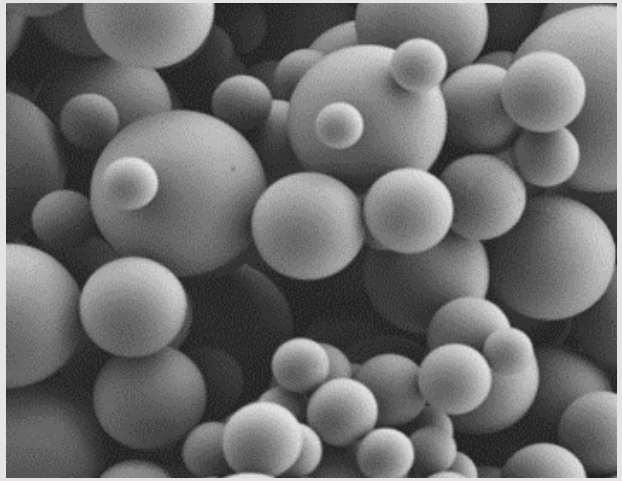
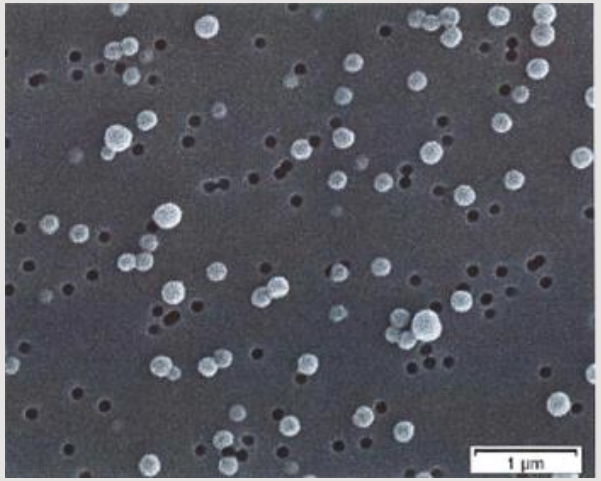
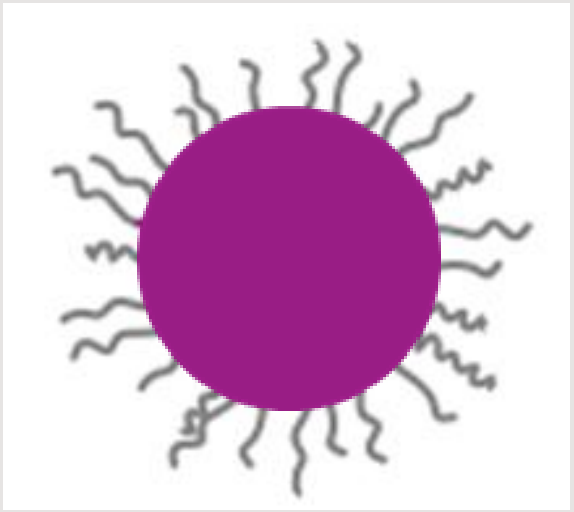
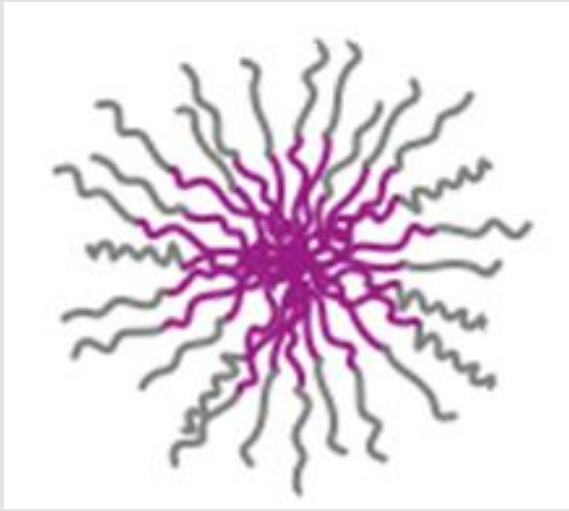
The Success of Long-Acting Injectable Microparticle Products Pave the Future for Bioabsorbable Nanoparticles









CHICAGOLAND PHARMACEUTICAL DISCUSSION GROUP
19 MAY 2023

Thomas Tice, PhD

Senior Director,
Global Strategic and Technical Marketing

Evonik Corporation
tom.tice@evonik.com

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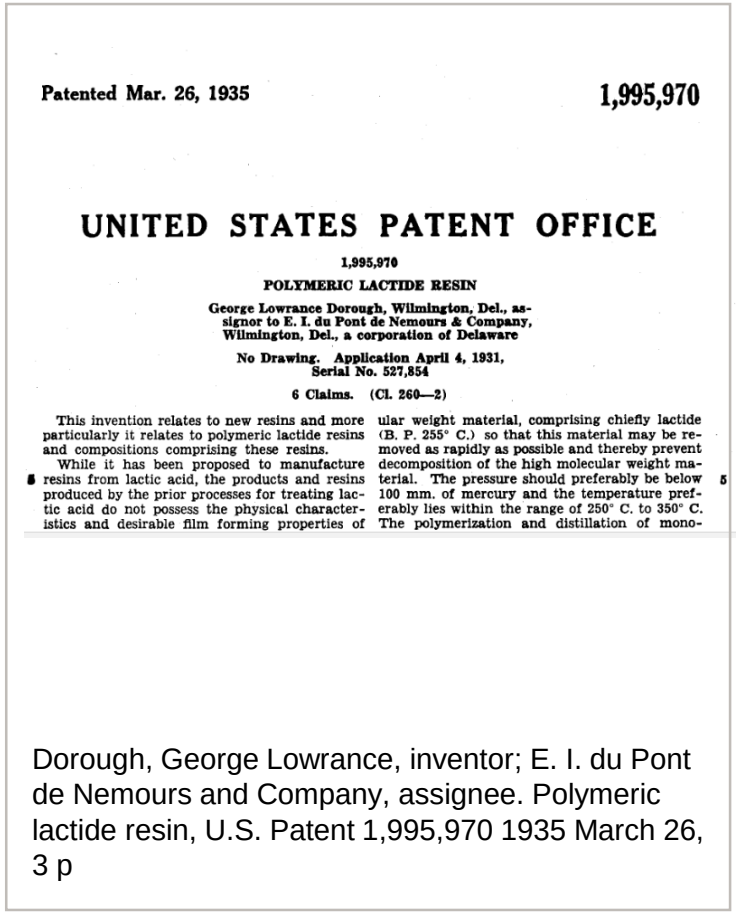
Early lactide/glycolide polymer (LG polymer) patents

First polymer patent in 1935. First drug delivery patent 1973.



Patented Mar. 26, 1935 1,995,970

UNITED STATES PATENT OFFICE

1,995,970

POLYMERIC LACTIDE RESIN

George Lowrance Dorough, Wilmington, Del., assignor to E. I. du Pont de Nemours & Company, Wilmington, Del., a corporation of Delaware

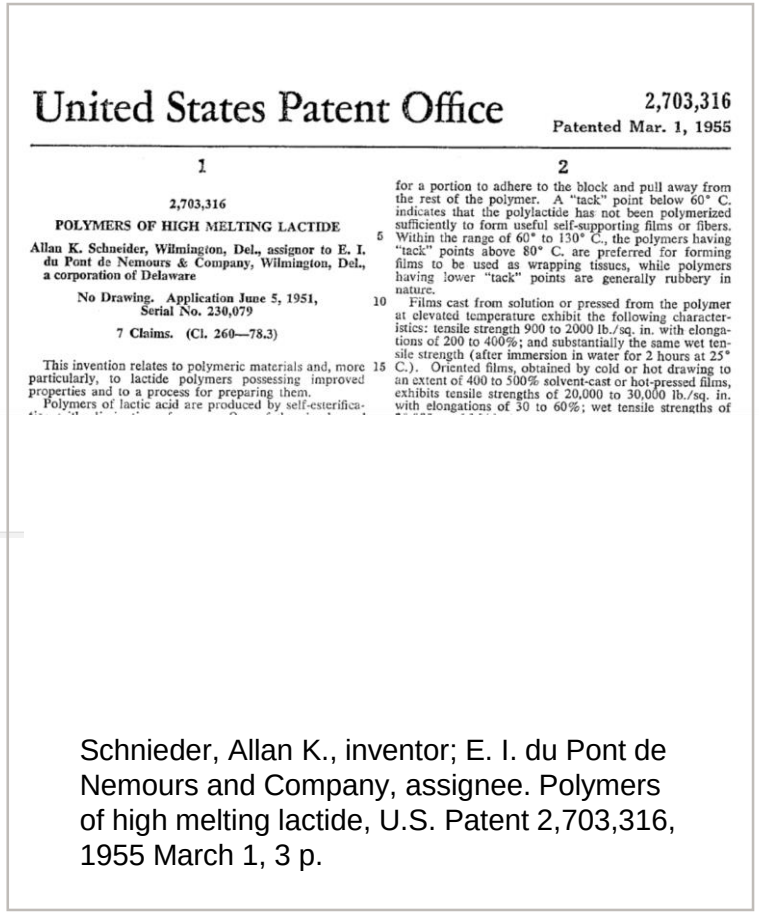
No Drawing. Application April 4, 1931, Serial No. 527,854

6 Claims. (Cl. 260—2)

This invention relates to new resins and more particularly it relates to polymeric lactide resins and compositions comprising these resins.

While it has been proposed to manufacture resins from lactic acid, the products and resins produced by the prior processes for treating lactic acid do not possess the physical characteristics and desirable film forming properties of ular weight material, comprising chiefly lactide (B. P. 255° C.) so that this material may be removed as rapidly as possible and thereby prevent decomposition of the high molecular weight material. The pressure should preferably be below 100 mm. of mercury and the temperature preferably lies within the range of 250° C. to 350° C. The polymerization and distillation of mono-

Dorough, George Lowrance, inventor; E. I. du Pont de Nemours and Company, assignee. Polymeric lactide resin, U.S. Patent 1,995,970 1935 March 26, 3 p



United States Patent Office 2,703,316 Patented Mar. 1, 1955

1

2,703,316

POLYMERS OF HIGH MELTING LACTIDE

Allan K. Schneider, Wilmington, Del., assignor to E. I. du Pont de Nemours & Company, Wilmington, Del., a corporation of Delaware

No Drawing. Application June 5, 1951, Serial No. 230,079

7 Claims. (Cl. 260—78.3)

This invention relates to polymeric materials and, more particularly, to lactide polymers possessing improved properties and to a process for preparing them.

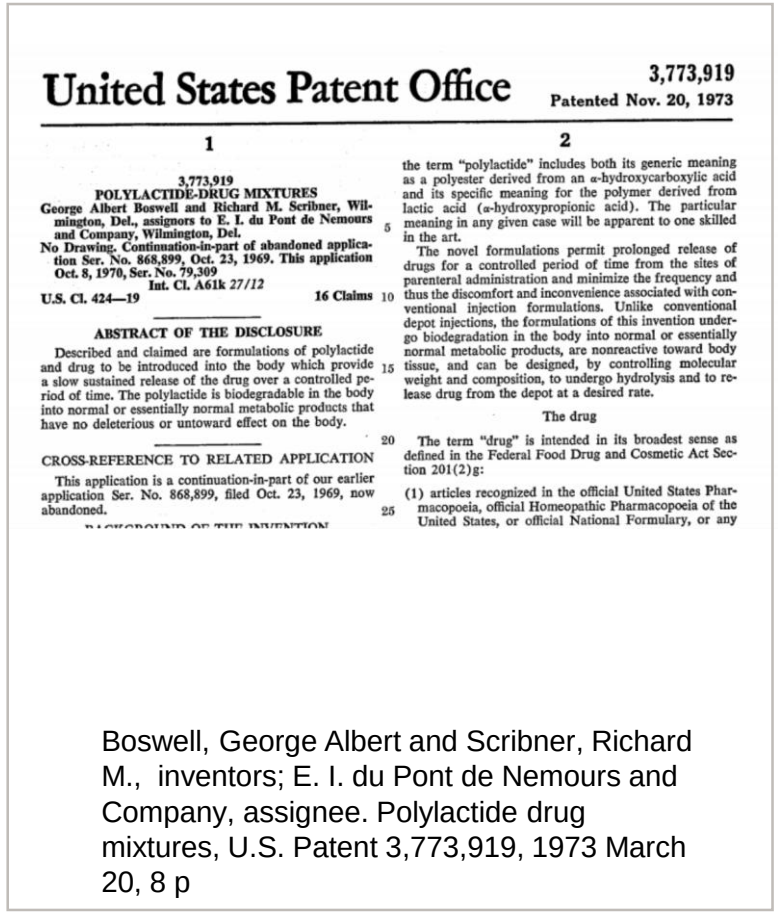
Polymers of lactic acid are produced by self-esterifica-

2

for a portion to adhere to the block and pull away from the rest of the polymer. A "tack" point below 60° C. indicates that the polylactide has not been polymerized sufficiently to form useful self-supporting films or fibers. Within the range of 60° to 130° C., the polymers having "tack" points above 80° C. are preferred for forming films to be used as wrapping tissues, while polymers having lower "tack" points are generally rubbery in nature.

Films cast from solution or pressed from the polymer at elevated temperature exhibit the following characteristics: tensile strength 900 to 2000 lb./sq. in. with elongations of 200 to 400%; and substantially the same wet tensile strength (after immersion in water for 2 hours at 25° C.). Oriented films, obtained by cold or hot drawing to an extent of 400 to 500% solvent-cast or hot-pressed films, exhibits tensile strengths of 20,000 to 30,000 lb./sq. in. with elongations of 30 to 60%; wet tensile strengths of

Schnieder, Allan K., inventor; E. I. du Pont de Nemours and Company, assignee. Polymers of high melting lactide, U.S. Patent 2,703,316, 1955 March 1, 3 p.



United States Patent Office 3,773,919 Patented Nov. 20, 1973

1

3,773,919

POLYLACTIDE-DRUG MIXTURES

George Albert Boswell and Richard M. Scribner, Wilmington, Del., assignors to E. I. du Pont de Nemours and Company, Wilmington, Del.

No Drawing. Continuation-in-part of abandoned application Ser. No. 868,899, Oct. 23, 1969. This application Oct. 8, 1970, Ser. No. 79,309

Int. Cl. A61k 27/12

U.S. Cl. 424—19 16 Claims

ABSTRACT OF THE DISCLOSURE

Described and claimed are formulations of polylactide and drug to be introduced into the body which provide a slow sustained release of the drug over a controlled period of time. The polylactide is biodegradable in the body into normal or essentially normal metabolic products that have no deleterious or untoward effect on the body.

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of our earlier application Ser. No. 868,899, filed Oct. 23, 1969, now abandoned.

2

the term "polylactide" includes both its generic meaning as a polyester derived from an α-hydroxycarboxylic acid and its specific meaning for the polymer derived from lactic acid (α-hydroxypropionic acid). The particular meaning in any given case will be apparent to one skilled in the art.

The novel formulations permit prolonged release of drugs for a controlled period of time from the sites of parenteral administration and minimize the frequency and thus the discomfort and inconvenience associated with conventional injection formulations. Unlike conventional depot injections, the formulations of this invention undergo biodegradation in the body into normal or essentially normal metabolic products, are nonreactive toward body tissue, and can be designed, by controlling molecular weight and composition, to undergo hydrolysis and to release drug from the depot at a desired rate.

The drug

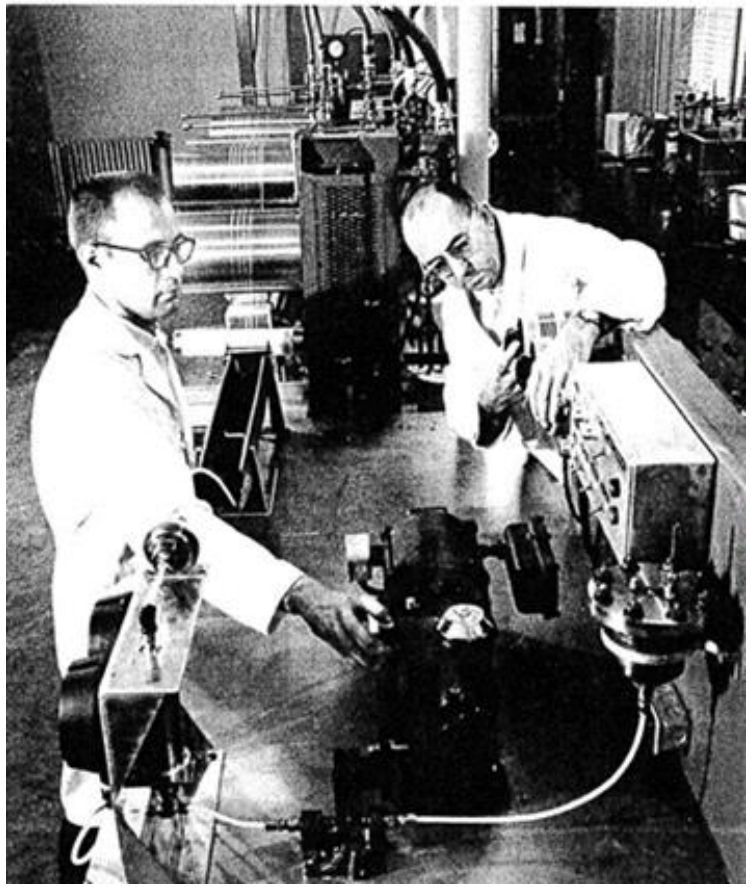
The term "drug" is intended in its broadest sense as defined in the Federal Food Drug and Cosmetic Act Section 201(2)g:

(1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any

Boswell, George Albert and Scribner, Richard M., inventors; E. I. du Pont de Nemours and Company, assignee. Polylactide drug mixtures, U.S. Patent 3,773,919, 1973 March 20, 8 p

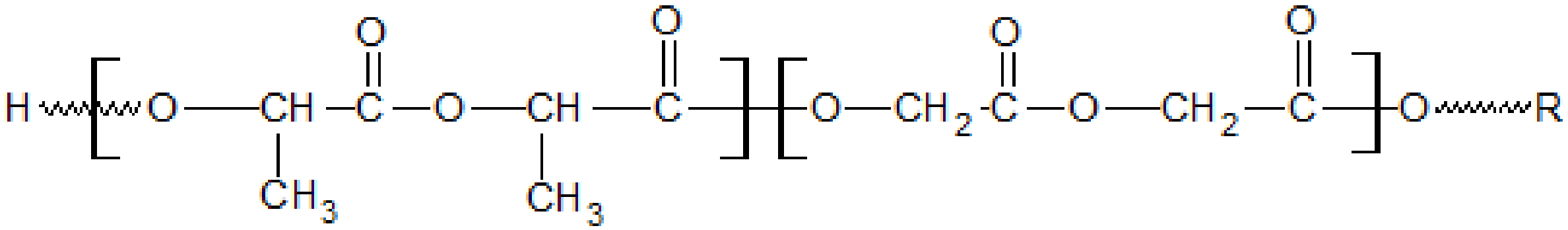
Developers of the first bioabsorbable suture (polyglycolide suture)

W. Curtis Stoner, Jr., A. C. Tanquary, R. B. Perkins



Poly(lactide-co-glycolide) parenteral functional excipients

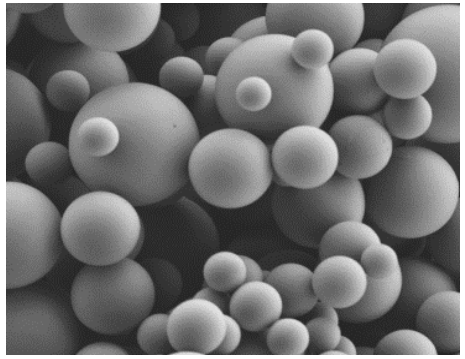
LG polymers



- Over 60 drug delivery products on the market worldwide
- Multiple medical devices on the market
- Excellent safety record – medical device and drug delivery products
- Polymer synthesis can tune physical and chemical properties for formulation processing and drug release
- LG polymers have many inherent properties that facilitate parenteral drug delivery
- Biocompatible and bioabsorbable
- Excellent commercial supply of GMP polymers

Polymeric bioabsorbable complex parenteral products made with LG polymers

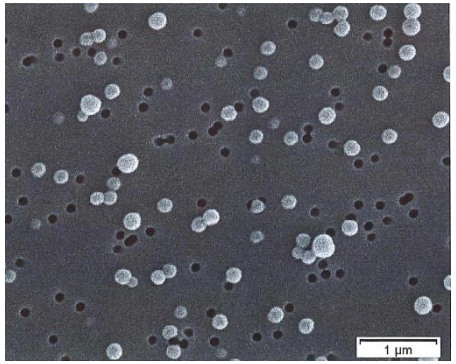
Microparticles

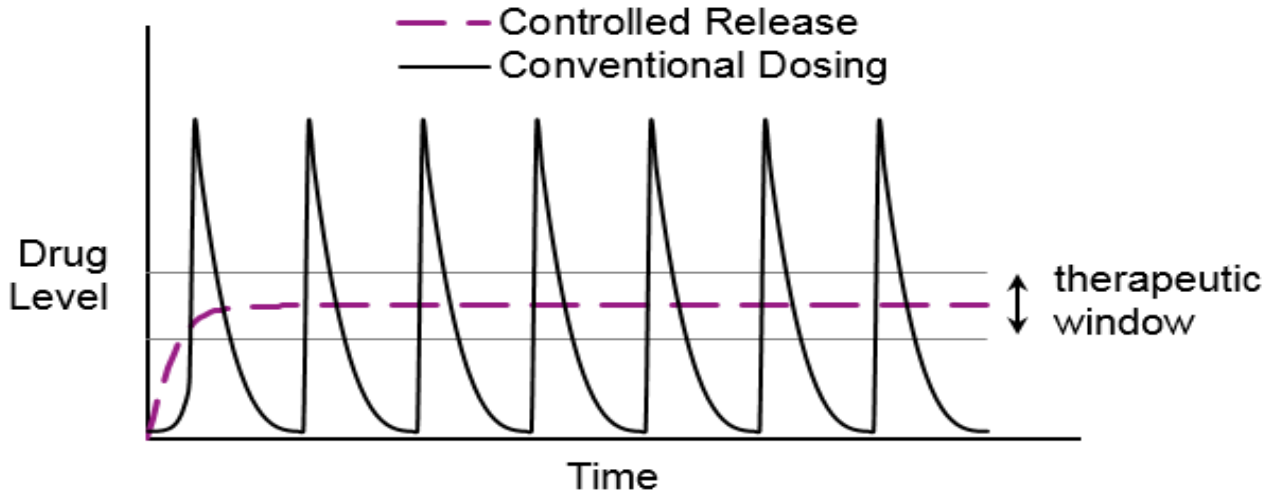


Implants

In-Situ Forming

Nanoparticles





Systemic delivery

- Efficacious plasma levels

Local delivery

- Knee
- Ocular
- Sinus

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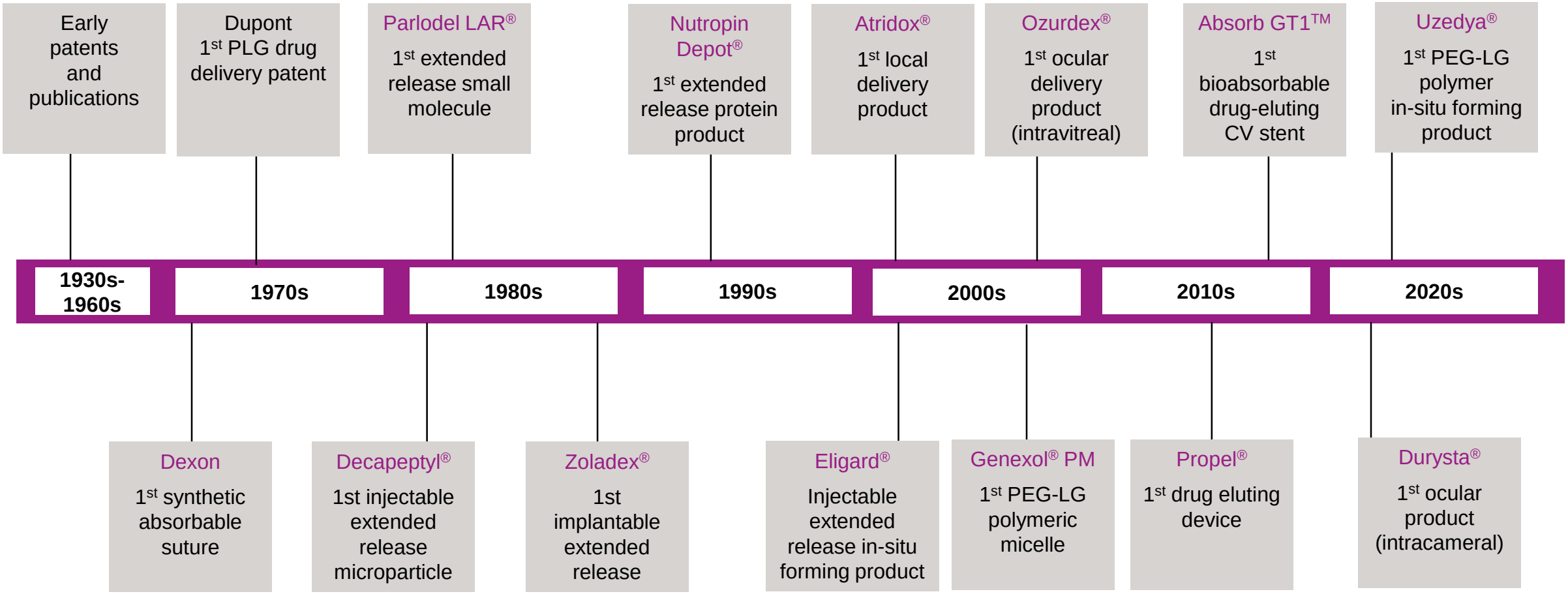
Milestones for drug delivery products made with LG polymers



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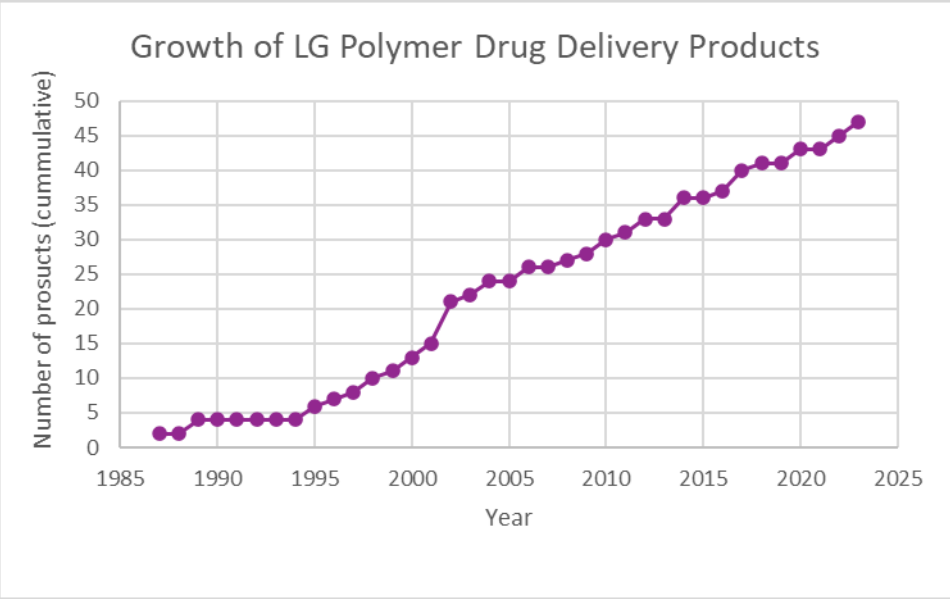
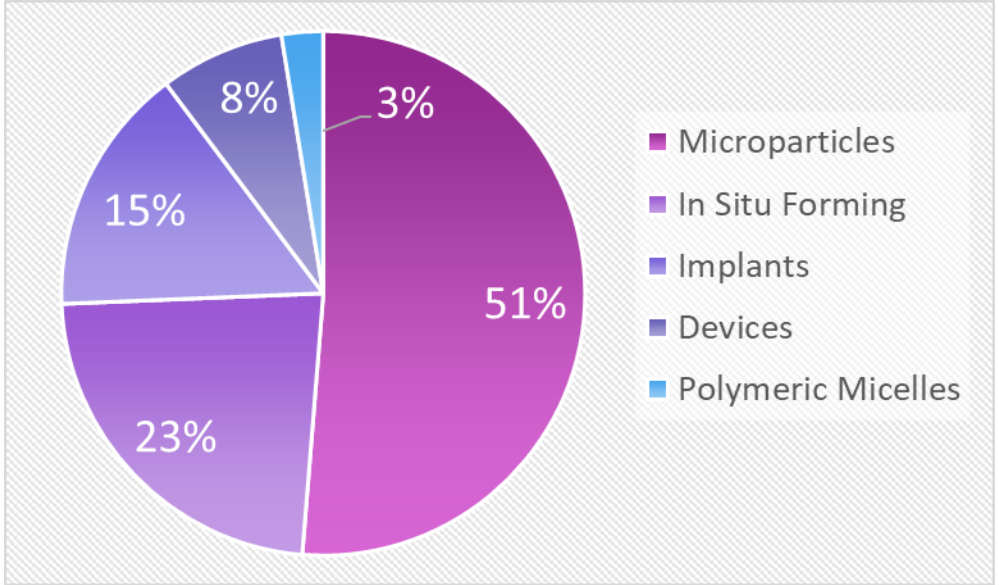
Market growth of LG polymer drug delivery products





Based on available product launch dates in major markets

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Complex parenteral products made with LG polymers
Extended-release microparticle and implant products

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www.goodrx.com

www.vivotrol.com


www.virbac.co.nz

www.janssencns.com

www.zilrettapro.com

www.trelstar.com

www.samyangbiopharm.com

www.allergan.com

www.orapharma.com

www.webmd.com

www.drugs.com

www.preciolandia.com

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Classes of drugs in LG polymer long-acting products

Peptides
Dosing 2 - 100 mg

- **Luteinizing hormone releasing hormone (LHRH)**
  - Prostate cancer
  - Endometriosis
  - Precocious puberty
- **Somatostatin**
  - Acromegaly
  - Carcinoid cancer
- **Glucagon-like peptide (GLP1)**
  - Type 2 diabetes
- **α-Melanocyte-stimulating hormone (αMSH)**
  - Erythopoietic protoporphyria

Small Molecules
Dosing 10 µg - 500 mg

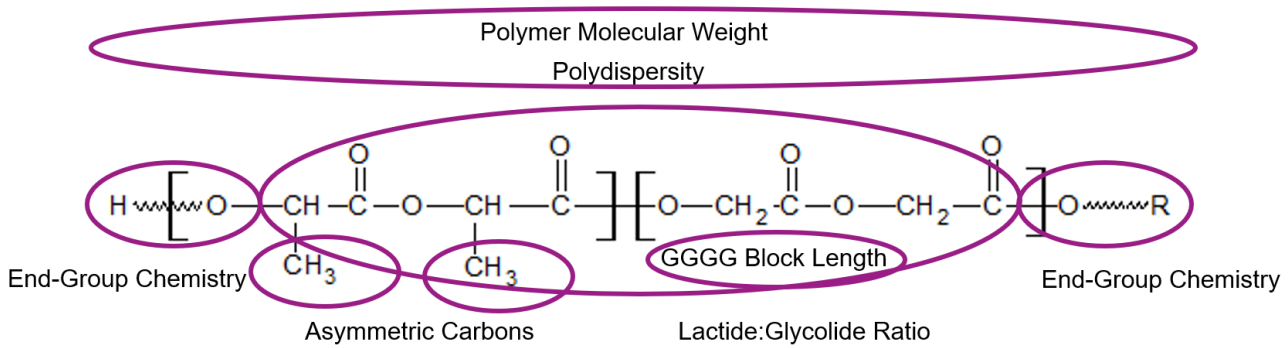
- Steroid
- Atypical antipsychotic
- Opioid antagonist
- Partial opioid agonist
- Antibiotic
- Dopamine agonist
- Antineoplastic
- Kinase inhibitor
- Prostaglandin
- Macrocyclic lactone endectocide
- Vitamin
- Mineral

Proteins
Dosing 22.5 mg

- Somatropin

LG polymer properties are tunable to achieve drug delivery performance

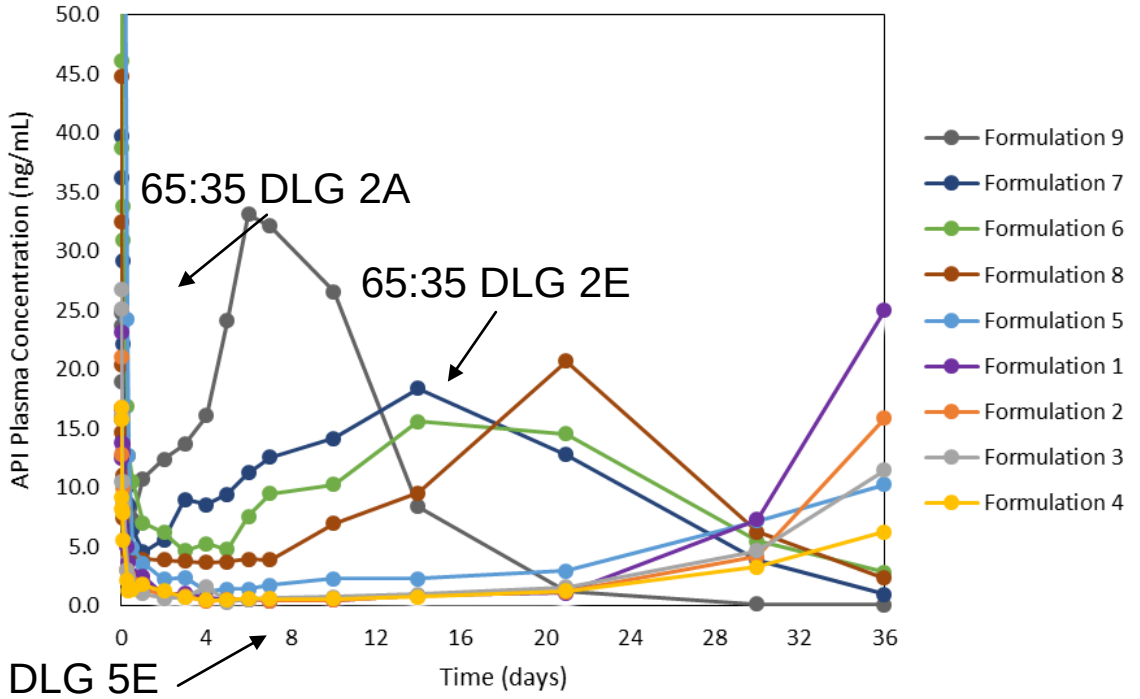
- Lactide/glycolide mole ratio
- Molecular weight
- Molecular weight distribution
- End-group chemistry
- Glass transition temperature
- Solvent solubility
- Drug solubility in polymer solution
- Polymer crystallinity (DL and L)
- GGGG block length
- Polymer purity (fit for purpose)
- Chain scission by e-beam and gamma radiation



Developing long-acting microparticle formulations by tuning LG polymer properties

Tune polymer molecular weight and end-groups
Based on formulations with standard polymers, synthesize select polymers with desired properties

Lot #	Theoretical Drug Loading (wt. %)	Polymer	Polymer Concentration (wt. %)
Formulation 1	22	65:35 DLG 5E	25
Formulation 2	30	65:35 DLG 5E	25
Formulation 3	35	65:35 DLG 5E	25
Formulation 4	30	65:35 DLG 5E	30
Formulation 5	40	65:35 DLG 5E	30
Formulation 6	22	65:35 DLG 2E	30
Formulation 7	40	65:35 DLG 2E	30
Formulation 8	30	65:35 DLG 2E	35
Formulation 9	30	65:35 DLG 2A	30



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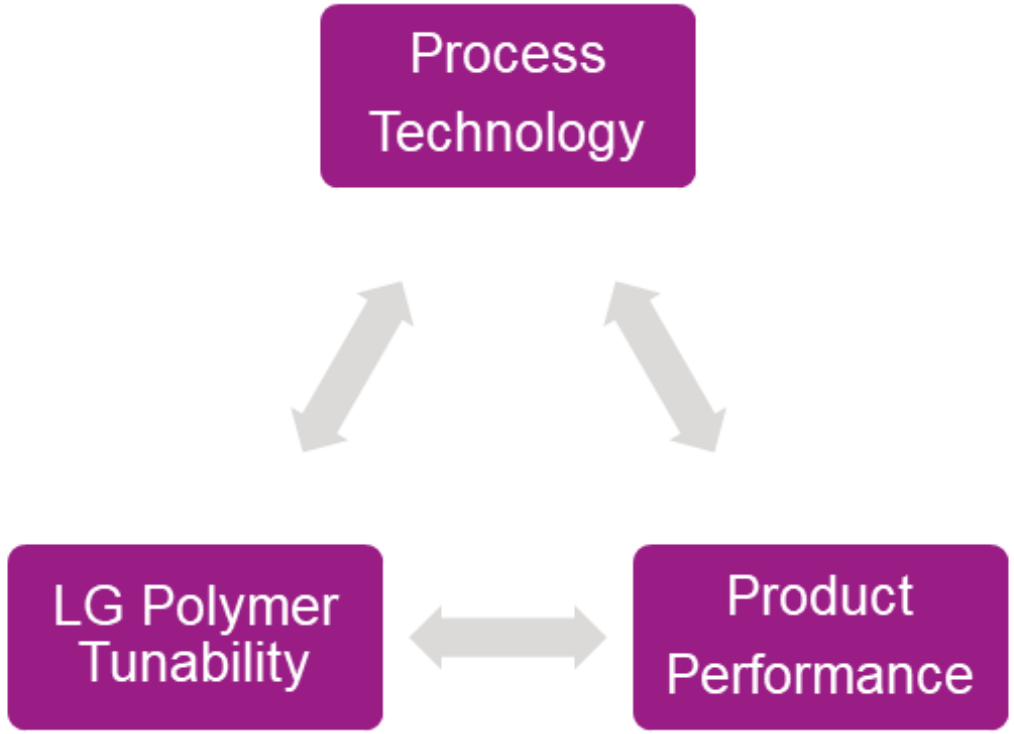
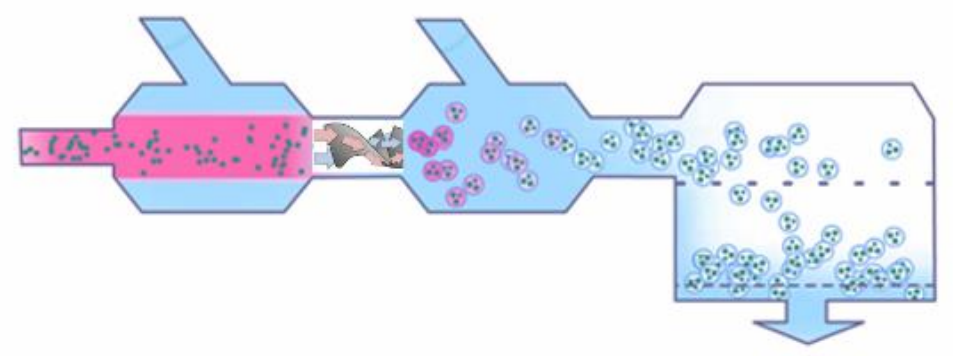
LG Polymer Microparticles

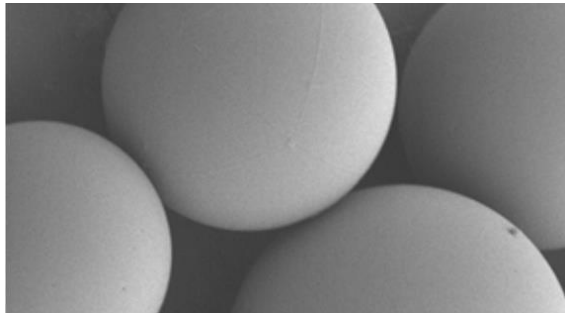
Developing LG polymer drug products
Product-by-process manufacturing



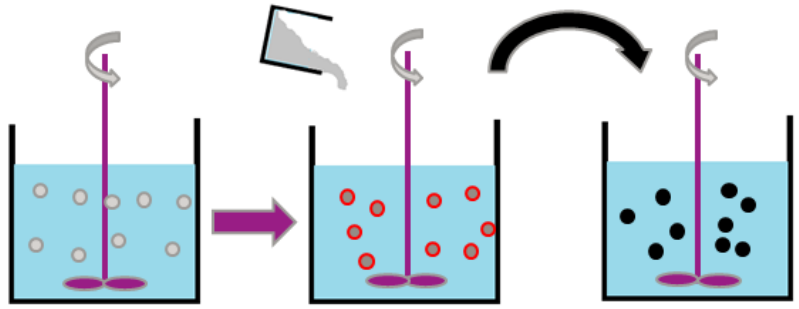
Microencapsulation process
Product by process

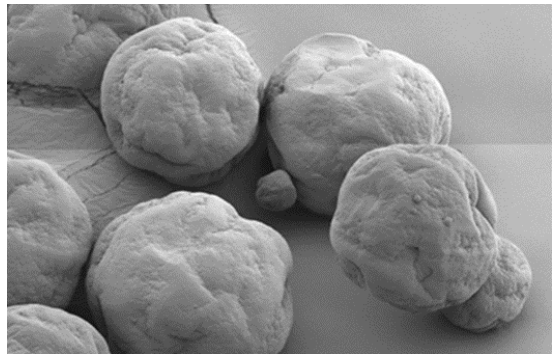
Solvent Extraction





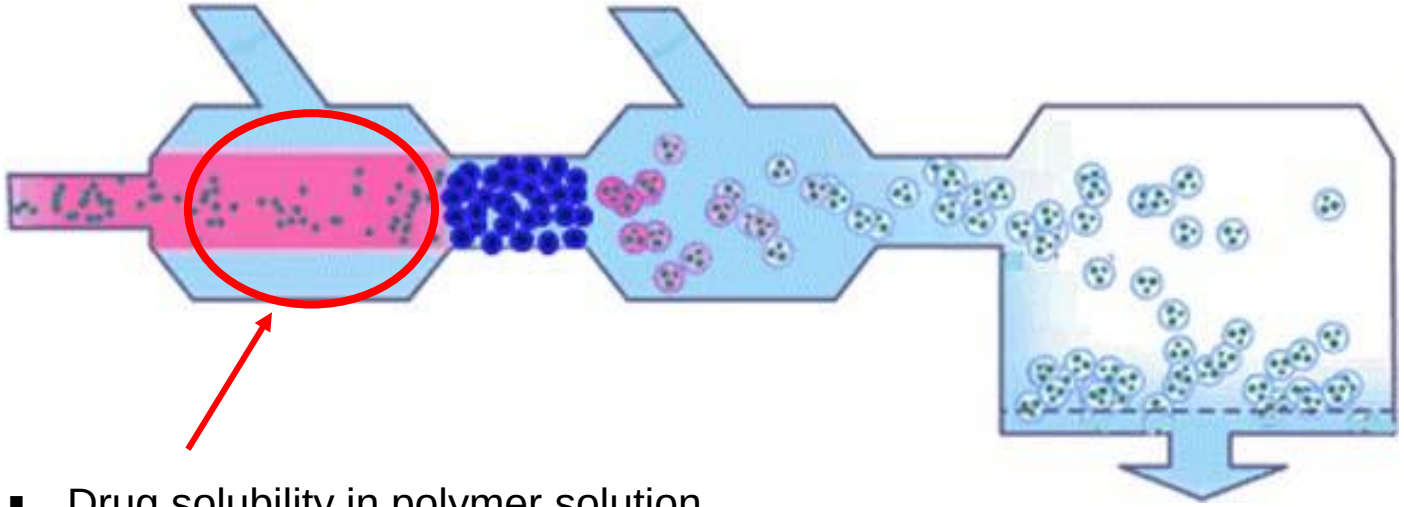
Phase Separation

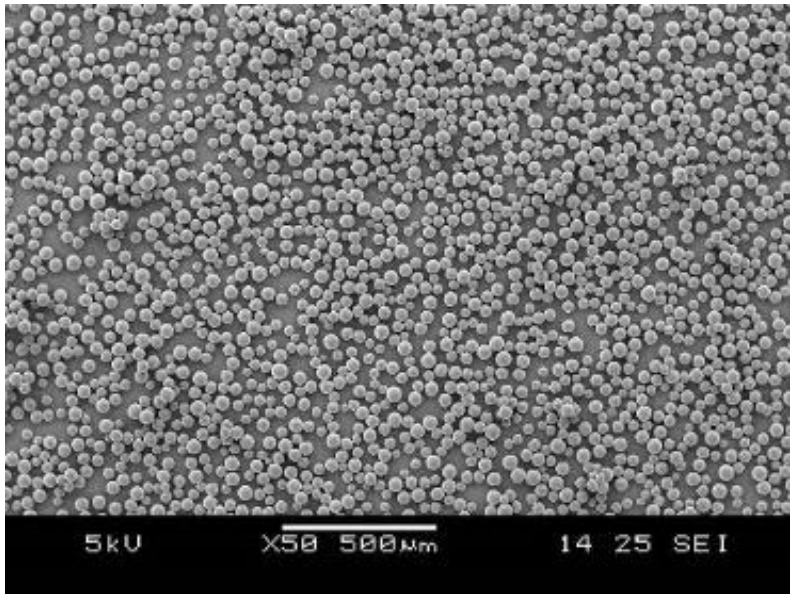




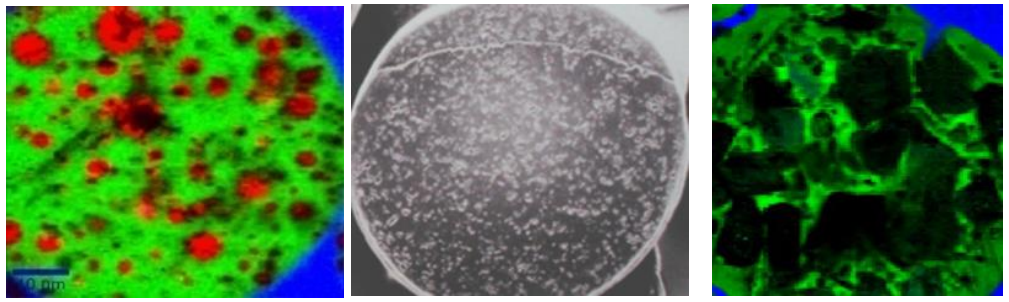
Drug properties for microencapsulation

Drug Polymer Polymer Solvent	Water Surfactant	Emulsion formation	Extraction of polymer solvent	Isolate and dry





- Drug solubility in polymer solution
- Drug water solubility for double emulsion
- Drug chemical stability



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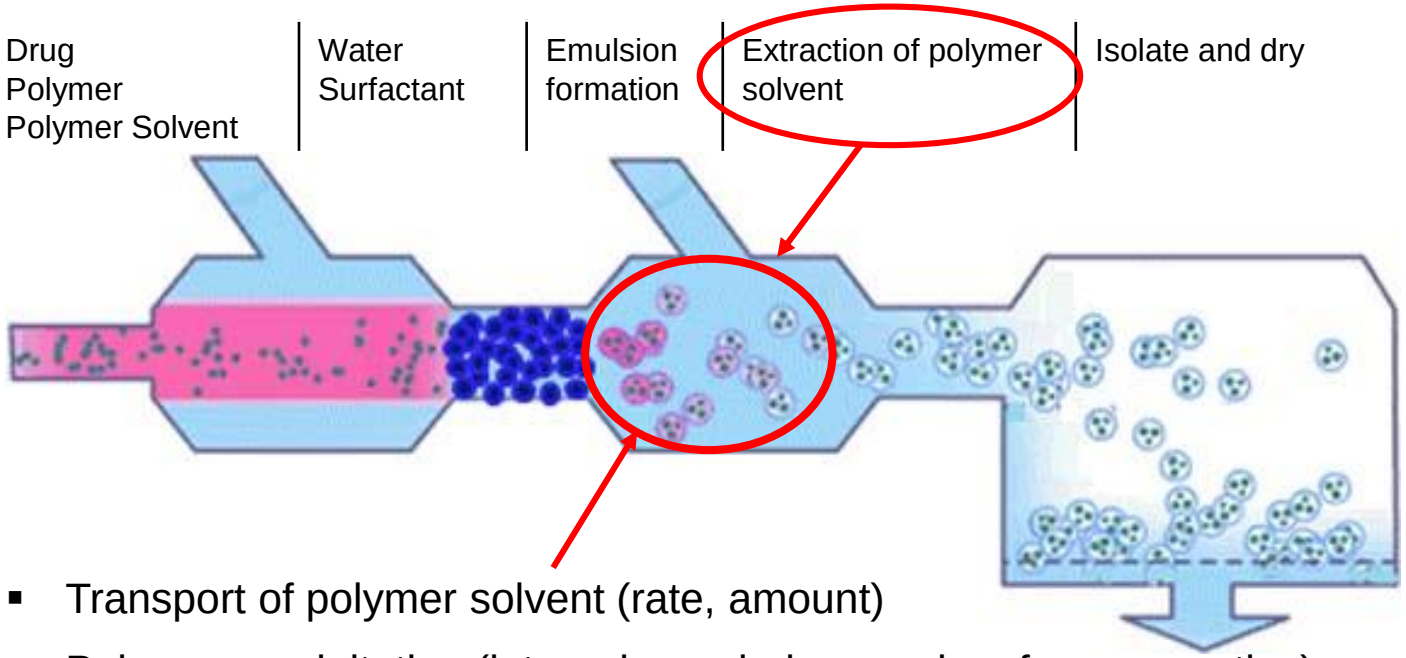
Continuous manufacturing

Process control during microparticles formation (solvent-removal step)



Product by Process

- Drug properties
- Polymer properties
- Process parameters
- Scale up

- Transport of polymer solvent (rate, amount)
- Polymer precipitation (internal morphology and surface properties)
- Drug precipitation or crystallization (physical properties of drug)
- Movement of drug
- Creation of microparticle surface (morphology, polymer orientation (surface charge, surface hydrophobicity)
- Microparticle shape

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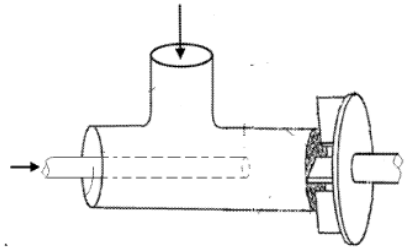
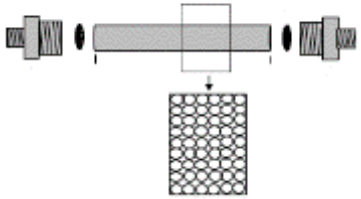
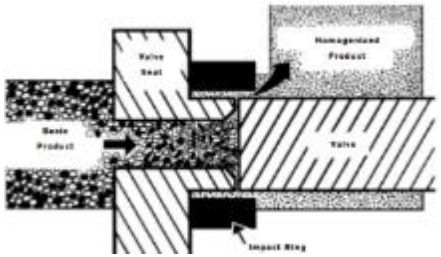
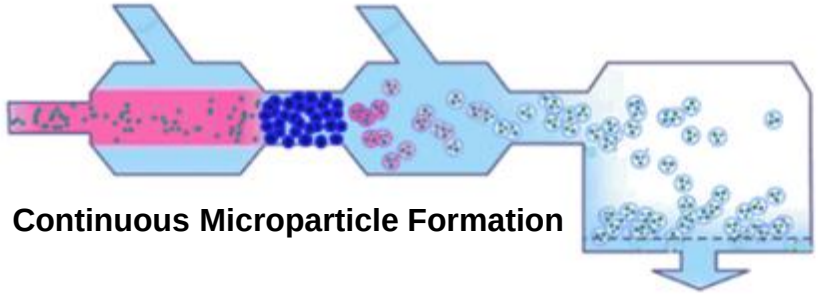
Emulsion generators

- FormEZE® column
- ‘416 work head
- Rotor / stator
- Static mixer
- Gap homogenizer
- Plates with openings
- Nozzles
- Ultrasonic nozzles
- Membranes









Continuous Microparticle Formation

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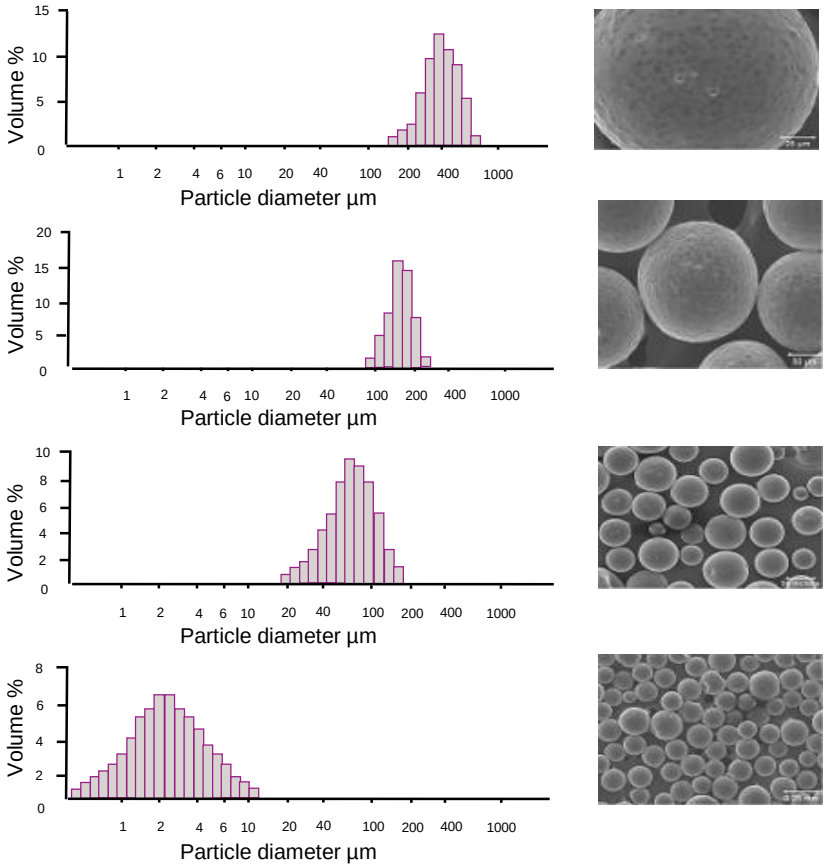
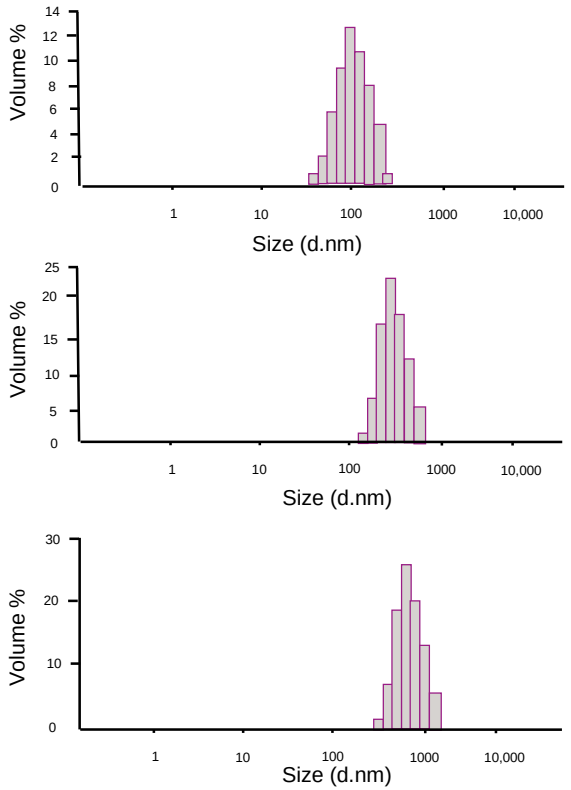
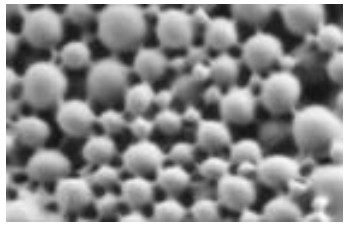
Microparticle size control

Microparticles



Nanoparticles





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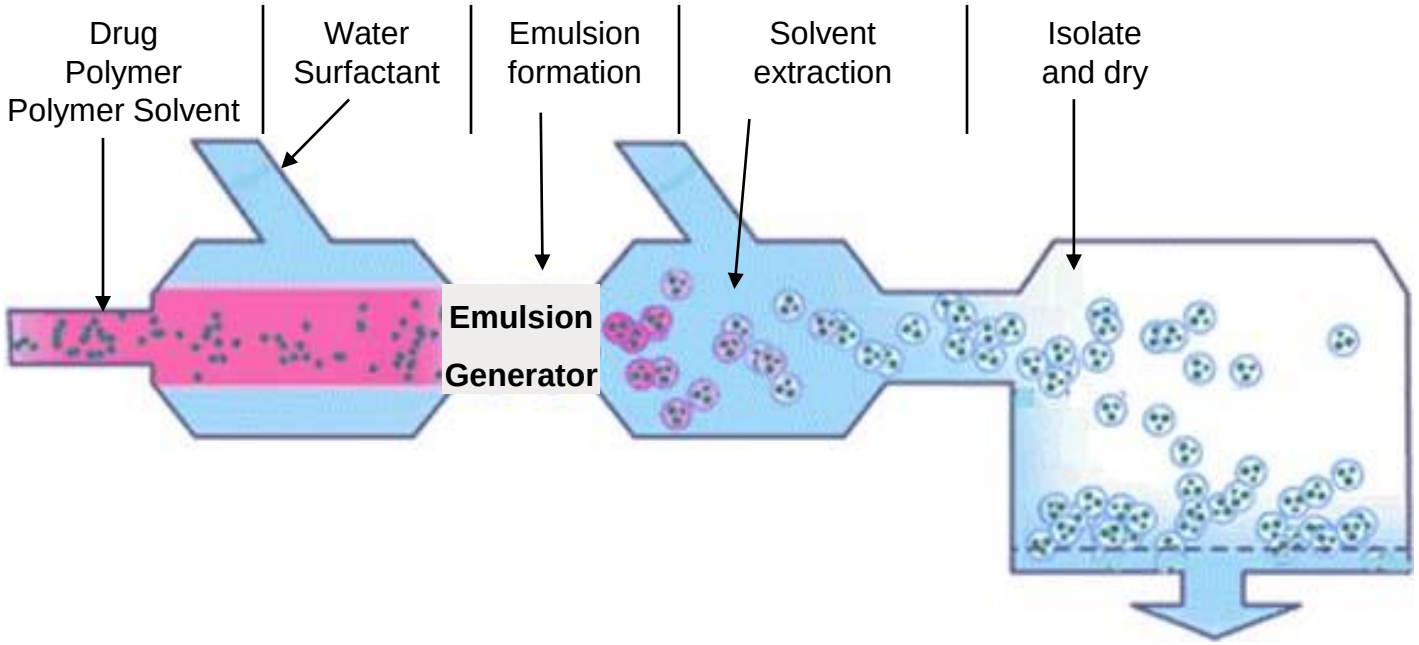
Manufacturing processes for complex parenterals - scale up

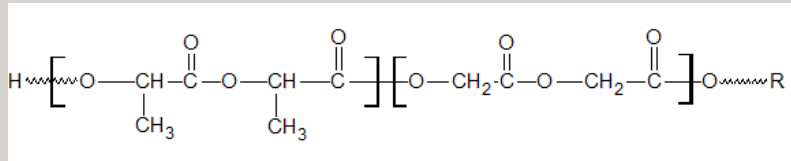
- Identify potential critical process parameters
- **Understand outcomes of:**
  - **Longer unit operations**
  - **Switching to a different process technology for scale-up**
  - **Using larger equipment for the same process technology for scale-up**
- Design of Experiment (QbD) activities to understand the process and to determine which:
  - Process parameters are critical (define surface of design space)
  - Excipient characteristics and other material characteristics are critical
- Understand and control critical process parameters
- Demonstrate a well-controlled, robust manufacturing process

Evonik microencapsulation by continuous solvent-extraction



Process conditions

Excipient properties



Drug Properties

- Peptides
- Small molecules
- Proteins

Critical Process Parameters

Critical Materials Parameters

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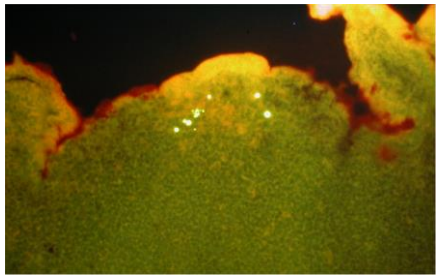
LG Polymer Nanoparticles

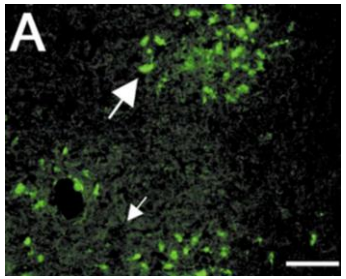
Particle size – microparticles v. nanoparticles

- **Microparticles**
  - 30 µm to 50 µm to achieve injection with 23-G to 27-G needles
  - < 10-µm taken up by macrophages, dendritic cells, Peyer's Patches, astrocytes
  - Flowable powders (helps with powder filling of vials)
  - IM / SC administration, not IV

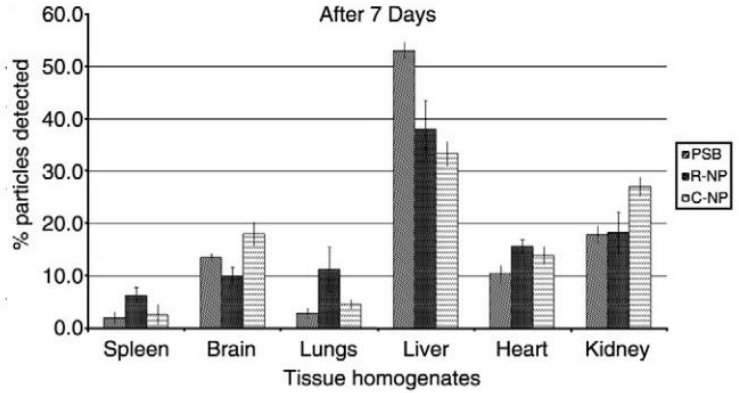
- **Nanoparticles**
  - ~1 nm to 100 nm (nano-range scale) (undetected by human eye)
  - Particles having properties or phenomenon that are attributable to their dimensions outside nano-range (< 1000 nm)
  - Nanoparticles not flowable (lyophilized cake)
  - Higher surface curvature than microparticles
  - Much higher surface area to volume than microparticles
  - Taken up by cells
  - Active targeting
  - Distribute to spleen and liver after IV administration



Peyer's Patches Uptake



Astrocyte uptake



Biodistribution following intravenous administration of 50:50 LG polymer nanoparticles loaded with rhodamine (R-NP) or coumarin (C-NP). (PSB-polystyrene nanoparticles)

Ref: B. Semete et al, Nanomedicine: Nanotechnology, Biology, and Medicine 6 (2010) 662–671

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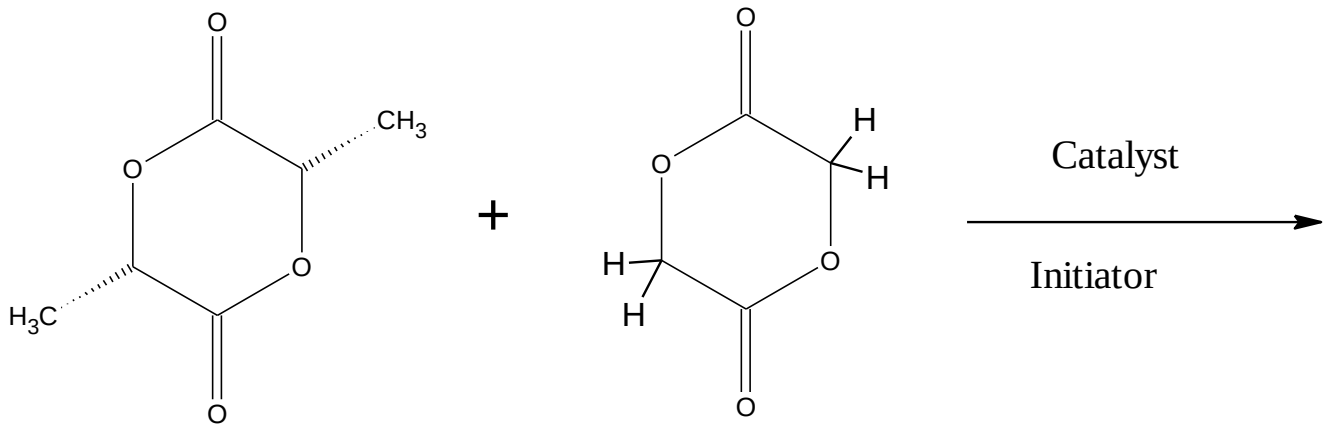
Poly(lactide-co-glycolide) synthesis

Process

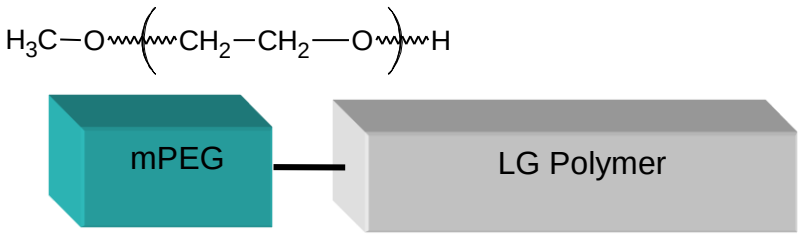
- Ring opening polymerization of lactide and glycolide monomers
- Melt polymerization
- Solvent free

Raw Materials

- Monomers
- Catalysts
  - Stannous Octoate – Primary
  - Stannous Chloride
- Initiators
  - Lauryl Alcohol (1-dodecanol)
  - Glycolic Acid
  - Glucose
  - PEG



Poly(ethylene glycol)-block-poly(lactide-co-glycolide) polymers



A-B Diblock Copolymers (mPEG)

- Methoxy-PEG (mPEG)
- Maleimide-PEG (mal-PEG)
- N-hydroxysuccinimide-PEG (NHS-PEG)
- Amino-PEG
- Carboxy-PEG

PEG block length (MW) → LG polymer composition → LG polymer block length (MW) → Derivatized PEGs for conjugation

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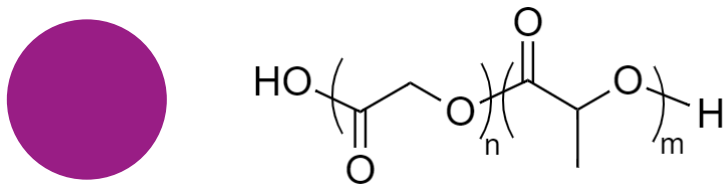
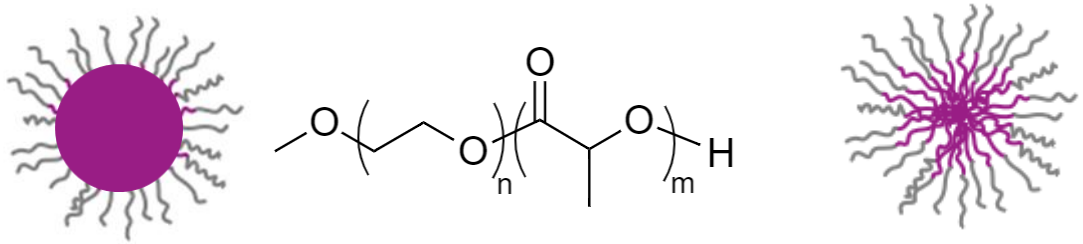
LG polymer and PEG-LG polymers for nanoparticles



Poly(lactide-*co*-glycolide)



methoxy-Poly(ethylene glycol)-*block*-polylactide

LG Polymers

- Copolymer composed of glycolide & lactide monomer units
- Tunable pharmacokinetics via copolymer molecular weight, monomer ratio, end-group chemistry
- Extensive use as excipient for clinical and commercial extended-release products
- Solid nanoparticles

PEG-Polylactide Block Copolymers

- Hydrophobic polylactide and hydrophilic PEGs
- Amphiphilic nature enables polymer orientation
- Molecular weight of PEG and polylactide tunable to adjust properties of polymer and formulation
- Solid or fluid (polymer micelles) nanoparticles
- Various monomer combinations can be used for hydrophobic block (lactide, glycolide, caprolactone)

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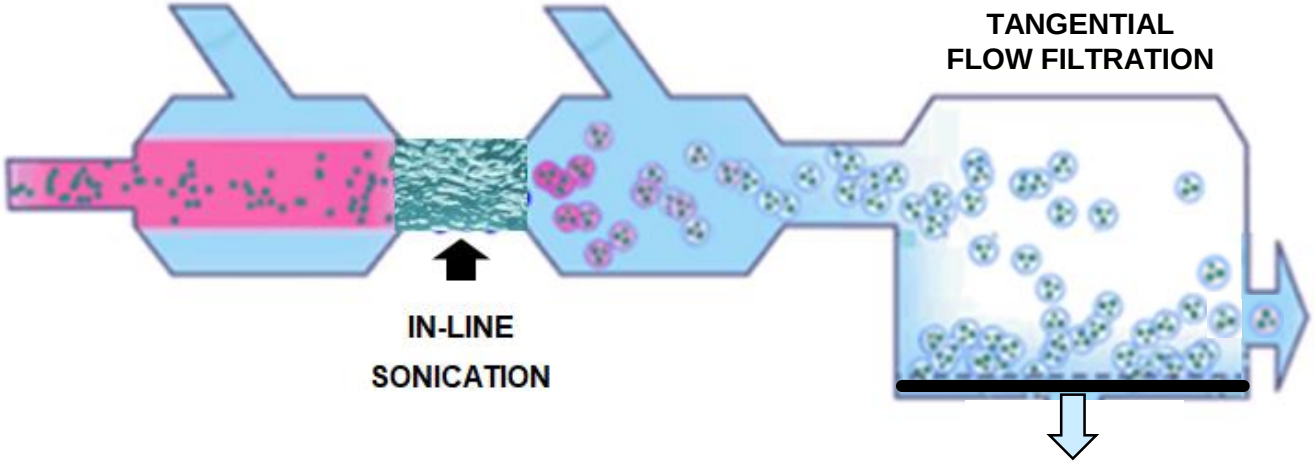
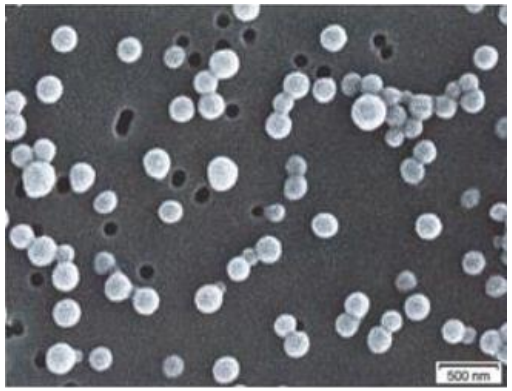
Manufacturing of LG polymer nanoparticles
Learnings from microencapsulation translated to nanoencapsulation

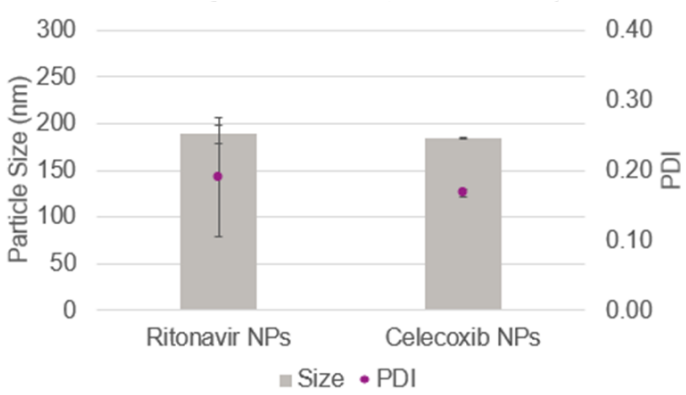
- **Advantages of continuous nanoencapsulation**
  - Emulsion-based processes
  - Challenges of double emulsions for nanoencapsulation
  - Advantages of emulsion-based nanoencapsulation over continuous precipitation nanoencapsulations
  - Advantages of continuous precipitation nanoencapsulations over batch precipitation nanoencapsulations
- **Nanoparticles**
  - Terminal sterilization - e-beam and sterile filtration (<150-nm nanoparticles)
  - Aseptic manufacturing
  - Encapsulation efficiencies
  - PEG roles – process and composition
- **Scale up**
  - Equipment considerations
  - Product isolation and drying
- **Product-by-process**
  - Process parameters make a difference
  - Material properties and purity make a difference

LG polymer nanoparticles made with continuous in-line sonication

Ritonavir and celecoxib nanoparticles







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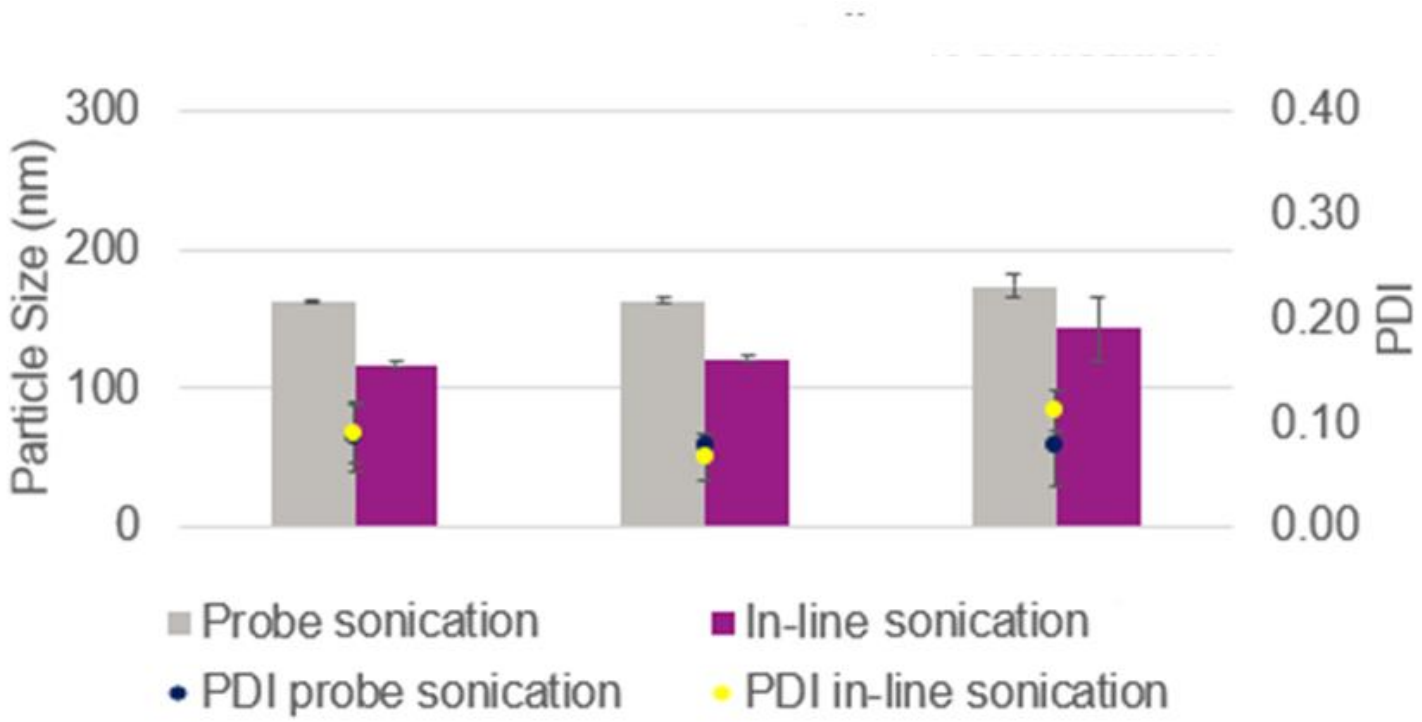
Peptide-loaded LG polymer nanoparticles
In-line sonication and probe sonication



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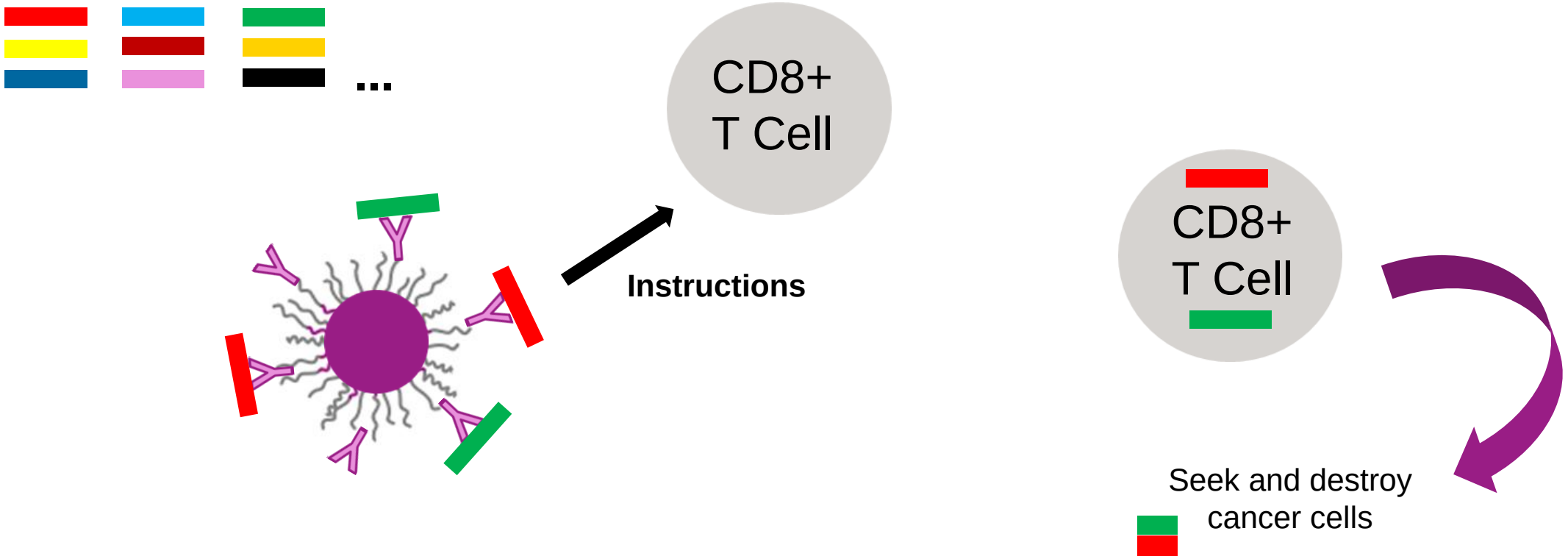
Formulation compositions and performance strategies for nanoparticles
Systemic drug delivery v. drug delivery within a cell

- Drug loading
- Amount of drug needed per number of cells
- Duration of drug release (short durations)
- Particle size optimization (performance and manufacturing)
- Cell biology & immunology
- Advantages of LG polymers (other excipients?)

Immunotherapy - oncology
Personalized medicine based on disease biomarkers

Vaccine peptide antigens (can be as many as 20)



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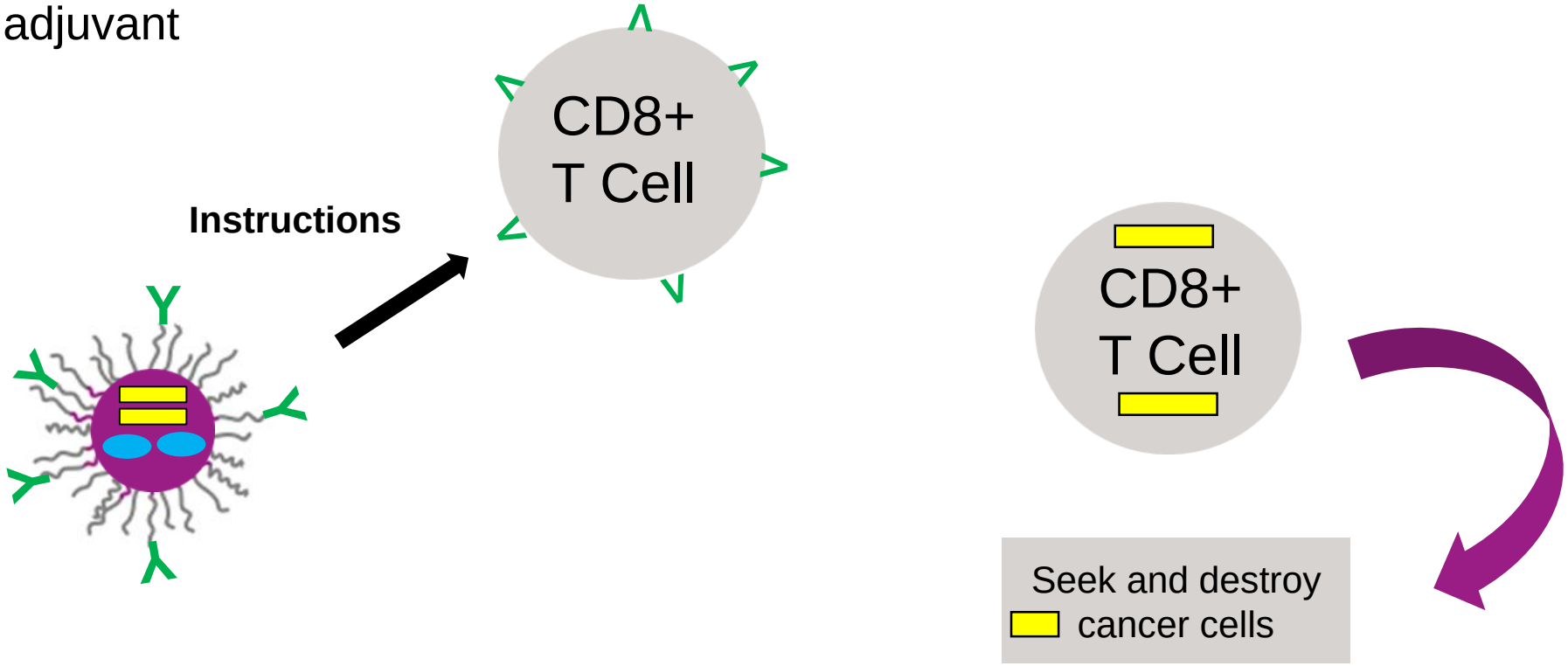
Active targeting of antigens, adjuvants or drugs with PEG-LG polymer nanoparticles

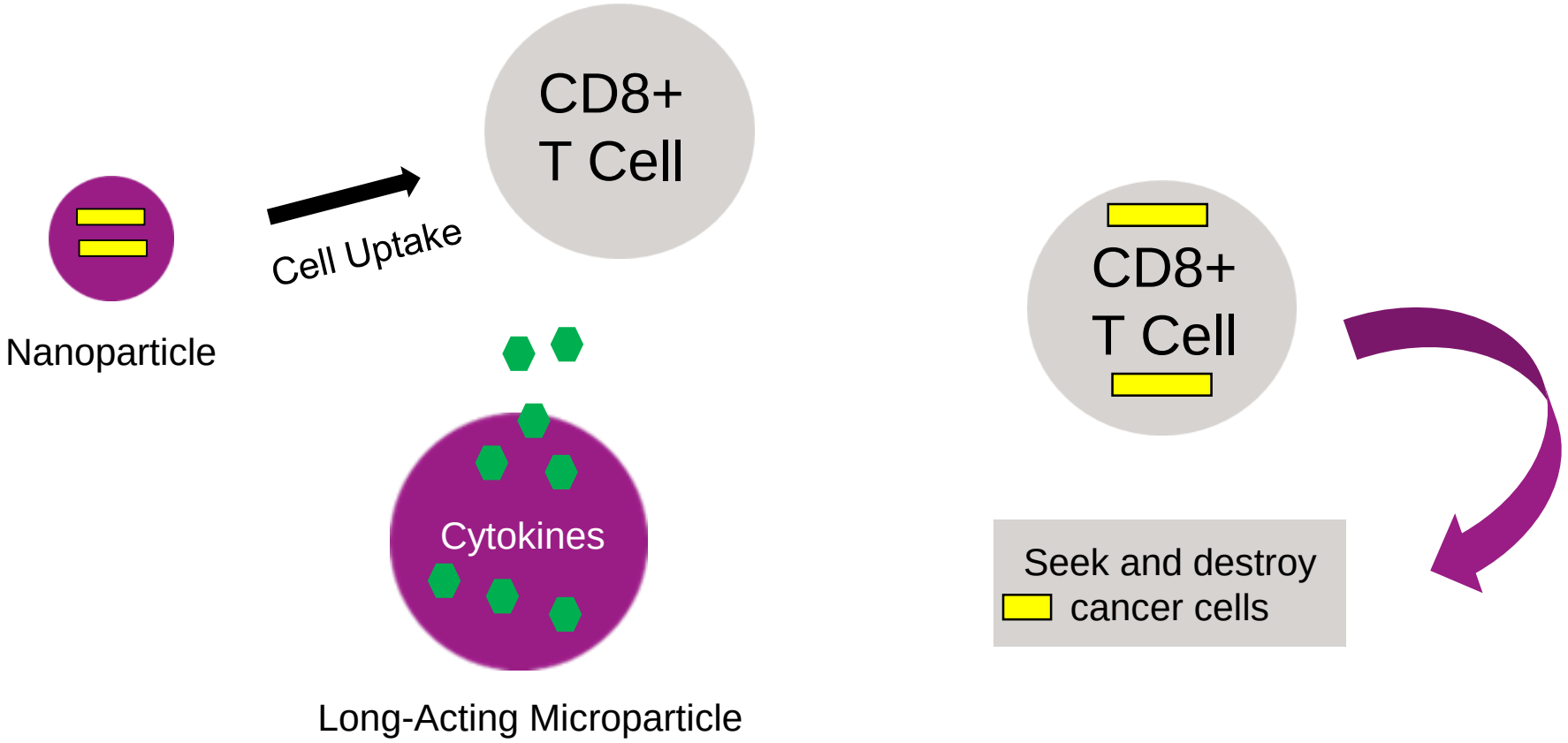
Vaccine peptide antigen

Vaccine adjuvant



Active targeting of antigens, adjuvants or drugs with PEG-LG polymer nanoparticles

Vaccine peptide antigen



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Treatment of autoimmune disease

Tolerogenic immune-modifying nanoparticles – moving from cell-base therapies

Delivery of antigens to antigen-specific $CD4^+$ and $CD8^+$ T-cells in the spleen and liver to inhibit and/or tolerize these cells and stop them from destroying of self tissue

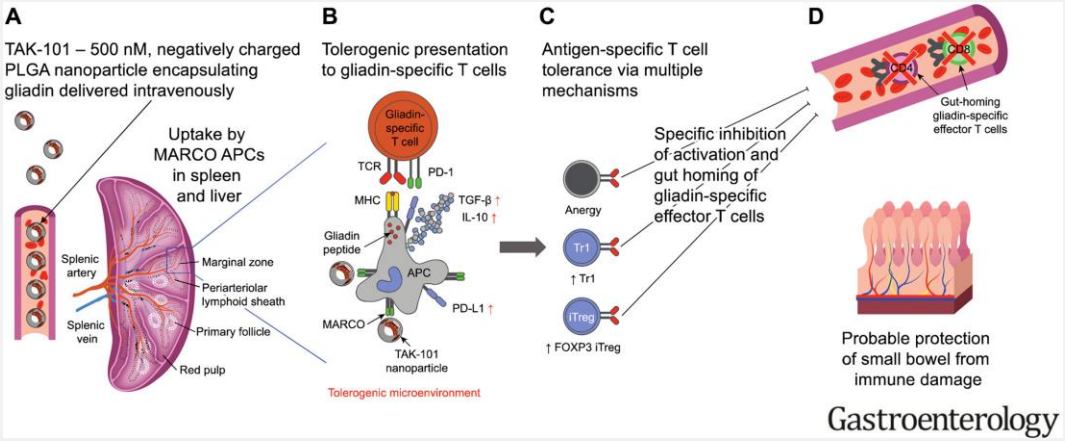
Diabetes Type 1, autoimmune arthritis, celiac disease

Treatment of autoimmune disease

Tolerogenic immune-modifying nanoparticles – moving from cell-base therapies

Celiac disease – Inducing Gluten Tolerance

- Negatively charged LG nanoparticles (500 nm) with encapsulated gliadin protein
- IV administration
- Nanoparticle uptake in the spleen and liver
- Tolerogenic presentation to gliadin-specific T-cells
- Gliaden-specific T-cell tolerance created via multiple mechanisms
- Specific inhibition of activation and gut homing of gliadin-specific effector T-cells
- Probable protection in small bowel from immune damage
- Clinical Status - Phase 1/2a



Ref: C.P. Kelly, et al., Gastroenterology, 2021, 161(1), 66-80

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Tolerogenic immune-modifying nanoparticles

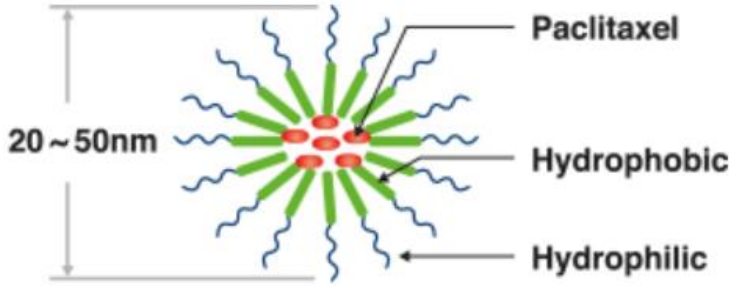
Other applications using LG-polymers

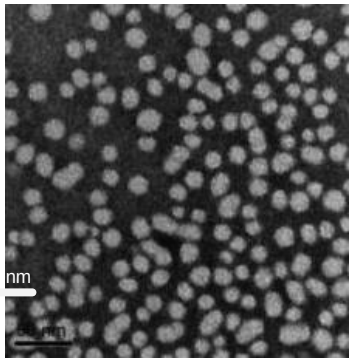
- **Anti-drug antibodies (nanoparticle adjuvant co-administered with PEGylated uricase) –** polylactide/PEG-polylactide blend, encapsulated rapamycin, iv administration, dendritic cells. clinical trials

- **Anti adeno-associated virus (AAV, gene delivery, nanoparticle adjuvant co-administered with AAV)** – polylactide nanoparticles, encapsulated rapamycin, 200 nm, iv administration

Enhanced drug solubility
Genexol® PM - PEG-polylactide polymeric micelles

samyangbiopharm.com





M.E. Werner et al., Int. J. Radiat Oncol Biol Phys., 2013, 86(1), 463-468

Transmission electron microscopy

- Paclitaxel – 30 mg and 100 mg
- 20- to 50-nm nanoparticle; polymeric micelle
- Intravenous administration
- 48-hour drug release Breast cancer, non-small cell lung cancer, ovarian cancer
- Monomethoxy-poly(ethylene glycol)-block-poly(DL-lactide)
- Improved solubility, reduced toxicity, improved efficacy, reduced hypersensitivity[a]
- Approved 2002

[a] Comparison of nanoparticle paclitaxel dose of 30 mg v. Cremophor paclitaxel dose of 30 mg

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LG polymer nanoparticle applications

- **Immunotherapy** – delivery of multiple peptide antigens, adjuvants
- **Tolerogenic immune-modifying**
- **Enhanced drug solubility and enhanced drug exposure** – for poorly water-soluble drugs
- **Extended drug release**
- **Multiple proprietary, novel applications for new modalities**

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Recent long-acting injectable publications and Evonik podcasts that may be of interest.

Recent long-acting injectable publications

Tice, T., Inspirational chemistry of long-acting injectables, Drug Delivery and Translational Research, Drug Delivery and Translational Research (2022) SpringerNature Link https://rdcu.be/cT486

Li, W., Tang, J.T., Lee, D., Tice, T.R., Schwendeman, S., Prausnitz, M., Clinical translation of long-acting formulations, Nature Reviews Materials, (2022) 7:406-420

Tice, T., Creekmore, R., Zhang, P., Wang, H., Chesterman, J., Koo, O., Sheehan, C., A practical approach to compendial nomenclature and testing for lactide and glycolide polymers and related polymeric excipients, USP Pharmacopeia Forum, (2022) 48(2).

Evonik Fireside Chat Links

Polymeric Drug Delivery – Long-Acting Injectables and Beyond
Episode 1 https://oncare.evonik.com/online_seminars/?vid=171
Episode 2 https://oncare.evonik.com/online_seminars/?vid=174
Episode 3 https://oncare.evonik.com/online_seminars/?vid=177


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