long-acting injectables

improved bioresorbable polymers for formulation success

Brad Minrovic, Ph.D
Technical Sales Account Manager, Pharmaceutical Injectables
Ashland
Bradley.Minrovic@ashland.com

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**.

Ashland™ always solving

comprehensive pharma excipient portfolio

Klucel™ hydroxypropylcellulose

Benecel™ hypromellose

Aquarius™ coating systems

Natrosol™ hydroxyethylcellulose

Aqualon™ and
Blanose™ sodium carboxymethylcellulose

Viatel™ bioresorbable polymers

Pharmasolve™ n-methyl-2-pyrrolidone

Vialose™ trehalose dihydrate

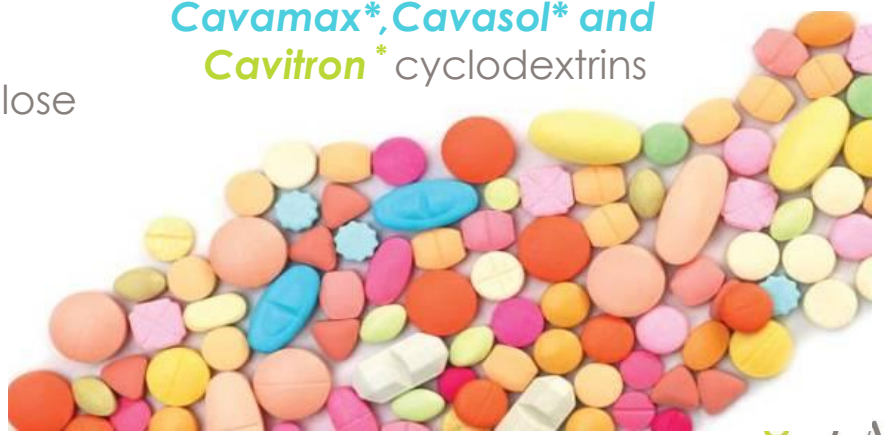
Aqualon™ ethylcellulose

Polyplasdone™ crospovidone

Plasdone™ povidone

Plasdone™ S-630 copovidone

Cavamax*,Cavasol* and Cavitron* cyclodextrins



*Registered trademark owned by Wacker Chemie AG. Ashland acts as a worldwide distributor for Wacker.

Ashland™ always solving

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

Ashland™ always solving

outline

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

- purpose of bioresorbable polymers in drug delivery
- commercial products

controlling drug release via BRP chemistry

- understanding the puzzle behind long-acting injectables

formulation selection process & chemistry for extended drug release

- choosing formulation process
- advantages of polymeric nanoparticles and customized polymers

viatel™ ultrapure : low residual monomer designed for more control

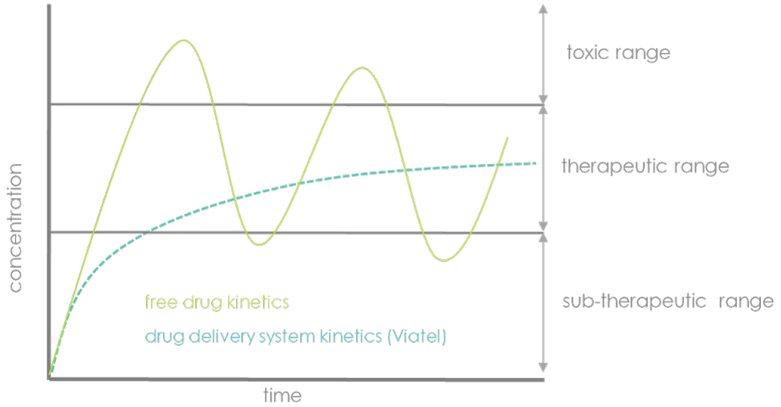
how ashland can support

Ashland™ always solving

purpose of BRPs in pharma

many drugs present

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



advantages of injectable sustained release drug delivery

- tuneable release profiles (days to months)
- decreased overall drug dosage and local delivery = reduced side effects
- consistent release within therapeutic window
- simplified drug stability by avoiding digestive system
- case dependent advantages (carriers, molecule types, other)

Ashland™ always solving

history of LG polymers in medical products

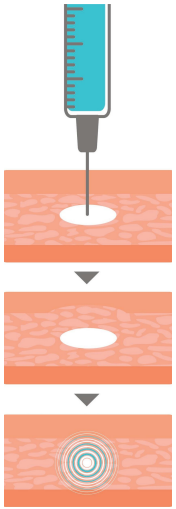
1930s-60s early patents and publications
1971 Dexon: first synthetic bioabsorbable suture
1973 DuPont: first lactide / glycolide drug delivery patent
1986 Decapeptyl*: first injectable extended-release microparticle product
1989 Zoladex*: first implantable extended-release implant product
2001 Atridox*: 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)

Ashland
always solving

LG-based drug delivery systems

in situ forming depots (API + LG polymer + solvent)

- formed in vivo, simplified formulation process
- cost effective
- administered through injection, larger initial burst effect, implant shape variance



In-situ forming system solution combined with drug injected SC

water causes system to solidify forming a depot to trap API

API releases as the polymer degrades over time

https://zilrettapro.com/how-zilretta-works/extended-release-microspheres/

Ashland™ always solving

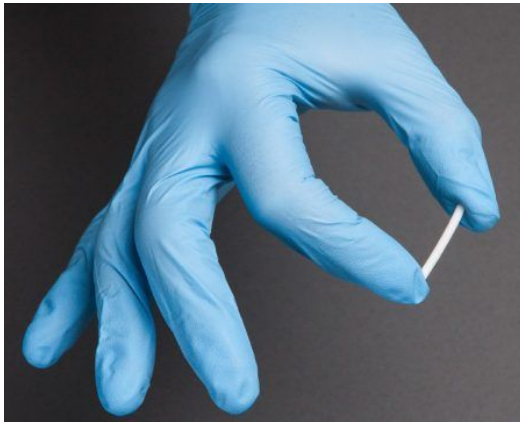
LG-based drug delivery systems

in situ forming depots (API + LG polymer + solvent)

- formed in vivo, simplified formulation process
- cost effective
- administered through injection, larger initial burst effect, implant shape variance

solid implants (API + LG polymer)

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



https://zilrettapro.com/how-zilretta-works/extended-release-microspheres/

LG-based drug delivery systems

in situ forming depots (API + LG polymer + solvent)

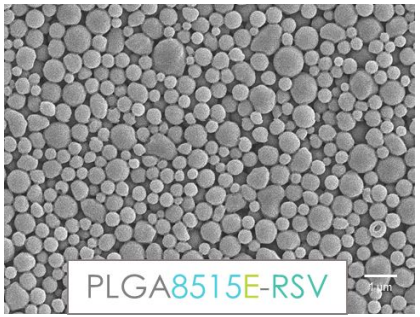
- formed in vivo, simplified formulation process
- cost effective
- administered through injection, larger initial burst effect, implant shape variance

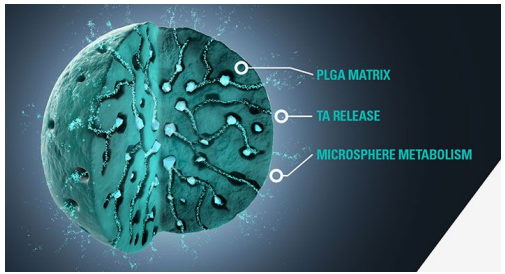
solid implants (API + LG polymer)

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

particle technologies (API + LG polymer + diluent)

- microspheres, nanoparticles
- smaller needles, tuneable profiles
- organic solvents, particle stability, complexity





https://zilrettapro.com/how-zilretta-works/extended-release-microspheres/

Ashland™ always solving

product examples

brand name	indication	company	drug substance	API Size (Da)	dose (mg)	months	needle
Eligard*	Prostate cancer	Sanofi-Aventis	Leuprolide acetate	1260 (peptide)	7.5 – 45	1, 3, 6	18 – 20 G
Sublocade*	Opioid dependency	Indivior	Buprenorphine	467.64 (SMD)	100, 300	1	19 G
Longrange*	Parasite treatment	Merial Limited	Eprinomectin	914 (SMD)	50	5	16 / 18 G
Bydureon*	Diabetes (II)	AstraZeneca	Exenatide	4187 (peptide)	2	0.25	23 G
Sandostatin* LAR	Acromegaly / flushing / cancer-induced diarrhea	Novartis	Octreotide acetate	1079 (peptide)	10 – 30	1	19 G
Decapeptyl* SR	Prostate cancer	Ipsen / Ferring	Triptorelin pamoate	1700 (peptide)	4 – 28	1, 3, 6	20 G
Scenesse*	Erythropoietic protoporphyria (light intolerance)	Clinuvel	Afamelanotide	1707 (peptide)	16	2	14 G
Zoladex® 1 / 3 month	Prostate / breast cancer	AstraZeneca	Goserelin Acetate	1269 (peptide)	3.6 – 10.8	1, 3	14 / 16 G
Revalor*	Growth promotion (animal)	Intervet / Merck Animal Health	Trenbolone / estradiol	270 / 272 (SMD)	140 / 14	6	Implant tool

in-situ

microspheres

implants

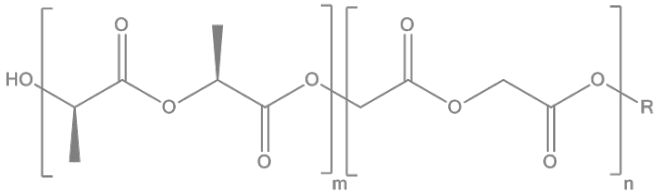
https://www.merck-animal-health-usa.com/product/cattle/Revalor-XS/1
https://www.indiamart.com/proddetail/zoladex-10-8mg-21620634848.html
https://www.labonline.com.au/content/life-scientist/article/clinuvel-success-in-scenesse-trial-1347661844
https://www.mims.com/hongkong/drug/info/sianifor%20lar
https://www.bi-vetmedica.com/species/cattle/products/longrange.htm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

Ashland™ always solving

controlling drug release via LG polymer chemistry

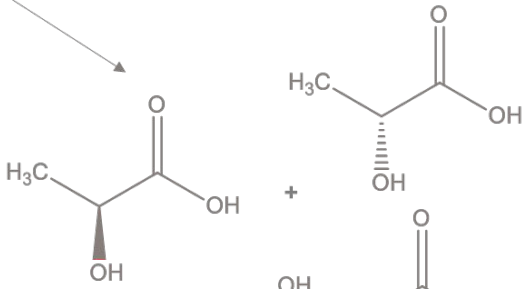
what happens LG polymers in the body?

- hydrolyzed and break down in vivo into naturally-occurring degradation by-products
- safely and easily absorbed by the body

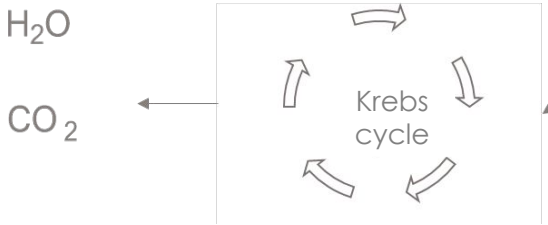


poly D, L lactide-co-glycolide (PLGA)

hydrolysis



lactic and glycolic acid



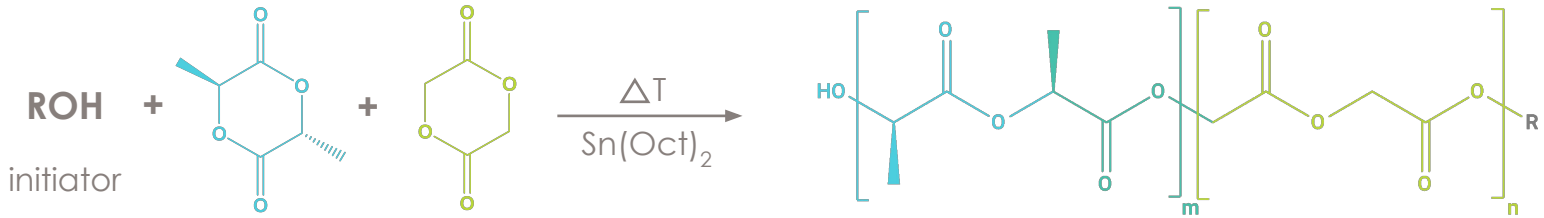
biodegradation process

1. water penetrates amorphous regions
2. cleavage of covalent bonds and a decrease in molecular weight
3. carboxylic end groups autocatalyze the process with mass loss beginning
4. solubilization

Ashland™
always solving

LG polymer synthesis and structure

ring-opening polymerization



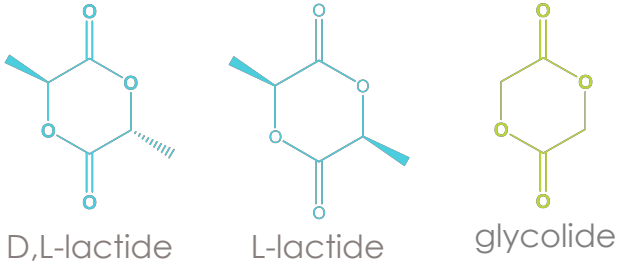
1 end group options

R = H = acid

R = CH_3 = ester

R = other

2 monomer options



3 chemical characteristics

inherent viscosity or molecular weight

no. of repeating **m** & **n** units

distribution of **m** & **n** units

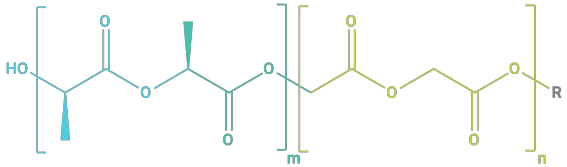
Ashland™ always solving

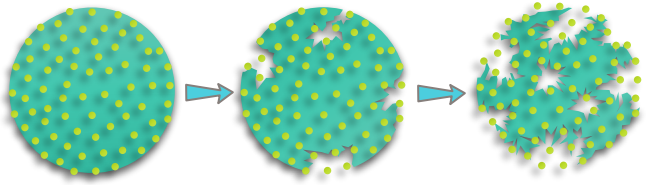
polymer chemistry controls release

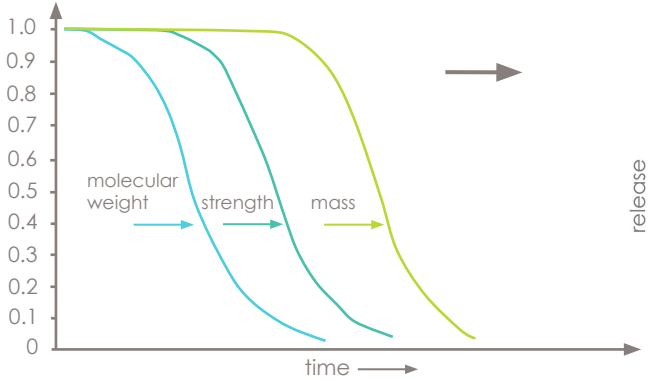
L:G ratio and distribution

molecular weight

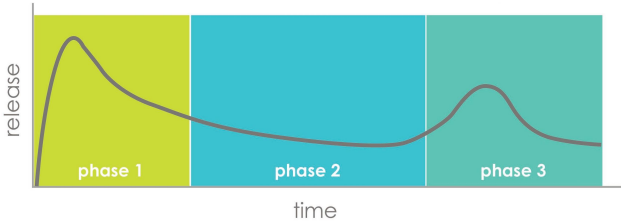
end-group and structure





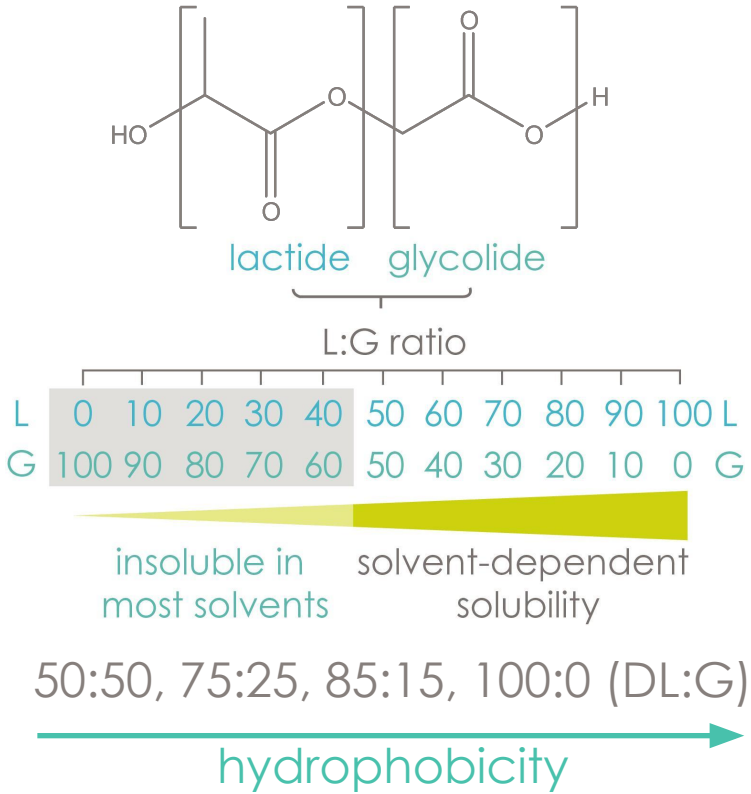


performance & release profile



Ashland™ always solving

lactide to glycolide ratio (L:G ratio)



Ashland
always solving

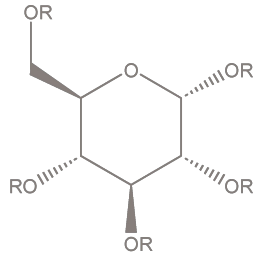
structure & microstructure

- structures
  - linear : randomized, di-block, tri-block
  - branched : glucose star initiated, dendritic

- microstructure: monomer distribution (block vs. random vs. blockiness)

alternating	L G L G L G L G L G L G
random	L L G L G G L G L G L G
increased blockiness (and block length)	L L L G G G G L L L G G

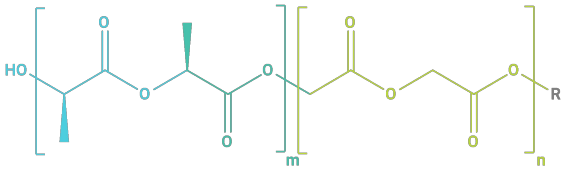
- impact on performance
  - solubility
  - drug release profile
  - processing



glucose star core

Ashland™ always solving

end group options



PLGA

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

initiator	end groups	effect
monofunctional alcohol	ester and hydroxyl	hydrophobic
Diol	hydroxyl and hydroxyl	
a-hydroxyl acid	carboxylic acid and hydroxyl	
polyethylene glycol methyl ether (mPEG)	PEG and hydroxyl	hydrophillic

Ashland™ always solving

theoretical polymer influence on release

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

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

Ashland
always solving

solving the “sustained release” puzzle

MOLAR MASS

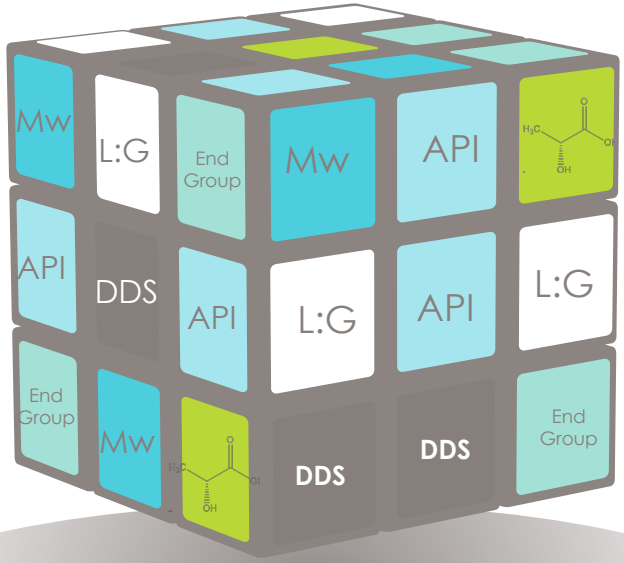
- IV, MW, PDI
- increased Mw= ++ hydrophobicity
- degradation & release implications
- viscosity implications

L : G RATIO

- increased L = more hydrophobic
- slowed degradation & release
- EE%, processing solvents, compatibility

END GROUP

- hydrophilicity : Ester > Acid > PEG
- swelling, release, degradation
- EE%, compatibility, other



DEPOT FORMAT & PROCESSING (DDS)

- category: Particle, ISI depot, implant
- particle type/size, surface area
- solvent type, processing conditions

POLYMER STRUCTURE

- linear, diblock, triblock, branched

API RELATED

- loading, encapsulation efficiency,
- drug form, molecule size & solubility
- drug dispersion

Ashland™ always solving

case : Eligard*

Eligard* (leuprolide acetate)

- long acting polymer
  - **poly D,L lactide-co-glycolide (PLGA)**
- biocompatible solvent
  - **N-methyl-2-pyrrolidone (NMP)**
- active pharmaceutical ingredient
  - **leuprolide acetate (API)**

4 long-acting variations

- 1 month : 7.5 mg **API** + 82.5 mg **PLGA 50:50 A** + 160 mg **NMP**
- 3 month : 22.5 mg **API** + 158.6 mg **PLGA 75:25 E** + 193.9 mg **NMP**
- 4 month : 30 mg **API** + 211.5 mg **PLGA 75:25 E** + 258.5 mg **NMP**
- 6 month : 45 mg **API** + 165 mg **PLGA 85:15 E** + 165 mg **NMP**

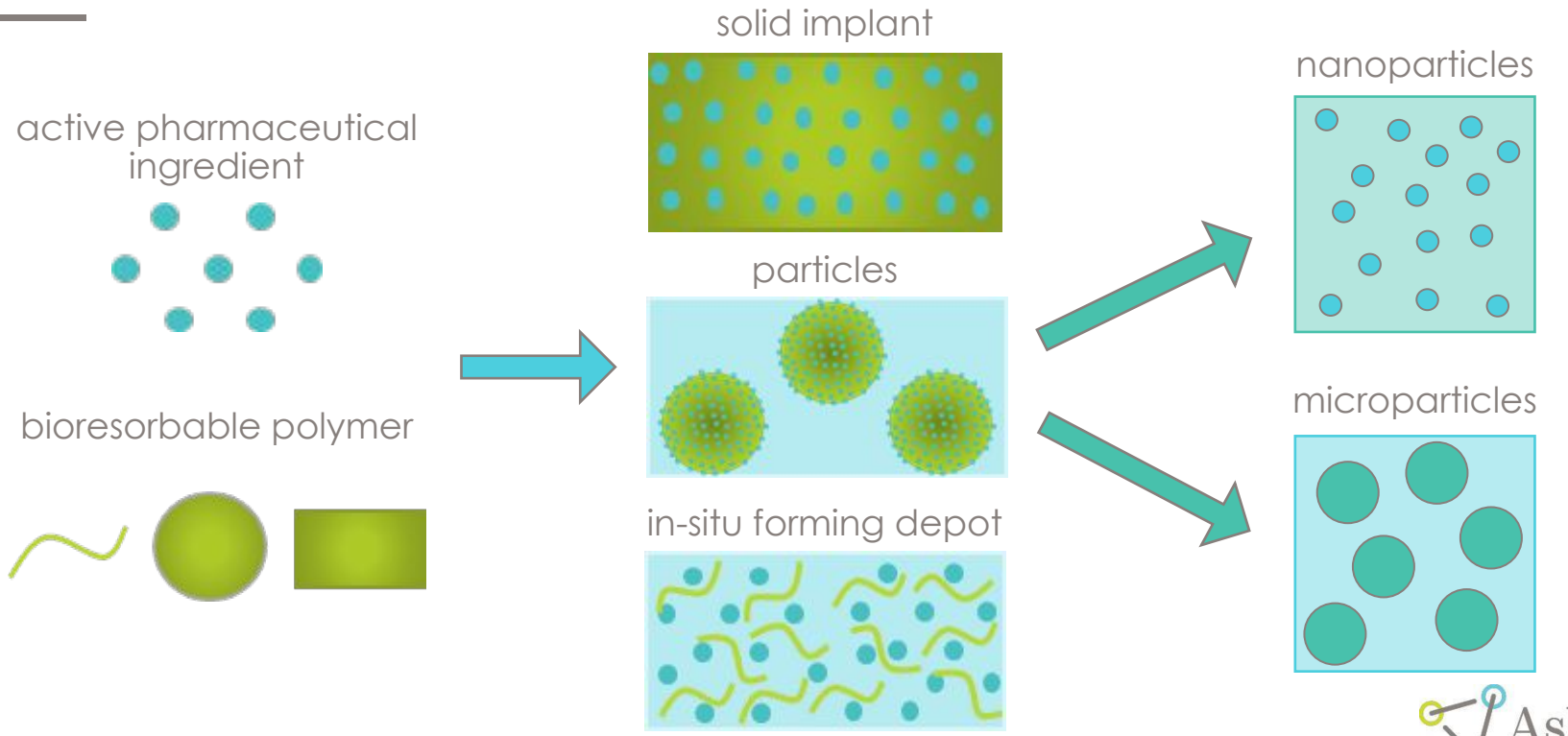
https://info.eligardhcp.com/all-topics/eligard-overview/description/
https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021731s005,021488s010,021379s010,021343s015lbl.pdf
http://products.sanofi.ca/en/eligard.pdf

Ashland™ always solving

formulation strategies & optimization

Ashland™
always solving

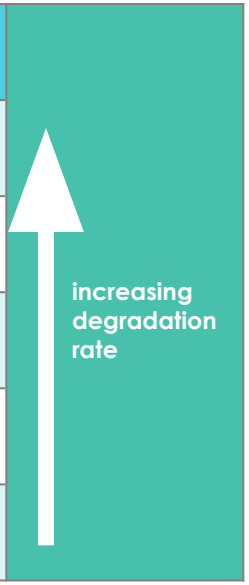
formulation options



Ashland
always solving

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

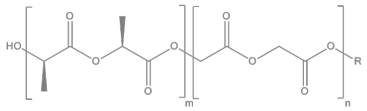


PEGylated polymers, such as PCL-PEGs, can decease melting temperature resulting in lower HME processing temperatures

Ashland™ always solving

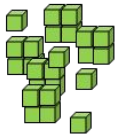
implants: hot melt extrusion process

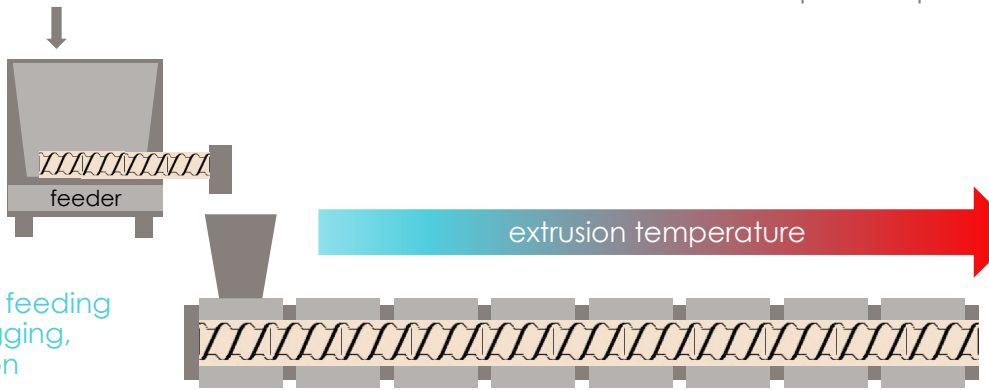
polymer



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

Ashland™ always solving

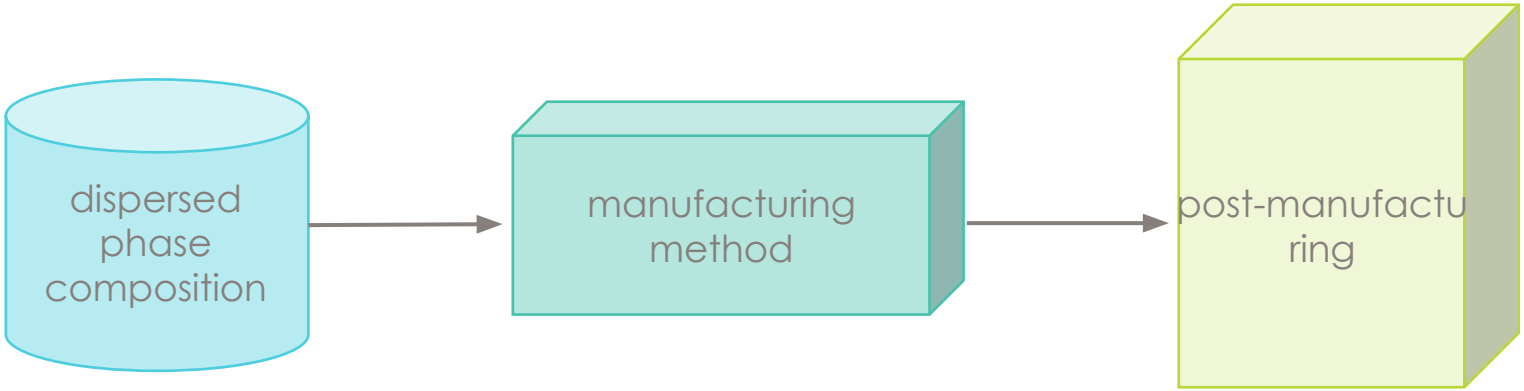
PLGA form enhancement for HME

fine particles improve HME formulations and lead to increased content uniformity

additional milling capabilities available for unique applications

Ashland™ always solving

microsphere process

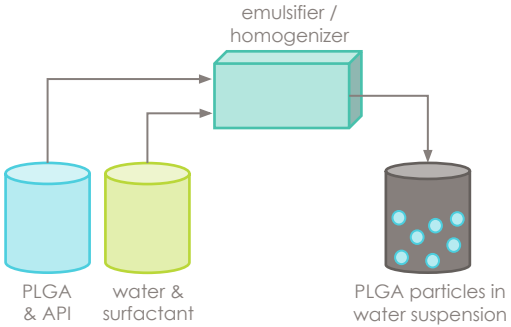


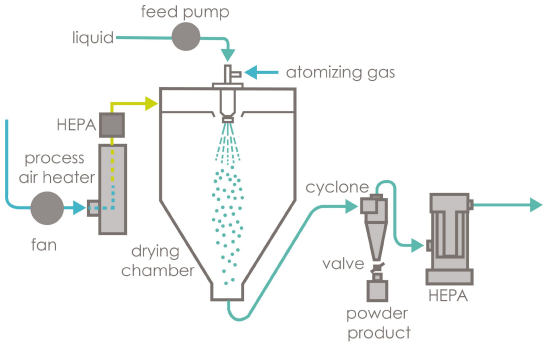
Ashland
always solving

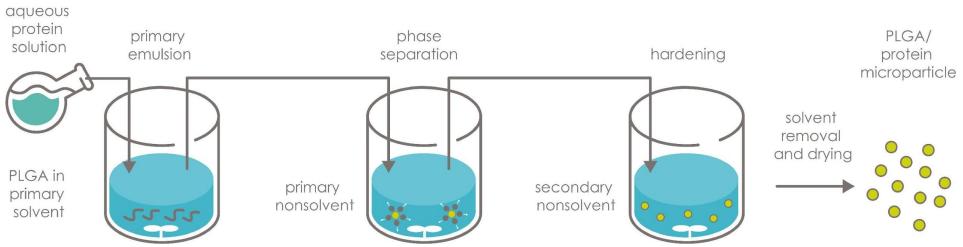
particle technologies

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

+ downstream handling





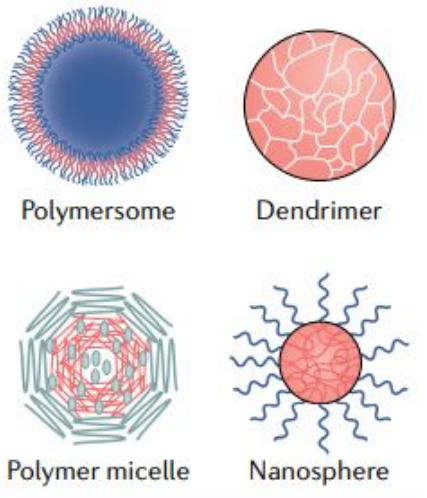


Ashland™ always solving

polymeric nanoparticle advantages

why use LG polymer NPs for drug delivery?

- enhanced drug stability and solubility
- transport across membranes allows intracellular delivery of all types of APIs, organic small molecules and biologics
- prolonged circulation times increases safety and efficacy
- flexibility in method of API incorporation
- amenable to small molecules, peptides, proteins or nucleic acids
- control of polymer and particle characteristics allows precise, targeted and controlled delivery



Banik, B.L., Fattahi, P. and Brown, J.L. (2016), Polymeric nanoparticles: the future of nanomedicine. WIREs Nanomed Nanobiotechnol, 8: 271-299.

Ashland™
always solving

PEGylated LG polymer NPs

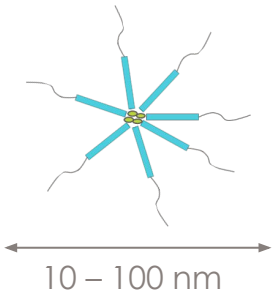
amphiphilic PLA-PEG di-block co-polymer

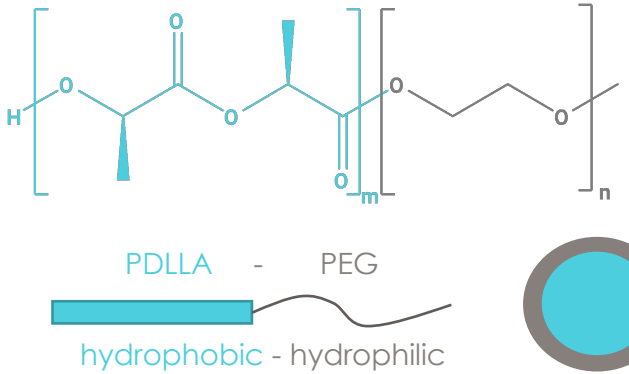
self-assembling micelles

EPR effect for passive targeting in tumors

PEG corona

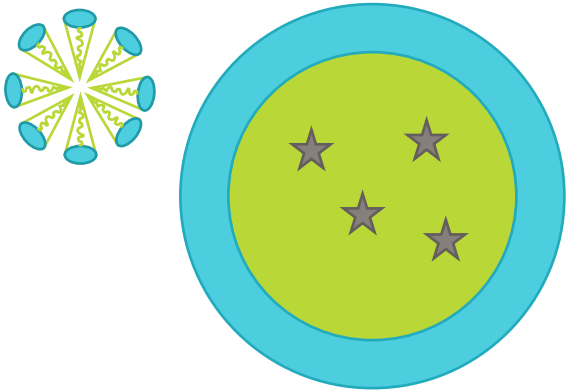
- avoid immune system (stealth effect)
- 2-5 kDa for desirable blood circulation profile
  - Less opsonization
  - Higher circulation time
  - Kidney elimination
  - Avoid liver clearance



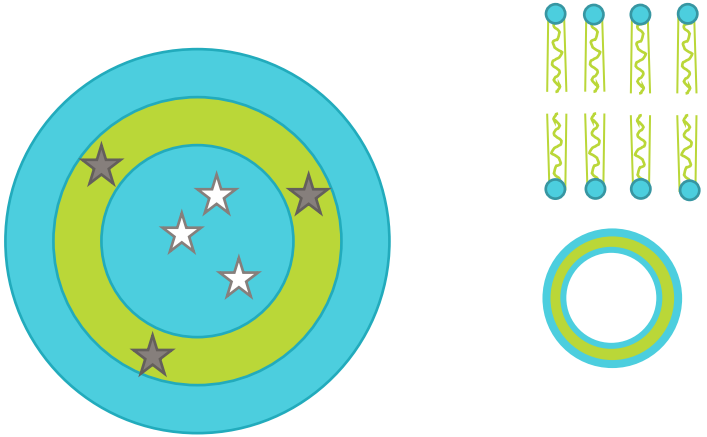


Ashland
always solving

micelles vs. vesicles: drug carrier



only hydrophobic drugs



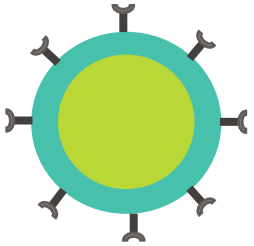
both hydrophobic and hydrophilic drugs

hydrophilic part
hydrophobic part

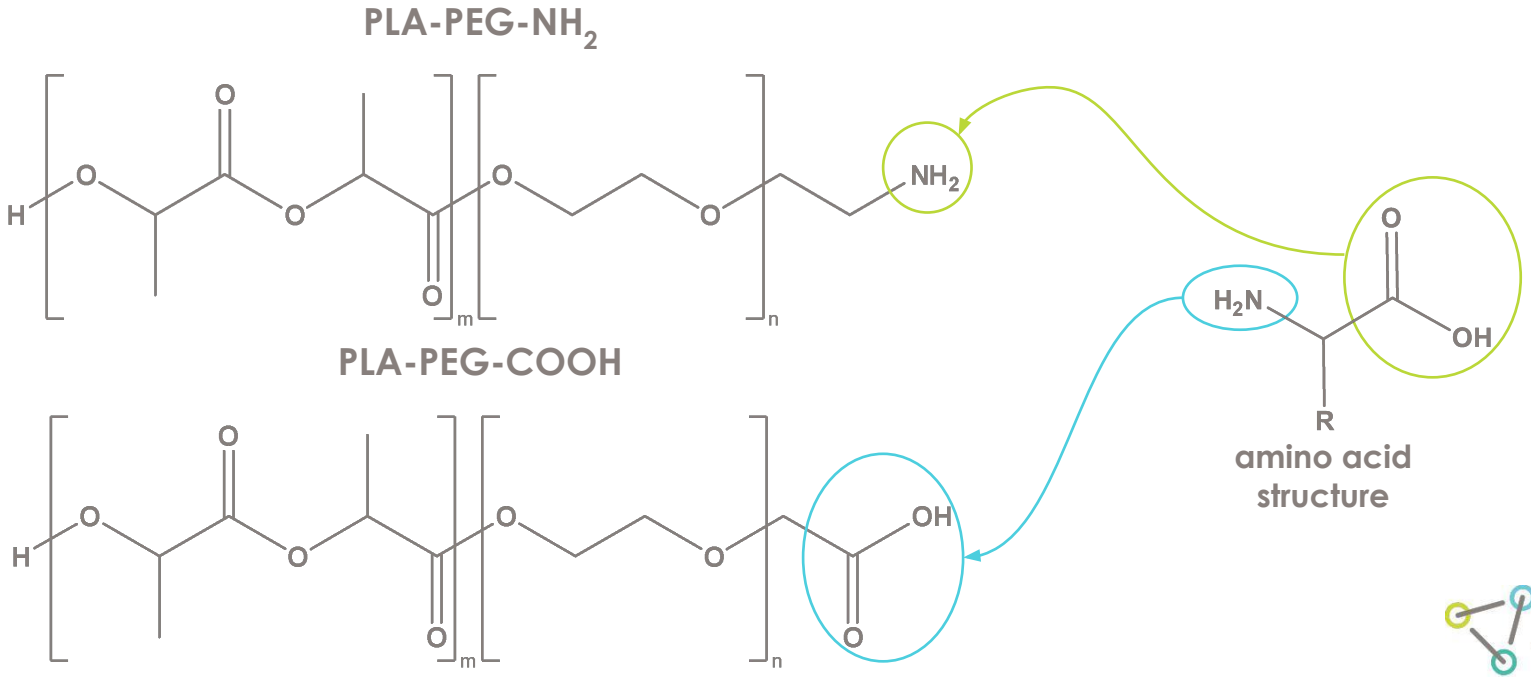
hydrophilic drug
hydrophobic drug

Ashland
always solving

functionalised LG-PEG NPs

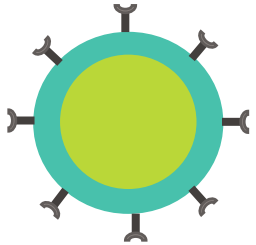


- from passive to active targeting

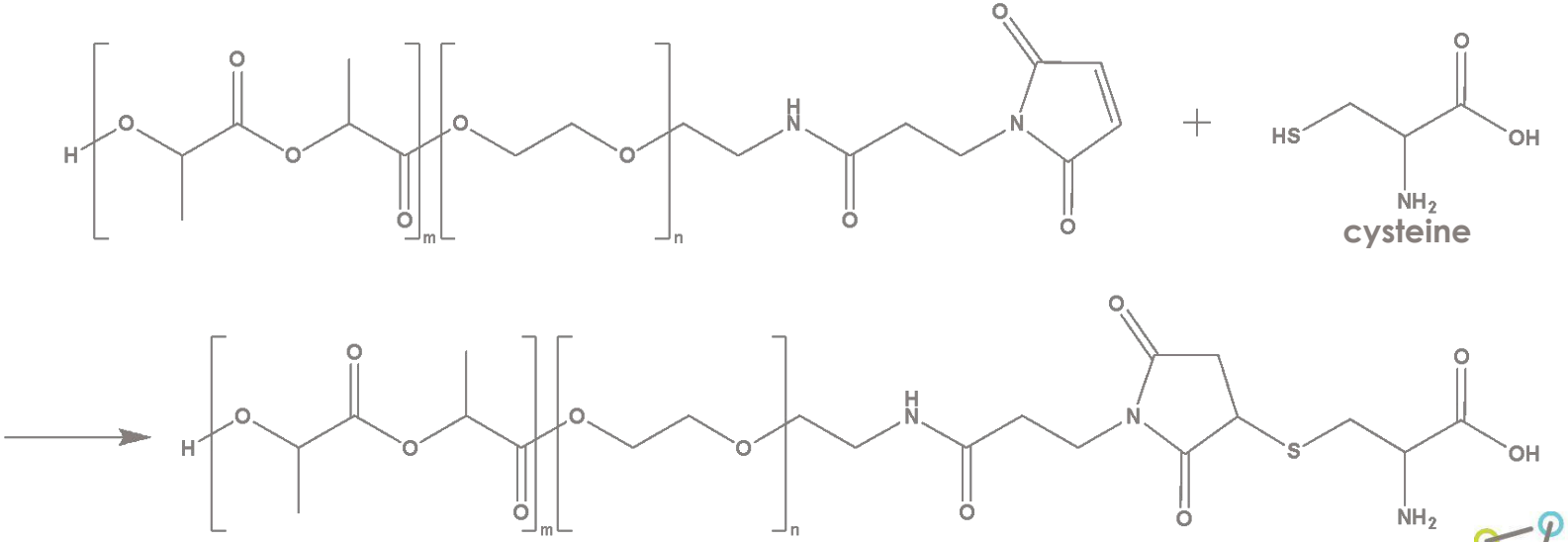


Ashland
always solving

functionalised LG-PEG NPs



PLA-PEG-MAL → more specific for thiol function – end-capping with ligands



Ashland
always solving

viatel™ ultrapure

Ashland™
always solving

viatel™ ultrapure : introduction

what is it? lowered residual monomer

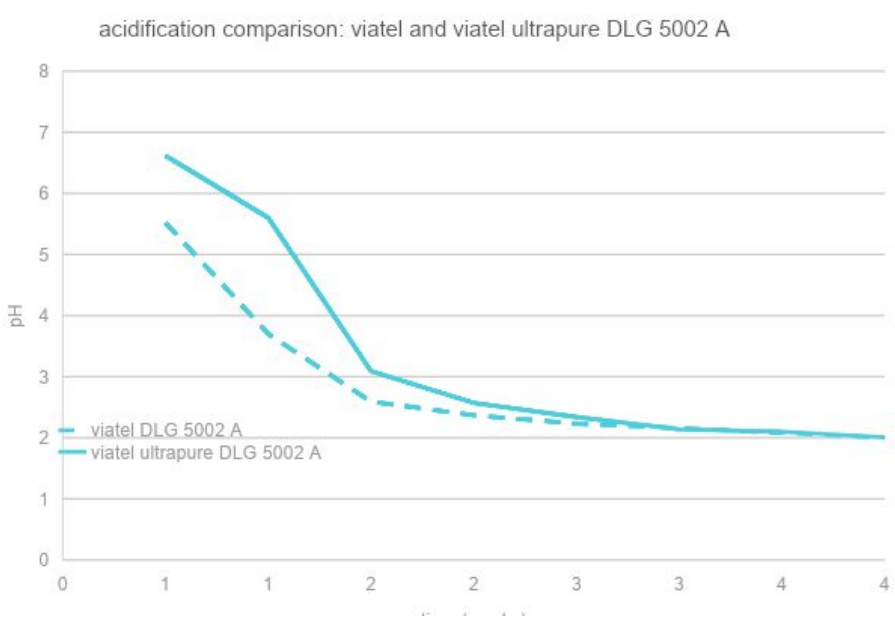
key features

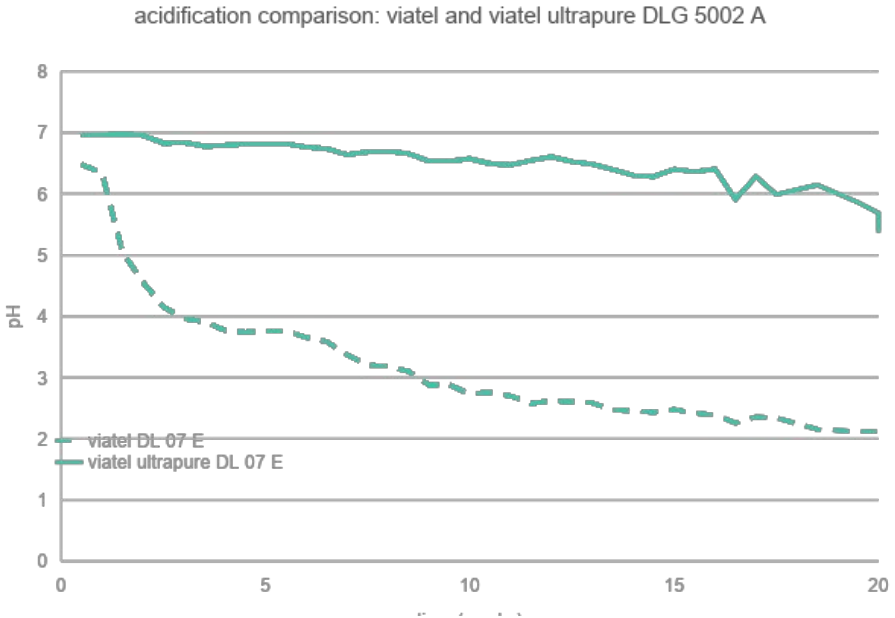
- lowered residual monomer : ≤ 0.5% total, typical batch results of 0.1%
- pre-filtered polymer during additional purification process to ensure exceptional quality

benefits

- reduced acidity
  - improved API stability
  - improved shelf-life stability
- improved release consistency across all applications due to fewer variables
- extended release in hot melt extrusion and in situ forming depot applications

viatel™ ultrapure = less acidic



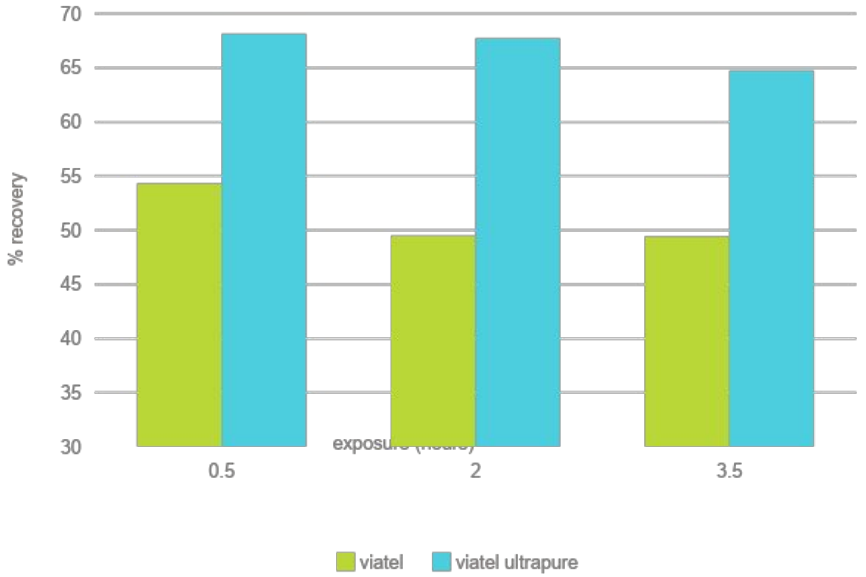


viatel™ ultrapure polymers exhibit decreased acidity when pH is monitored in PBS

Ashland
always solving

omeprazole stability

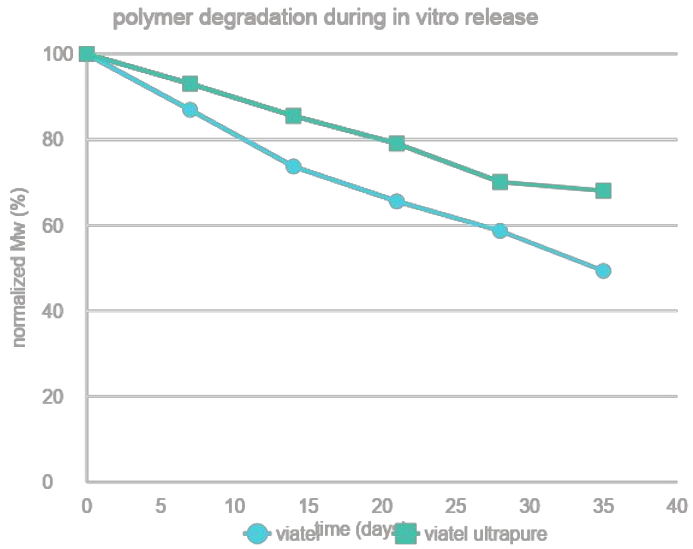
composition	viatel	viatel ultrapure
polymer	DL 02 A	
monomer	3%	0.2%
NMP	80%	
API	10% omeprazole	

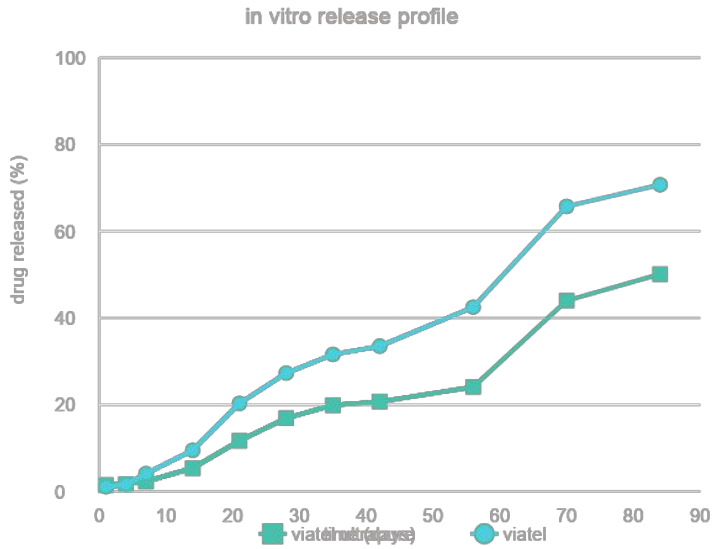


omeprazole exhibits increased stability with viatel™ ultrapure

Ashland™ always solving

dexamethasone implant results

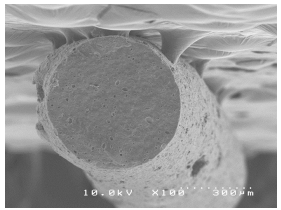
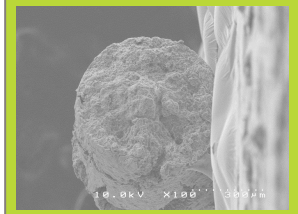
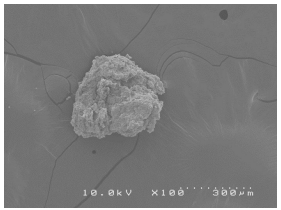
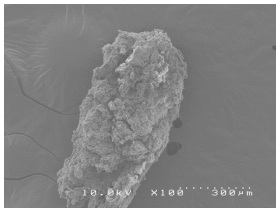
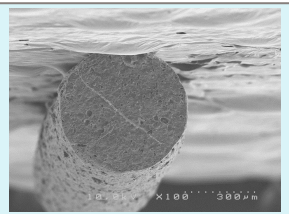
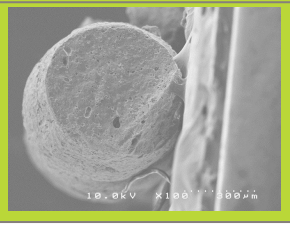
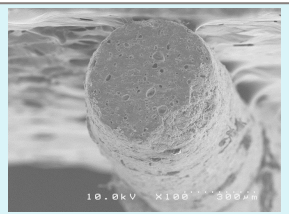
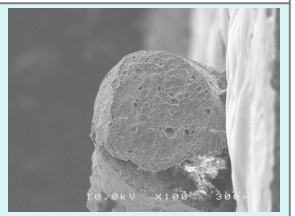




dexamethasone implant formed with viatel™ ultrapure displays preserved molecular weight during release and extended release

Ashland
always solving

dexamethasone implant morphology during release

polymer	time (weeks)			
	1	2	3	4
viatel™				
viatel™ ultrapure				

Ashland™ always solving

Ashland's offerings

Ashland™
always solving

viatel™ lactide/glycolide platform

amorphous copolymers

- poly D,L lactide-co-glycolide (PLGA or PDLGA)
- poly D,L-lactide (PDLLA)
- PEGylated PLA's / PLGA's (mPEG-PLA / mPEG-PLGA)

semi-crystalline copolymers

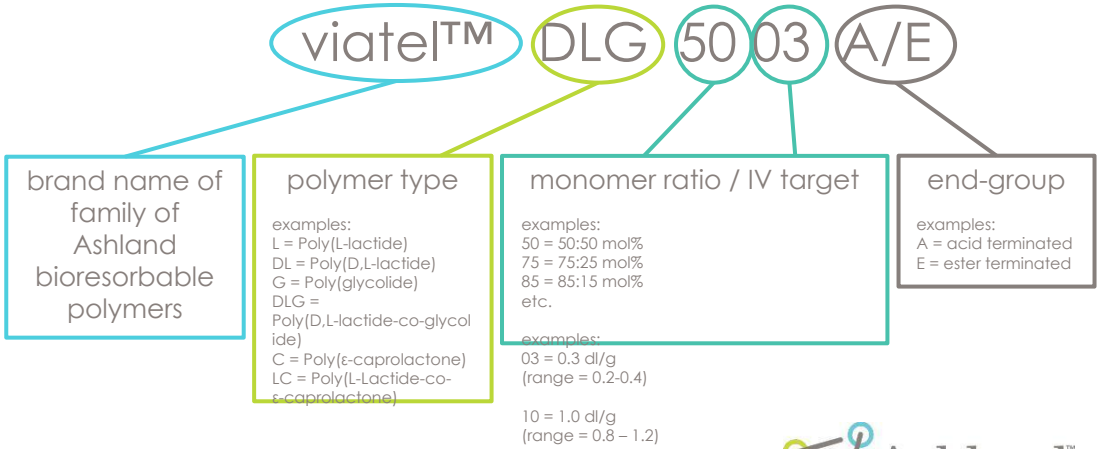
- poly L lactide (PLLA)
- poly caprolactone (PCL)
- poly L-lactide-co-glycoilde (P-L-LGA)

all products have high purity

- low residual tin
- new: viatel™ ultrapure

other

- custom specifications available
- de-formulation / PLGA matching



Ashland™
always solving

expanded grade offering

polymer	molar ratio	inherent viscosity range (dl/g)	end group	product code
poly(D,L-lactide-co-glycolide)	50:50	0.1 – 0.3	Acid / Ester	Viatel™ DLG 5002 A/E
		0.2 – 0.4	Acid / Ester	Viatel™ DLG 5003 A/E
		0.4 – 0.6	Acid / Ester	Viatel™ DLG 5005 A/E
		0.6 – 0.8	Acid / Ester	Viatel™ DLG 5007 A/E
		0.8 – 1.0	Acid / Ester	Viatel™ DLG 5009 A/E
		1.0 – 1.2	Acid / Ester	Viatel™ DLG 5011 A/E
		1.2 – 1.4	Acid / Ester	Viatel™ DLG 5013 A/E
	55:45	0.2 – 0.4	Acid / Ester	Viatel™ DLG 5503 A/E
		0.4 – 0.6	Acid / Ester	Viatel™ DLG 5505 A/E
	65:35	0.2 – 0.4	Acid / Ester	Viatel™ DLG 6503 A/E
	75:25	0.1 – 0.3	Acid / Ester	Viatel™ DLG 7502 A/E
		0.2 – 0.4	Acid / Ester	Viatel™ DLG 7503 A/E
		0.4 – 0.6	Acid / Ester	Viatel™ DLG 7505 A/E
		0.6 – 0.8	Acid / Ester	Viatel™ DLG 7507 A/E
		0.8 – 1.0	Acid / Ester	Viatel™ DLG 7509 A/E
		1.0 – 1.2	Acid / Ester	Viatel™ DLG 7511 A/E
		1.2 – 1.4	Acid / Ester	Viatel™ DLG 7513 A/E
	80:20	0.1 – 0.3	Acid / Ester	Viatel™ DLG 8002 A/E
		0.2 – 0.4	Acid / Ester	Viatel™ DLG 8003 A/E
	85:15	0.1 – 0.3	Acid / Ester	Viatel™ DLG 8502 A/E
		0.2 – 0.4	Acid / Ester	Viatel™ DLG 8503 A/E
		0.4 – 0.6	Acid / Ester	Viatel™ DLG 8505 A/E
		0.6 – 0.8	Acid / Ester	Viatel™ DLG 8507 A/E
		0.8 – 1.0	Acid / Ester	Viatel™ DLG 8509 A/E
		1.0 – 1.2	Acid / Ester	Viatel™ DLG 8511 A/E
		1.2 – 1.4	Acid / Ester	Viatel™ DLG 8513 A/E

polymer	molar ratio	inherent viscosity range (dl/g)	end group	product code
poly(D,L-lactide)	100:0	0.1 – 0.3	Acid / Ester	Viatel™ DL 02 A/E
		0.2 – 0.4	Acid / Ester	Viatel™ DL 03 A/E
		0.4 – 0.6	Acid / Ester	Viatel™ DL 05 A/E
		0.6 – 0.8	Acid / Ester	Viatel™ DL 07 A/E
		0.8 – 1.0	Acid / Ester	Viatel™ DL 09 A/E
		1.0 – 1.2	Acid / Ester	Viatel™ DL 11 A/E
		1.2 – 1.4	Acid / Ester	Viatel™ DL 13 A/E
poly(ethylene glycol) methyl ether-block-poly(D,L lactide)	-	0.33 – 0.38 *	--	Viatel™ DL 03 PEG5K
poly(L-lactide)	-	0.8 – 1.2	Ester	Viatel™ L 10 E
	-	1.2 – 1.6	Ester	Viatel™ L 14 E
	-	1.6 – 2.0	Ester	Viatel™ L 18 E
poly(ε-caprolactone)	-	1.0 – 1.4	Ester	Viatel™ C 12 E
	-	1.6 – 2.0	Ester	Viatel™ C 18 E
poly(L-lactide-co-ε-caprolactone)	60:40	1.0 – 1.4	Ester	Viatel™ LC 6012 E
	70:30	1.0 – 1.4	Ester	Viatel™ LC 7012 E
	80:20	1.0 – 1.4	Ester	Viatel™ LC 8012 E
	90:10	1.0 – 1.4	Ester	Viatel™ LC 9012 E

GMP viatel™ ultrapure grades will be available for LG polymers

Ashland™ always solving

quality and regulatory status

good manufacturing processes (GMP) compliance

- USP <1078> and Joint IPEC-PQG GMP Guide for Pharmaceutical Excipients (IPEC, 2017)
- manufactured in an ISO Class 8 clean room
- ISO 13485:2016 certified since 2013 (Notified Body: LRQA Lloyds)

regulatory status

- type IV DMF filed with FDA 33847
- FDA chemical registration completed

lead times

- in-stock materials : **2 – 3 weeks** for shipping
- made-to-order : **5 – 8 weeks** for shipping

Ashland announces expansion of Viatel™ bioresorbable polymers manufacturing and R&D capabilities in Mullingar, Ireland

August 30, 2022 17:00 ET | Source: Ashland, Inc.

Ashland announces expansion of Viatel™ bioresorbable (globenewswire.com)

custom structures

tailored LG copolymers

- narrowed specifications : useful to standardise release (± 0.02 dl/g)
- DOE studies : varying L:G, Mw, end groups (incremental batches)
- test specification limits: batch provision at high, middle and low end of specification
- batch consistency testing : repeat lots within target range

adjusted polymer structures

- composition: lactide, glycolide, caprolactone, PEG, other
- linear, di-block, tri-block, branched/dendritic structures
- end groups for active targeted delivery (e.g. maleimide)

new chemistries

- new polymers for sustained release
- surface eroding polymers

Ashland™
always solving

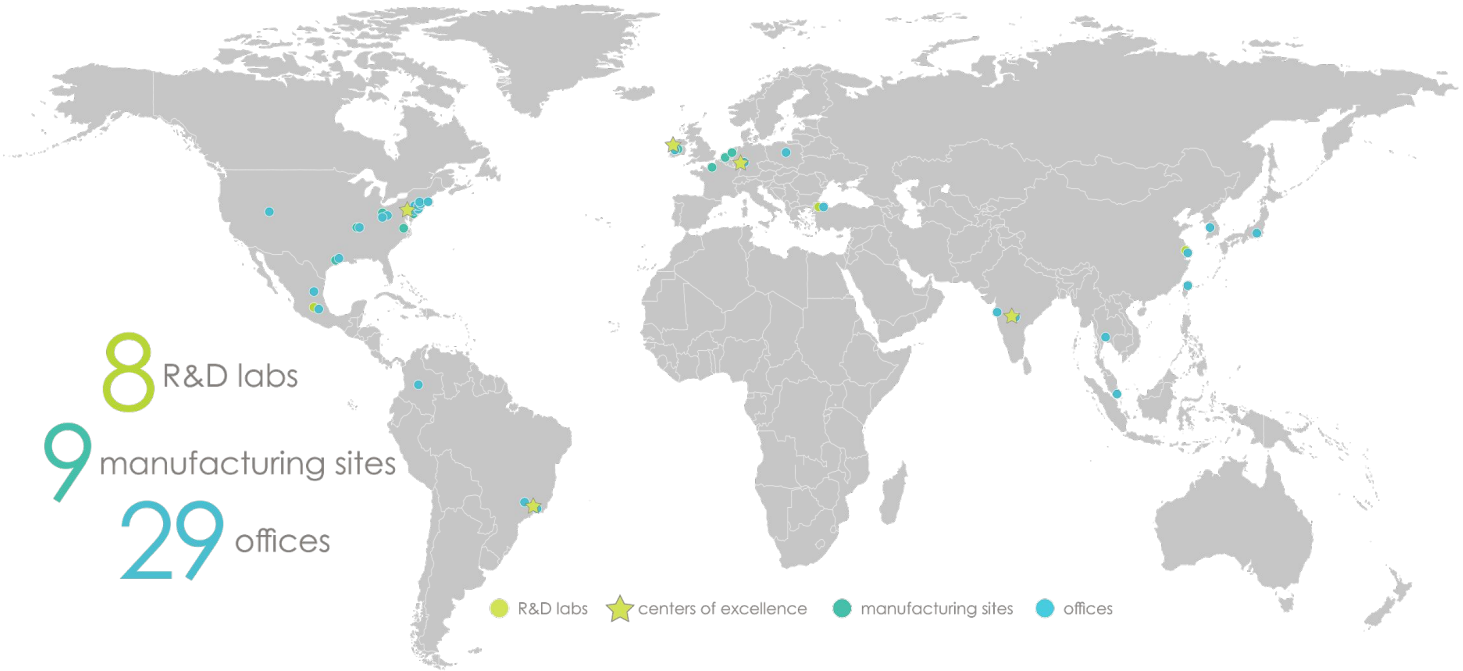
Azhari, Z., **McMahon, S.,** Pierucci, L., Wang, W.*, Cameron, R.* 'Short Poly(ethylene glycol) Block Initiation of Poly(L-lactide) Di-block Copolymers: A Strategy for Tuning the Degradation of Resorbable Devices'. *POLYMER INTERNATIONAL*, 2018, 67, 726-738, DOI: 10.1002/pi.5563.

made-to-order (MTO) examples

- example 1 : DOE study example - increment at ± 0.02 dl/g
- example 2 : lot-to-lot variability & spec setting - repeat batches within ± 0.01 dl/g
- MTO batch options: 0.1 kg, 0.5 kg, 1.5 kg, 3.5 kg, 10 kg, 20-30 kg
- typical MTO lead time : 5 - 8 weeks to ship

rational	viatel™ grade	L:G ratio	IV request (dl/g)	batch #	IV result	Mw	quantities
DOE study	DLG 7505 A	75:25	0.38 – 0.42	2619314	0.38 dl/g	42.7 kDa	1 kg
			0.42 – 0.46	2619063	0.43 dl/g	45.8 kDa	1 kg
			0.46 – 0.50	2619881	0.46 dl/g	53.0 kDa	1 kg
			0.50 – 0.54	2567897 2601092 2594415	0.50 dl/g 0.50 dl/g 0.51 dl/g	60.8 kDa 59.5 kDa 61.7 kDa	3 x 1 kg
lot-to-lot variability & specification establishment (high, mid, low)	DL 02 A	100:0	0.15 – 0.17	2585007	0.17 dl/g	13.8 kDa	500 g
				2588391	0.16 dl/g	13.2 kDa	500 g
				2586589	0.15 dl/g	11.8 kDa	500 g

committed to supporting customers



Ashland™
always solving

common challenges

chemistry

- how to select / optimize appropriate polymer?
- troubleshooting issues?
- residual monomer

partnering - CMO/CDMO engagement

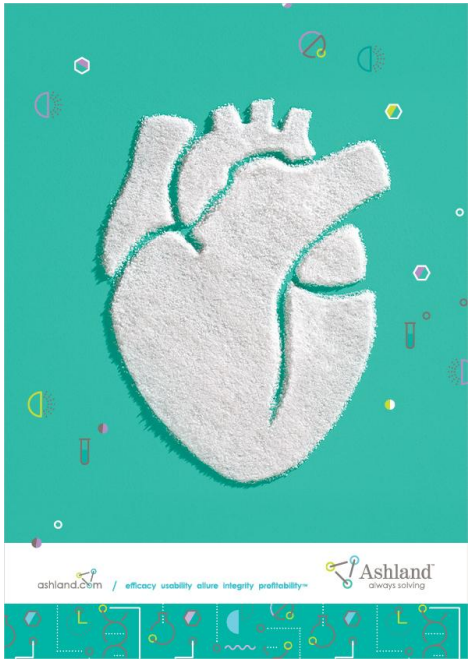
formulation

- pro's / con's / limits of formulation formats
- melt based technology
  - HME, 3D printing, injection molding, etc.
  - Particle form benefits
- solvent based technologies
  - solvent solubility can be chemistry dependant
  - solvent impact on particle size / morphology & solvent removal
  - adjusting ISI formulation composition for required release

terminal sterilization

- options, pros vs. cons and risk mitigation

many project specific challenges!!



Ashland™
always solving

disclaimer

The information contained in this presentation and the various products described are intended for use only by persons having technical skill and at their own discretion and risk after they have performed necessary technical investigations, tests and evaluations of the products and their uses. This material is for informational purposes only and describes the scientific support for the use of the products described herein as an ingredient intended to enhance performance of an end product. **Certain end uses of these products may be regulated pursuant to rules governing medical devices or other regulations governing drug uses. It is the purchaser's responsibility to determine the applicability of such regulations to its products.** While the information herein is believed to be reliable, we do not guarantee its accuracy and a purchaser must make its own determination of a product's suitability for purchaser's use, for the protection of the environment, and for the health and safety of its employees and the purchasers of its products.

Neither Ashland nor its affiliates shall be responsible for the use of this information, or of any product, method, formulation, or apparatus described in this brochure. Nothing herein waives any of Ashland's or its affiliates' conditions of sale, and no statement, information and data is to be taken as a guarantee, an express warranty, or an implied warranty of merchantability or fitness for a particular purpose, or representation, express or implied, for which Ashland and its affiliates assume legal responsibility. We also make no warranty against infringement of any patents by reason of purchaser's use of any information, product, method or apparatus described in this presentation.

The testing information (the "Testing Information") has been gratuitously provided by Ashland. The Testing Information is based on many factors beyond Ashland's control, including but not limited to, the conditions prevailing when the testing was conducted, and in some cases, is based on data generated with development samples of the Active Ingredient. Although it is intended to be accurate, ASHLAND DISCLAIMS ANY AND ALL LIABILITY, EITHER EXPRESS OR IMPLIED. The Testing Information is confidential or proprietary to Ashland, and may not, except as provided below, be disclosed to any third party. You may not make commercial use of the Testing Information, or make claims with respect to your products based the Testing Information, without the written agreement with Ashland covering such use.

Ashland™
always solving

- samples, orders & support: Bradley.Minrovic@Ashland.com
- visit the Ashland booth 206