sustained drug release injectables

polymer design, formulation, and processing for success

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core strengths

tablet binding

Ashland produces binders for wet granulation, dry granulation, direct compression and roller compaction, as well as hot-melt extrusion.

modified release

Our extensive product lines offer various degrees of both hydrophilicity and molecular weights, providing you with a host of options.

tablet disintegration

Polyplasdone™ crospovidone provides rapid disintegration and dissolution of oral solid-dosage forms, even at low use levels.

drug solubilization

High-quality excipients that improve the solubility of your API.

film coatings

Fully formulated film-coating systems, easily dispersed and provides a range of functions to suit almost any tablet core.

parenteral applications

Ashland provides a suite of products that are be suitable for use in **parenteral, controlled release drug delivery systems**.

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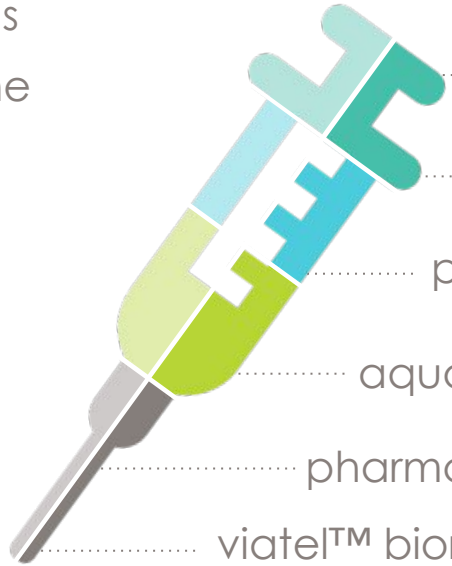
excipients for parenteral use

parenteral applications require excipients of the highest quality

Ashland's high-purity excipient portfolio



- plasdone™ povidone – C grades
- vialose™ trehalose dihydrate
- parenteral-grade cavitron™ cyclodextrins meets industry standards
- aqualon™ CMC BET grades
- pharmasolve™ n-methyl-2-pyrrolidone (NMP)
- viatel™ bioresorbable polymers

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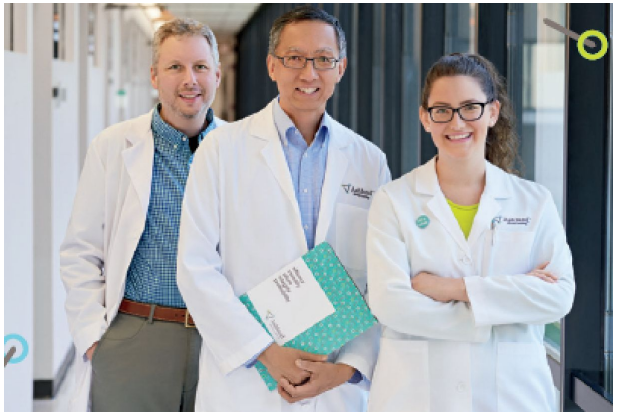
outline

overview of drug delivery strategies using bioresorbable polymers (BRP's)

- purpose of bioresorbable polymers in drug delivery
- introduction to formulation formats
- commercial products



controlling drug release via BRP chemistry

- detail natural polymer degradation pathway
- controlling formulation degradation by polymer selection

formulation selection process & chemistry for extended drug release

- choosing formulation process
- breakdown of multiple formulation options

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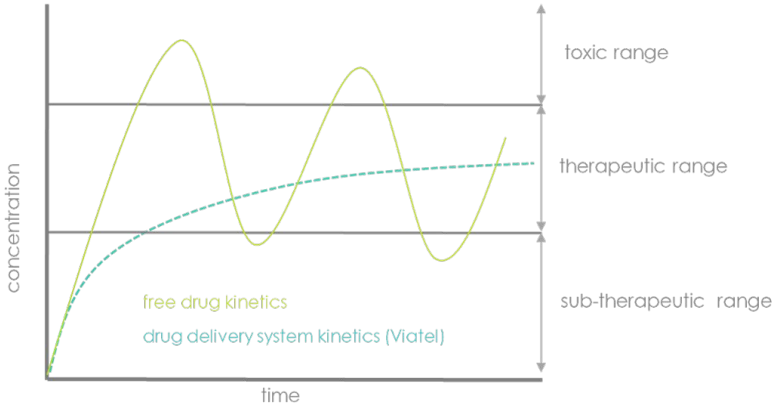
purpose of BRPs in pharma

many drugs present

- toxicity, fast metabolism and excretion
- low uptake / PK variability after oral administration
- low concentrations in the desired location via oral routes



advantages of injectable sustained release drug delivery

- tuneable (days – months) drug release
- decreased overall drug dosage / local delivery = reduced side effects
- therapeutic window
- simplify drug stability through digestive system and metabolic variance
- case dependent advantages (carriers, molecule types, other)

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viatel™ BRP product families

for drug delivery

- poly D,L-lactide (PDLLA)
- poly D,L-lactide-co-glycolide (PLGA)
- poly caprolactone (PCL)
- poly D,L-lactide-co-caprolactone (PLCL)

all products have high purity

- no residual solvents
- low residual tin

other

- 70+ in-stock offerings
- custom polymers available

in-stock offerings			
monomer composition	**co-monomer ratio(s)**	**end-cap**	**inherent viscosity ranges (dL/g)**
poly(D,L-lactide) (PDLLA)	--	acid ester	0.1 - 1.4 (multiple grades)
poly(D,L-lactide-co-glycolide) (PLGA)	50:50 55:45 65:35 75:25 85:15	acid ester	0.1 - 1.4 (multiple grades)
polycaprolactone (PCL)	--	ester	1.0 - 2.0 (multiple grades)
poly(L-lactide-co-caprolactone) (PLCL)	60:40 70:30 80:20 90:10	ester	1.0-1.4

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PLGA parenteral products history

1930s-60s	early patents and publications
1971	Dexon: first synthetic bioabsorbable suture (not drug delivery)
1973	DuPont: first lactide / glycolide drug delivery patent
1986	Decapeptyl*: first injectable extended-release microparticle product
1989	Zoladex*: first implantable extended-release implant product
2001	Atridox*: first local delivery product
2002	Eligard*: first injectable extended-release lactide/glycolide in-situ forming product
2006	SmartShotB12: first injectable microparticle for animals
2007	Genexol* PM: first nanoparticle
2009	Ozurdex*: first product for ocular delivery
2011	Propel*: first drug-eluting device
2011	Revalor*: XS First implantable for animals
2016	Reseligo: first generic implantable
2016	Absorb GT1*: first bioabsorbable drug-eluting cardiovascular stent
2017	Zilretta*: first micro-particle product for intra-articular delivery (knee)

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PLGA-based sustained release formulations

in situ forming systems

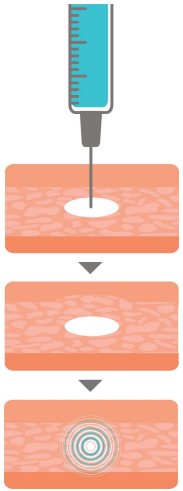
- API + PLGA + solvent
- formed in vivo, simplified process and costs,
- administered through injection, larger burst effect, implant shape variance

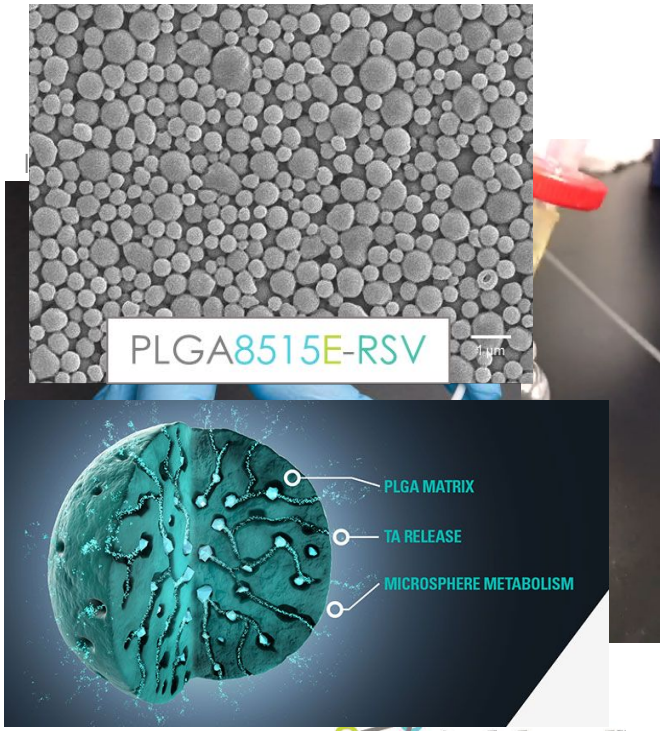
solid implants

- API + PLGA
- no organic solvents, good stability, lower burst effect
- extrusion (thermal deg.), administered through surgery or injection

particle technologies

- API + PLGA + diluent
- microspheres, nanoparticles
- smaller needles, tuneable profiles
- organic solvents, particle stability, complexity (aggregation)





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commercial product examples

- in situ forming depot
  e.g., Eligard*—leuprolide acetate
  (sub cutaneous injection; 1, 3, 4 or 6 monthly)

- microsphere technologies
  e.g., Bydureon*—exenatide depot
  (weekly self-administered subcutaneous injection)

- solid implants
  e.g., Ozurdex*—intravitreal dexamethasone implant (injection)

https://www.empr.com/drug/ozurdex/
https://www.bydureon.com/
https://www.mims.com/malaysia/drug/info/eligard

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product examples

brand name	indication	company	drug substance	API Size (Da)	dose (mg)	months
Eligard*	Prostate cancer	Sanofi-Aventis	Leuprolide acetate	1260 (peptide)	7.5 – 45	1, 3, 6
Sublocade*	Opioid dependency	Indivior	Buprenorphine	467.64 (SMD)	100, 300	1
Longrange*	Parasite treatment	Merial Limited	Eprinomectin	914 (SMD)	50	5
Bydureon*	Diabetes (II)	AstraZeneca	Exenatide	4187 (peptide)	2	0.25
Sandostatin* LAR	Acromegaly / flushing / cancer-induced diarrhea	Novartis	Octreotide acetate	1079 (peptide)	10 – 30	1
Decapeptyl* SR	Prostate cancer	Ipsen / Ferring	Triptorelin pamoate	1700 (peptide)	4 – 28	1, 3, 6
Scenesse*	Erythropoietic protoporphyria (light intolerance)	Clinuvel	Afamelanotide	1707 (peptide)	16	2
Zoladex® 1 / 3 month	Prostate / breast cancer	AstraZeneca	Goserelin Acetate	1269 (peptide)	3.6 – 10.8	1, 3
Revalor*	Growth promotion (animal)	Intervet / Merck Animal Health	Trenbolone / estradiol	270 / 272 (SMD)	140 / 14	6

https://www.merck-animal-health-usa.com/product/cattle/Revalor-XS/1
https://www.indiamart.com/proddetail/zoladex-10-8mg-21620634848.html
https://www.labonline.com.au/content/life-scientist/article/clinuvel-success-in-scenesse-trial-1347661844
https://www.mims.com/hongkong/drug/info/signifor%20lar
https://www.bi-vetmedica.com/species/cattle/products/longrange.html

needle delivery format

product	formulation type	needle size
Fensolvi*	in situ gel	18 G
Sublocade*	in situ gel	19 G
Perseris*	in situ gel	18 G
Lupron* Depot PED	microsphere	23 G
Bydureon*	microsphere	23 G
Decapeptyl* SR 11.25 mg	microsphere	20 G
Ozurdex*	implant	22 G
Zoladex*	implant	3.6 mg dosage: 16 G 10.8 mg dosage: 14 G

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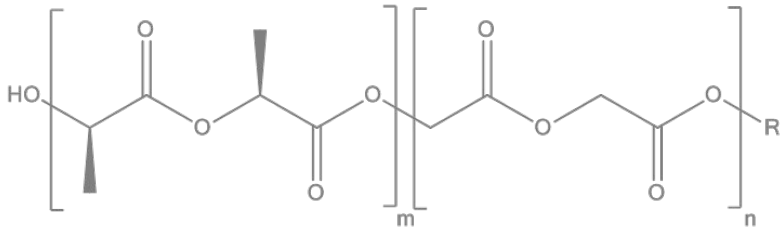
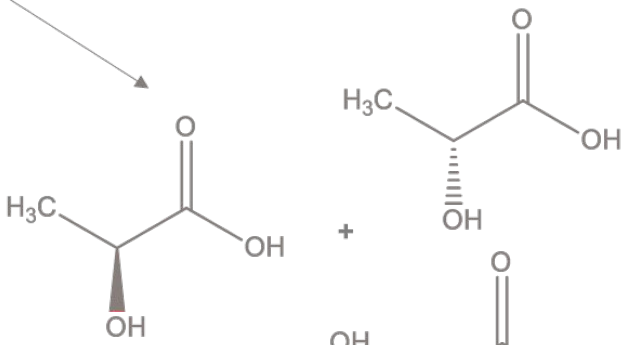
controlling drug release via BRP chemistry

what happens to PLGA in the body?

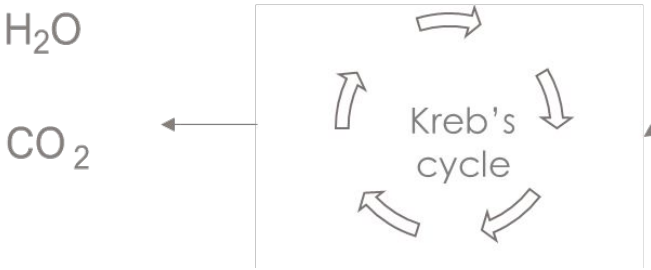


poly D, L lactide-co-glycolide (PLGA)

hydrolysis



lactic and glycolic acid



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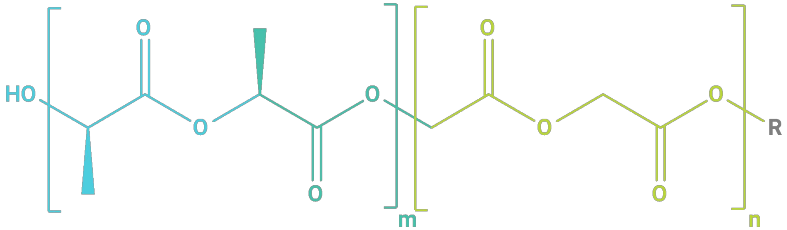
BRP chemistry & structure

poly D, L lactide-co-glycolide (PLGA)



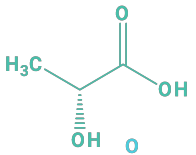
end group options

R = acid

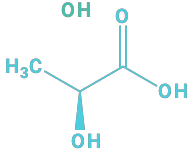
R = ester

R = other

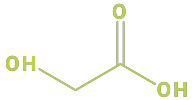
monomer options



= D - lactic acid



= L - lactic acid



= glycolic acid

chemical characteristics

inherent viscosity or molecular weight and polydispersity:

no. of repeating m & n units and chain length variance

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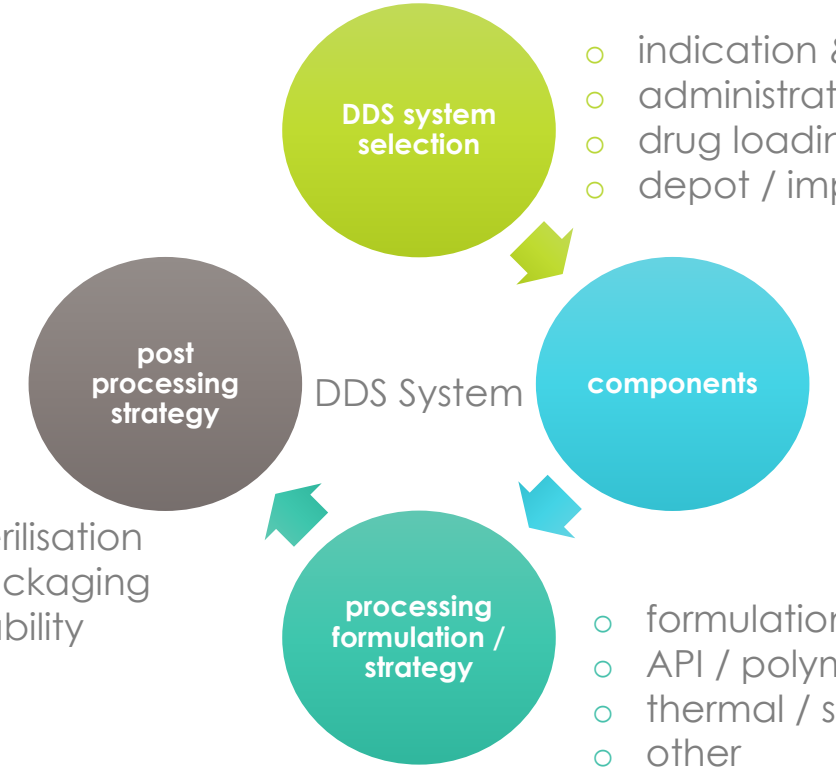
theoretical polymer influence on release

polymer characteristic	option & effect
molecular weight / inherent viscosity	○ higher Mw / inherent viscosity = increased release duration
lactide : glycolide content	○ increased lactide content = increased hydrophobicity = increased release duration
polymer end-cap	○ acid = hydrophilic ○ ester = hydrophobic = increased release duration

drug delivery system – we can help



- indication & delivery strategy
- administration site
- drug loading
- depot / implant form

- API
- polymer
  - viatel™ BRPs
- solvents
  - pharmasolve™ NMP
- diluents, suspending agents
  - aqualon™ CMC BET

- formulation
- API / polymer loading
- thermal / solvent processing
- other

- sterilisation
- packaging
- stability

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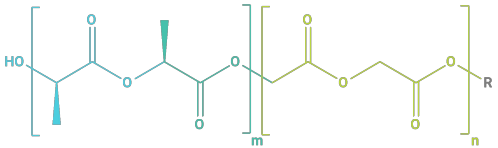
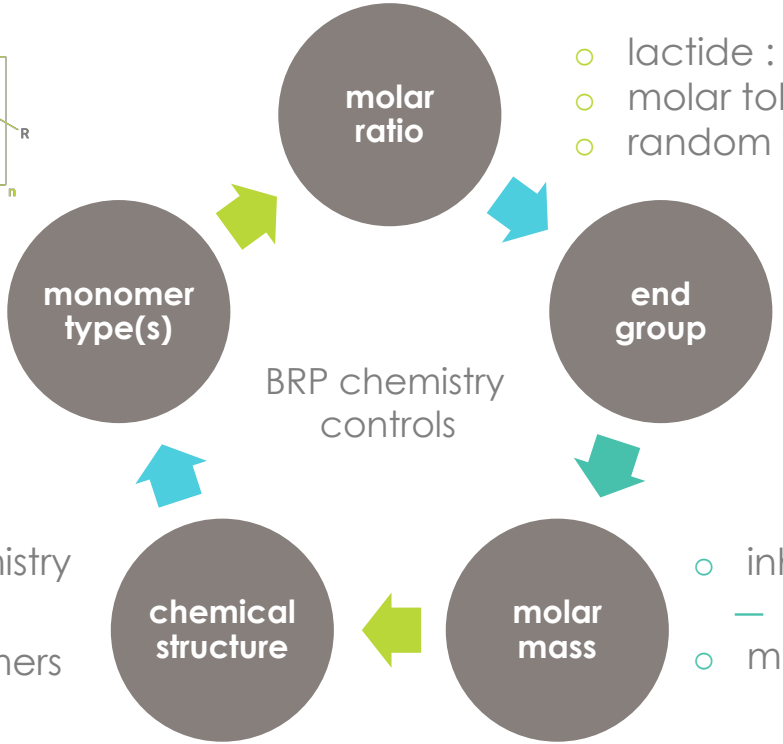
polymer functions to control release



- monomer inclusion
  - D,L lactide
  - glycolide
  - L lactide
  - ε-caprolactone



- lactide : glycolide ratio
- molar tolerance (±3)
- random vs. blockiness

- hydrophilicity of end group
  - PEG > acid > ester
- API sensitivity / stability

- inherent viscosity (IV) dl/g
  - increased IV = slower release
- molecular weight (Mw, Mn, PDI)

- incorporate other chemistry
  - e.g., glucose
  - star / dendritic polymers
  - new polymers

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put the theory to the test

Eligard* (leuprolide acetate)

- long-acting polymer
  - 82.5 mg poly D,L lactide-co-glycolide 50:50 A
- biocompatible solvent
  - 160 mg N-methyl-2-pyrrolidone (NMP)
- active pharmaceutical ingredient

long-acting variations			
month(s)	leuprolide acetate (mg)	polymer	solvent
1	7.5	PLGA 50:50 A	NMP
3	22.5	PLGA 75:25 E	NMP
6	45	PLGA 85:15 E	NMP

https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021731s005,021488s010,021379s010,021343s015lbl.pdf
http://products.sanofi.ca/en/eligard.pdf

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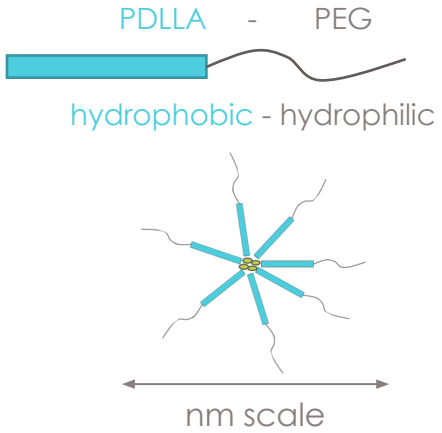
other polymer structures

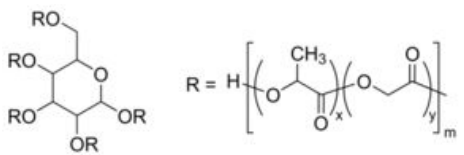
chain end-group

- PEG addition – stability, faster water uptake, and release
- tune degradation (PCL-PEG example)
- amphipathic structure (e.g. Genexol*)



monomer composition & polymer structures

- caprolactone, lactide, glycolide
- structure: di- and tri-block structures, glucose-star, dendritic copolymers
- varied release profiles, stability, physicochemical properties



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Azhari, Z., McMahon, S., Pierucci, L., Wang, W.*, Cameron, R.* 'Short Poly(ethylene glycol) Block Initiation of Poly(L-lactide) Di-block Copolymers: A Strategy for Tuning the Degradation of Resorbable Devices'. *POLYMER INTERNATIONAL*, 2018, 67, 726-738, DOI: 10.1002/pi.5563.

formulation strategies & optimization

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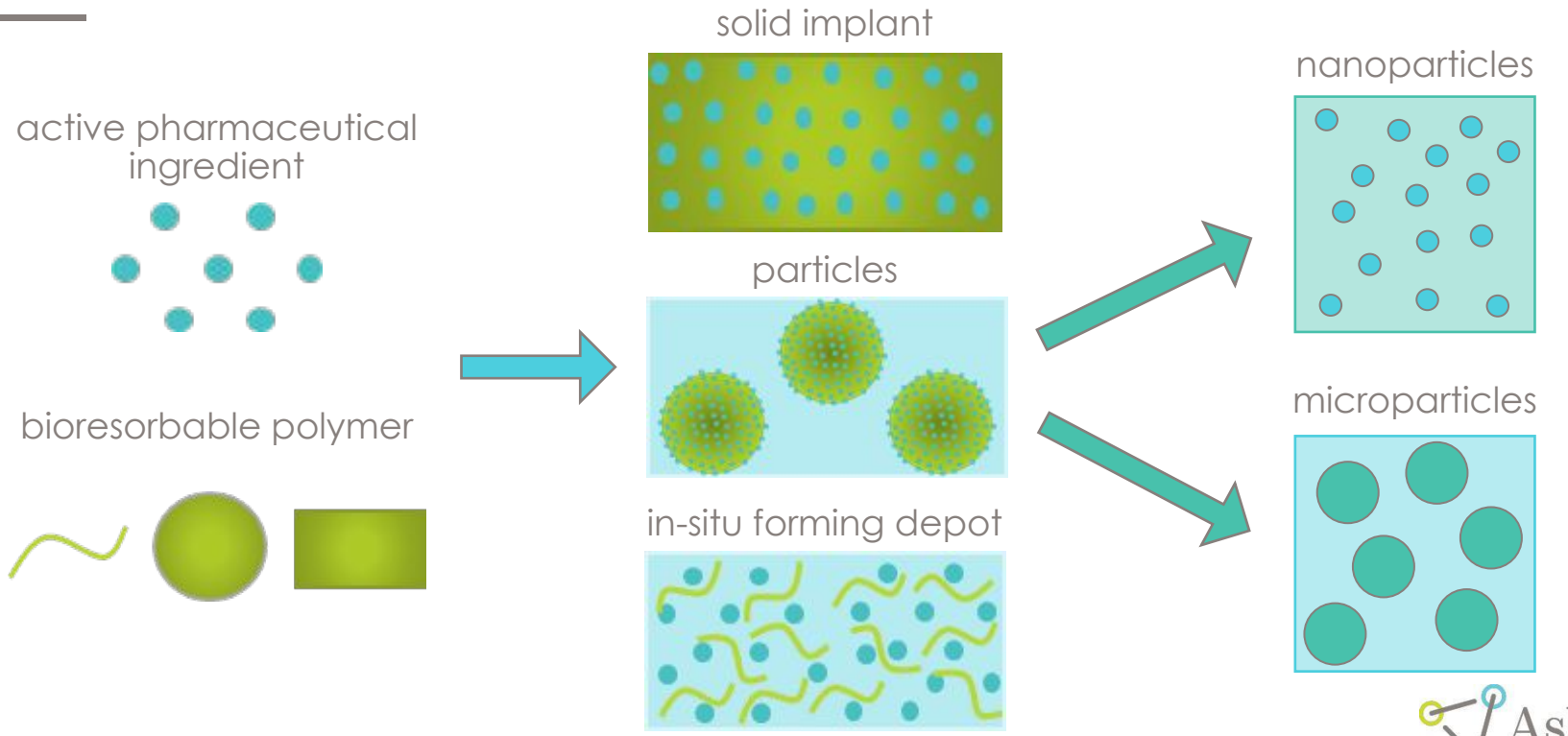
formulation options



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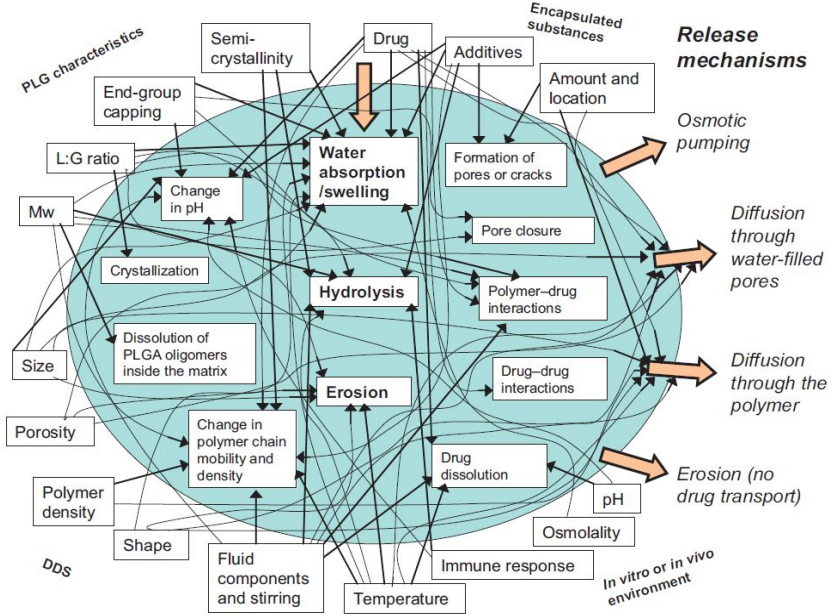
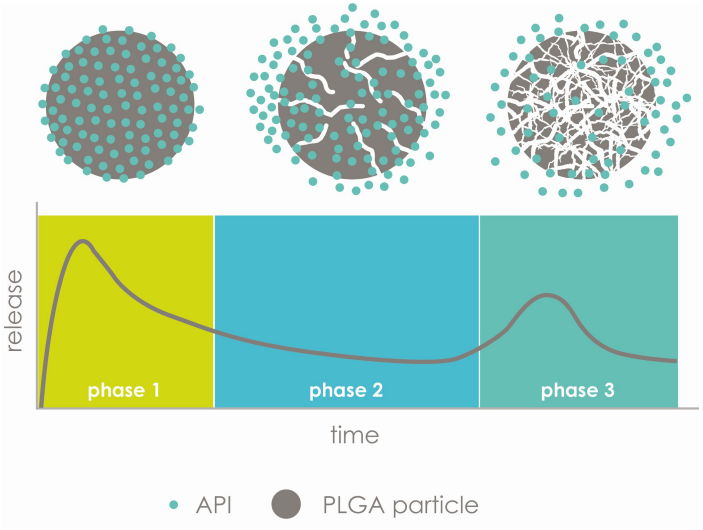
PLGA formulation degradation mechanisms





picture credit: S. Fredenberg et al. / International Journal of Pharmaceutics 415 (2011) 34– 52

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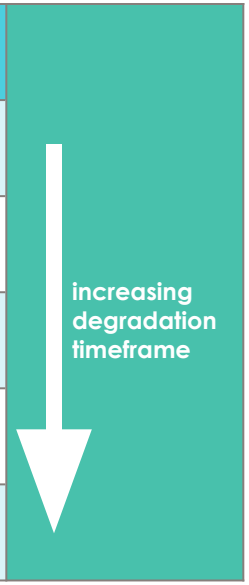
polymer thermal properties can alter choice of formulation process

polymer	Tg (°C)	Tm (°C)	structure
PGA	35 – 45	220-233	Semi-crystalline
PLGA	35 – 55	Amorphous	Amorphous
PDLLA	45 – 60	Amorphous	Amorphous
PLCL	10 - 20	130 - 155	Amorphous
PCL	-65 to -60	55 - 65	Semi-crystalline



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API can alter choice of formulation process

API type

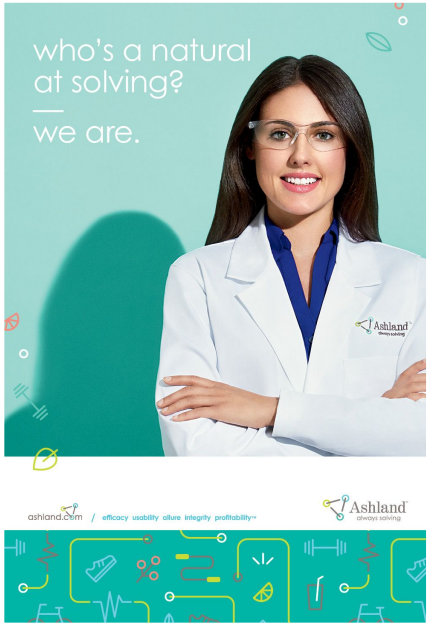
- organic small molecule
- protein
- peptide
- monoclonal antibody
- DNA / RNA

solubility

- hydrophobic vs. hydrophilic vs. amphiphilic
- water solubility

dosage requirements and duration

- therapeutic level
- possibility for increased bioavailability vs. current dosing



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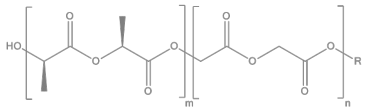
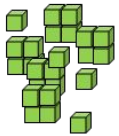
hot melt extrusion process

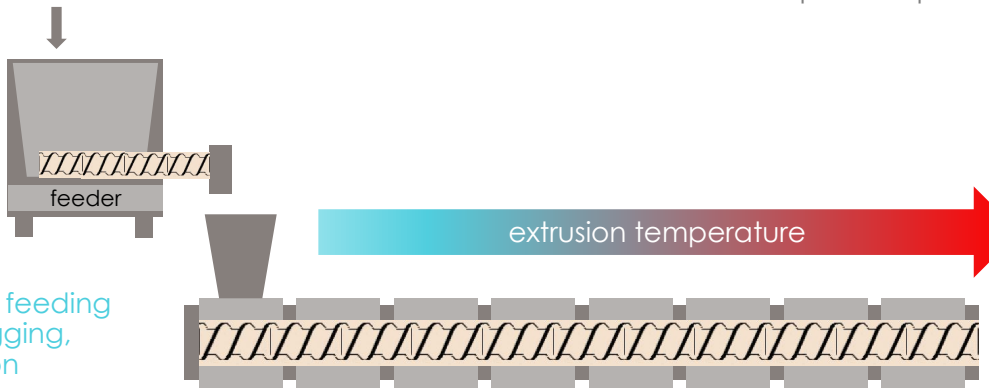
polymer



poly D, L lactide-co-glycolide (PLGA)

drug





1

common feed issues: feeding rate, static, flow, clogging, drug / PLGA dispersion

2

degradation due to excessive thermal and shear stress

3

poor content uniformity in extrudate

how can we improve HME performance of PLGA?

- dense flowing particles
- flexible particle size for drug / PLGA dispersion
- tune process parameters and optimise

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PLGA form enhancement for HME

Avg. particle diameter (µm)	Max. particle diameter (µm)	Min. particle diameter (µm)
351	1326	10.3

Avg. particle diameter (µm)	Max. particle diameter (µm)	Min. particle diameter (µm)
2795	4230	2106

*** Data obtained via Light Microscopy inspection. Sample size of 100 particles used for each case ***

fine particles improve HME formulations

- through multiple studies, it was determined that fine particles provide better mixing and decreased molecular weight reduction during melting process

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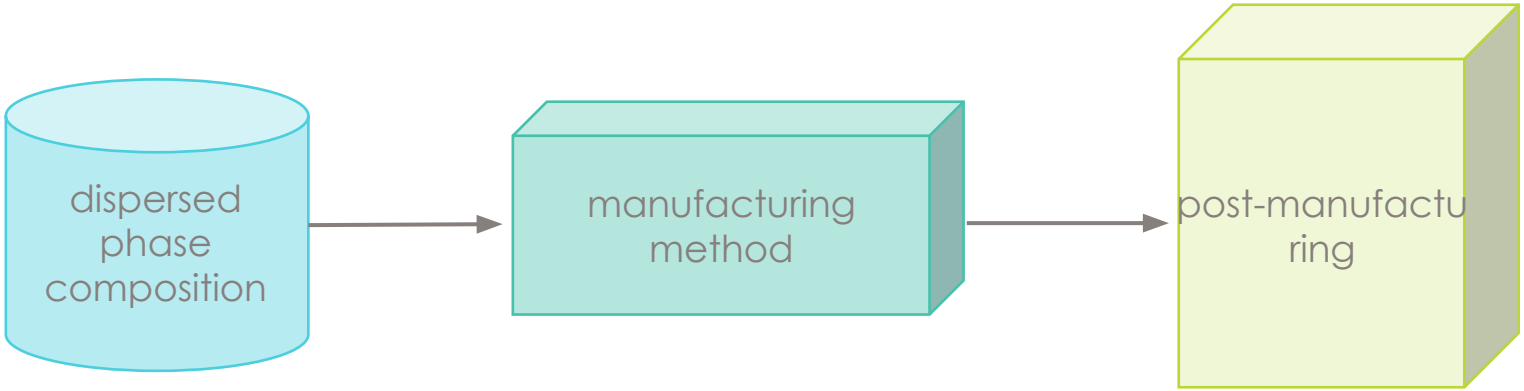
microsphere process



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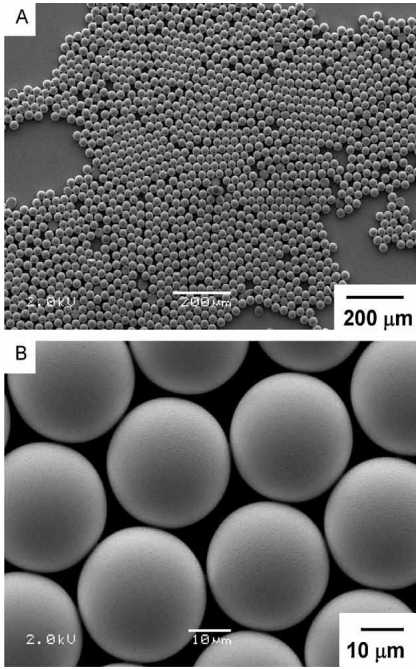
particle technologies

- single / double emulsions
- coacervation
- spray drying
- microfluidics
- membrane emulsification
- nano-precipitation
- vibration assisted printing
- self-assembly (micelle tech)
- electro-spinning / electro-spraying

+ downstream handling



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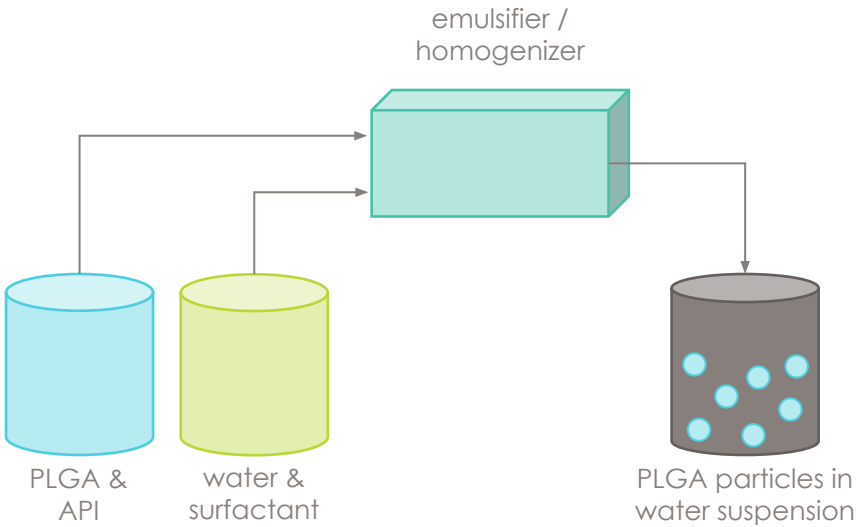
single emulsion



pros

- production of large quantities very quickly and easily
- control of precipitation rate, which effects the release profile

cons

- advantageous to use organic solvents with least water solubility
- requires ability to process quickly downstream due to large volumes
- large quantities of waste

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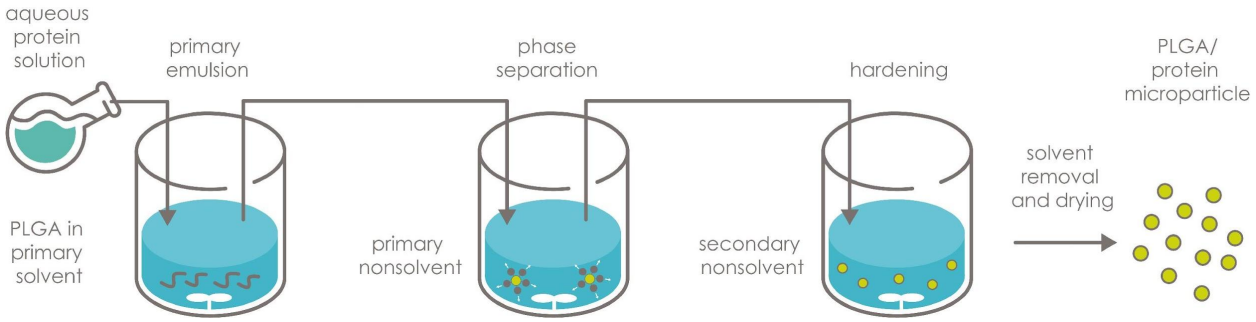
coacervation



pros

- high encapsulation of hydrophilic drugs
- limited total waste quantity

cons

- use of and disposal of explosive hazardous organic solvents
- challenges in scale-up
  - time factor of transferring into non-solvents
  - stirring dynamics different with larger equipment

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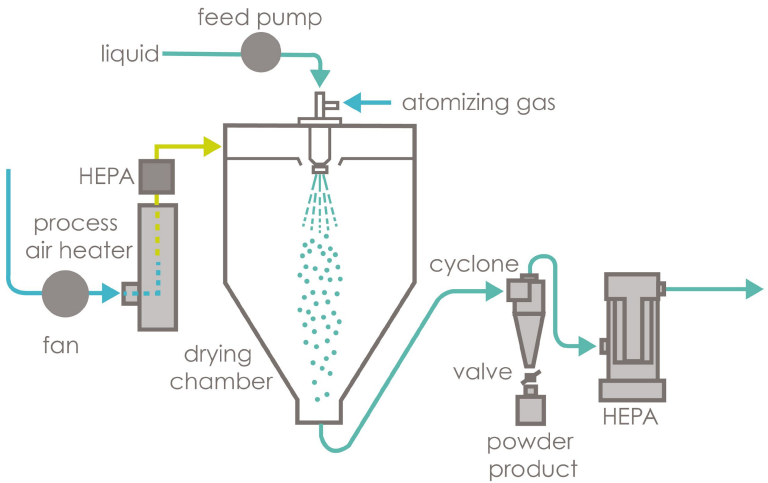
spray drying



pros

- high encapsulation of hydrophilic drugs, with caveat that water is not advantageous to use
- more uniform particle size distribution
- can utilize any volatile organic solvent, including acetone
- produces a solid powder with low residual organic solvents and no down-stream processing is needed

cons

- slow process
- manufacturing:
  - custom spray dryers must be made to fit each project's aseptic process/requirements
  - cleaning equipment for re-use

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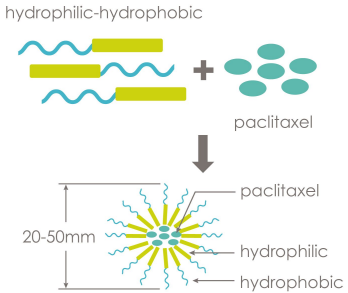
nanoparticle & hydrogels

rational

- increased stability, reduced toxicity
- + penetration ability, smart targeting using polymer

examples

- Genexol*
- mAb loaded nanoparticles



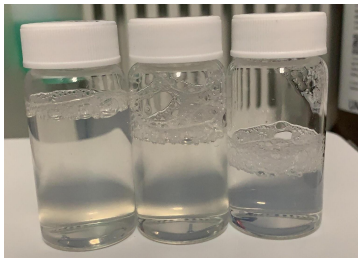
	Genexol®PM	Conventional paclitaxel
API	Paclitaxel 30mg	Paclitaxel 30mg
Solubilizer	mPEG-PDLLA* 150 mg	Cremophor 2,645mg
MTD	390 mg/m2	175 mg/m2
Character	• Improved solubility • Reduced toxicity • Improved efficacy • Reduced hypersensitivity	• Low MTD • Cremophor induced - Toxicity - Hypersensitivity reaction and neuropathy

tri-block polymer rational

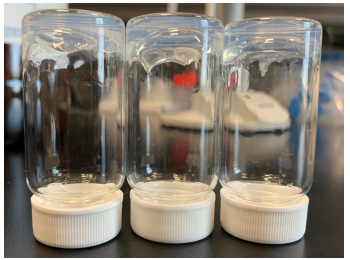
- water rich matrix to support structure of large molecules & cells
- does not require harsh processing (no org. solvents or temperature)

example

- thermosensitive hydrogels based on tri-block copolymer structure



0 – 25 ˚C = solution



30 – 40 °C = hydrogel

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Genexol® PM. - Pharmaceuticals - Product Samyang Holdings Biopharmaceuticals Division (samyangbiopharm.com)

common challenges

chemistry

- how do I select appropriate polymer for project target and how to optimise?
- drug depot performance versus process needs

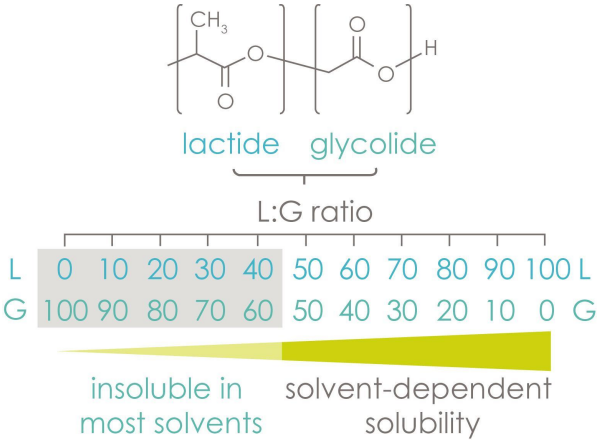
formulation

- weighing pros – cons of formulation formats that exist
- solvent based technologies
  - solvent compatibility is chemistry and drug dependant
  - solvent impact on formulation

terminal sterilization

- options, pros vs. cons and typical approaches
- accounting for sterilization impacts

many project specific challenges!



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summary

relevant excipients

- viatel™ bioresorbable polymers
- aqualon ™ CMC BET
- pharmasolve™ NMP (N-methyl-2-pyrrolidone)

technical support

- 70+ off-the-shelf viatel™ bioresorbable polymers grades
- custom polymer synthesis
  - monomer choice
  - end-cap
  - molecular weight (inherent viscosity)
  - branched / armed polymers

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