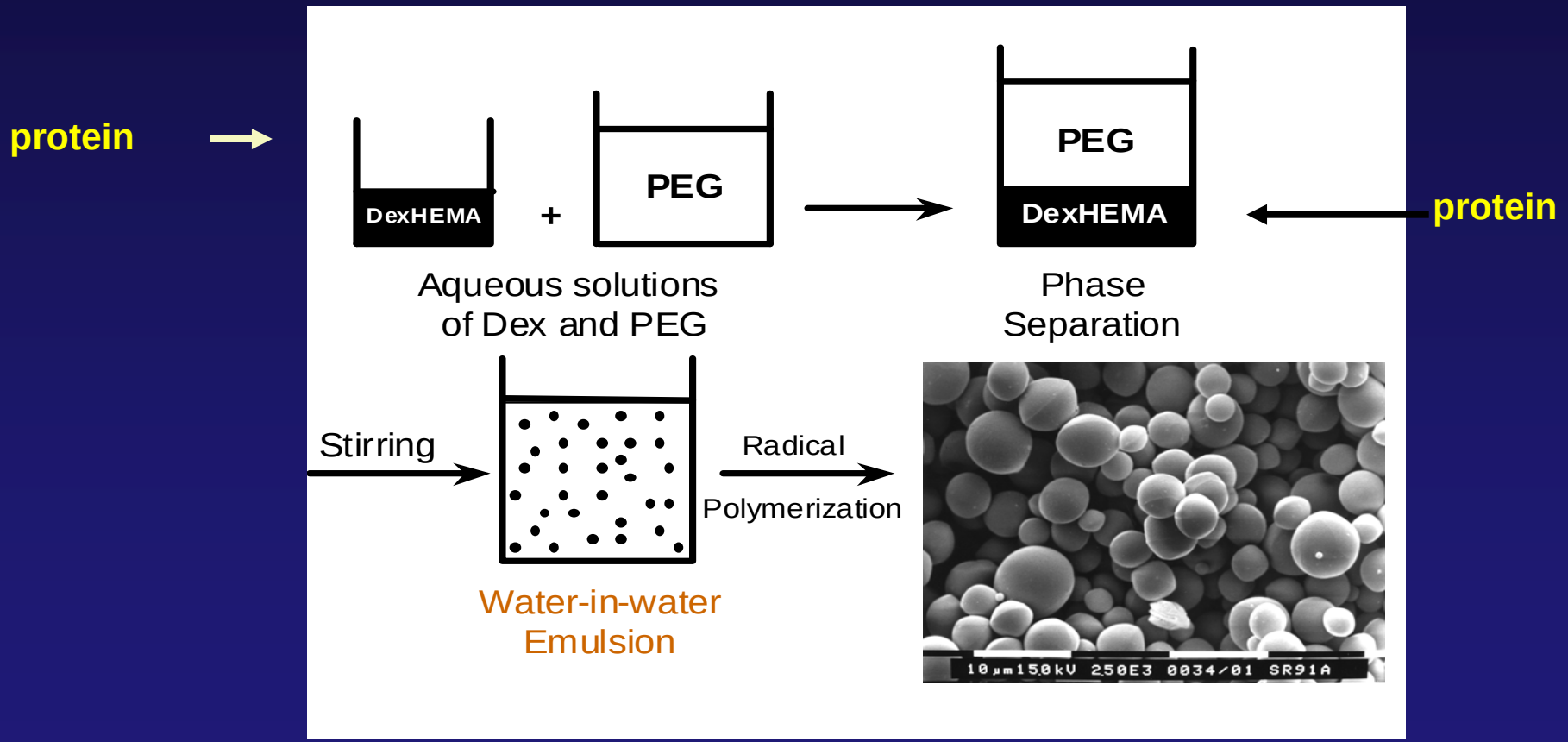
Hydrogel formation



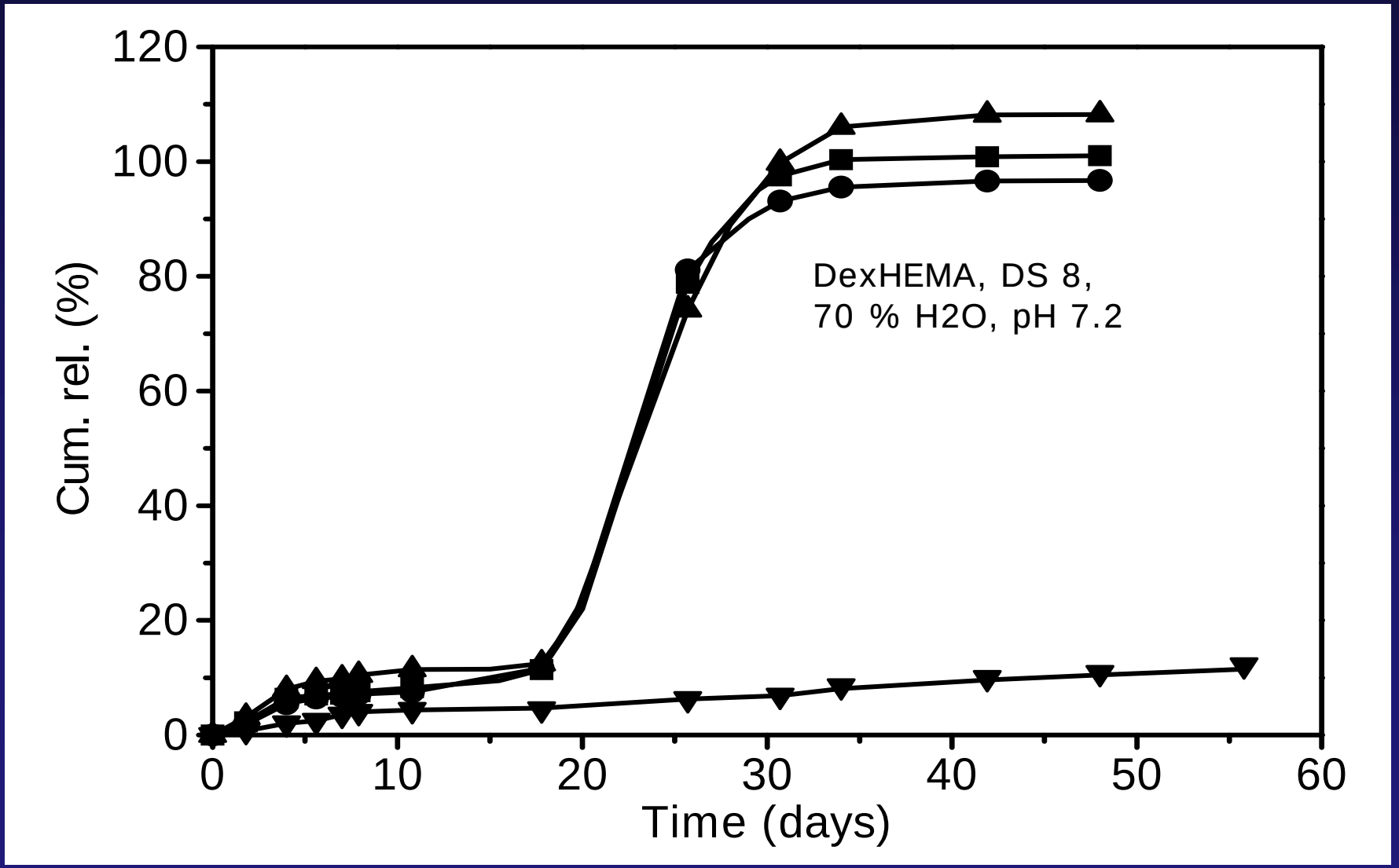
Hennink et al.

Cross-linked dextran-based microspheres

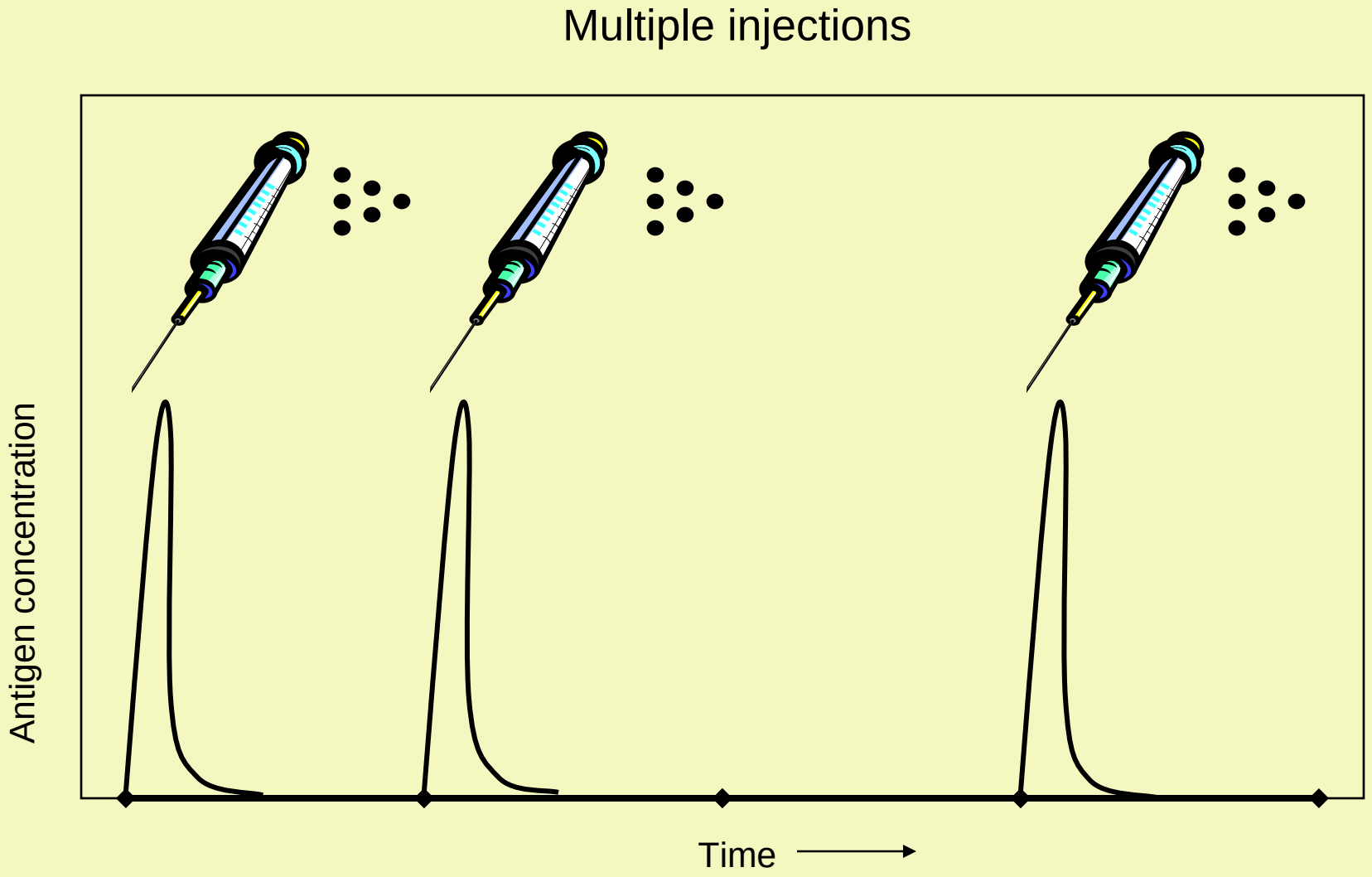
Schematic representation of the microsphere preparation process: ***NO ORGANIC SOLVENT***



Liposome Release from dextran microspheres

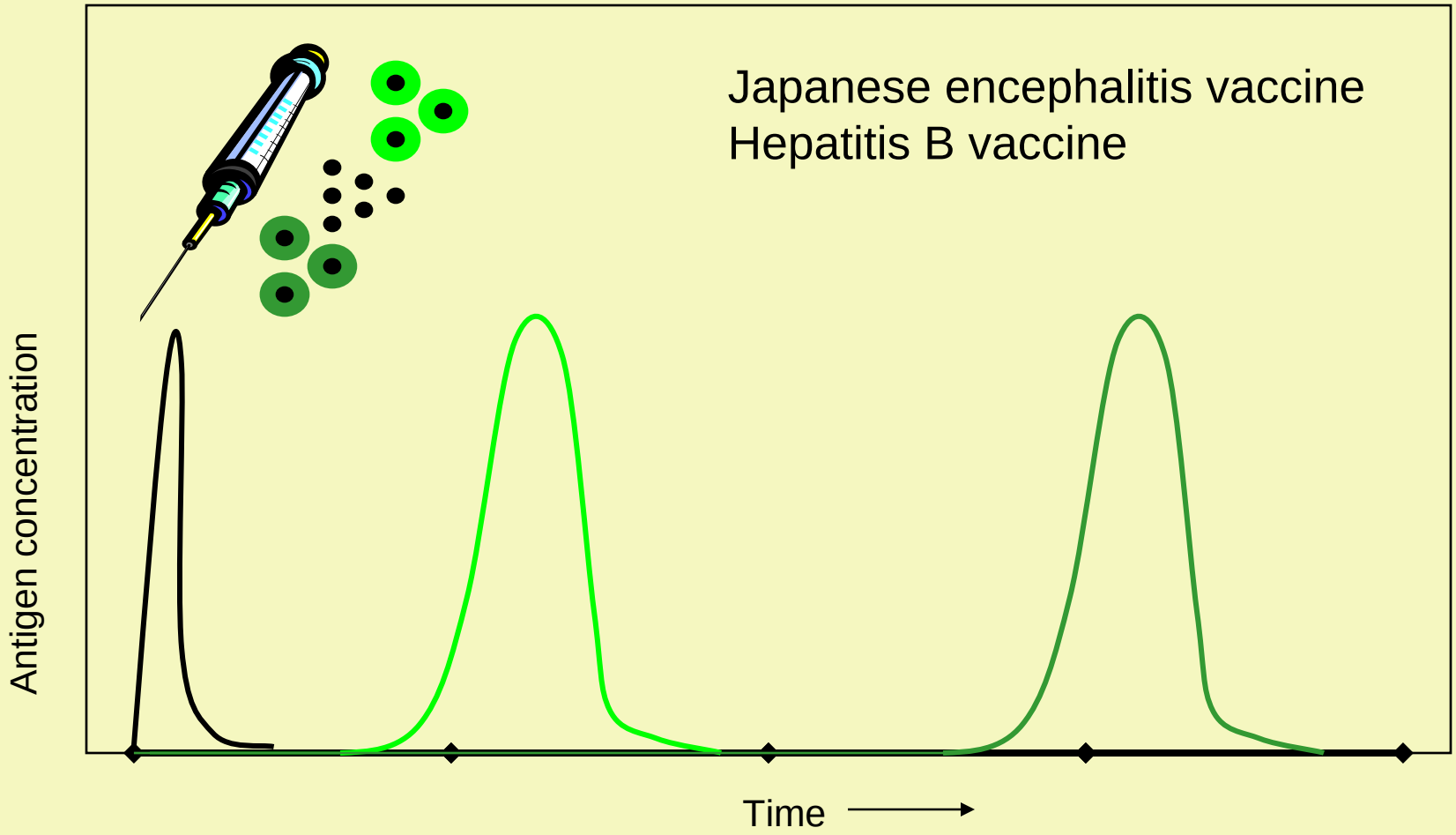


Conventional Vaccines:



Single Shot Vaccines with OctoDEX™

Combining a priming dose with controlled release microspheres



Why Parenteral *Depot* Formulations?

- Elimination half-life time is short
- Controlled release is required

Options are now becoming available