

Importance of Regulatory Research Funding for Long Acting Release (LAR) Drug Products

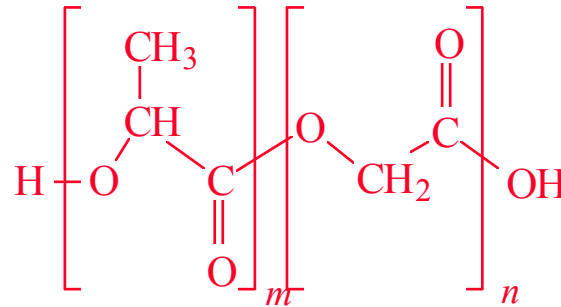
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Poly(lactic-co-glycolic acid) (PLGA) for controlled release

- Structure



e.g., PLGA 50/50, $m/n = 1$

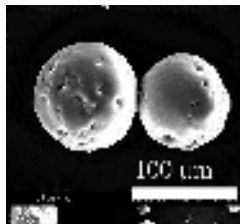
PLGA 75/25, $m/n = 3$

$M_w \sim 10 \text{ kDa} - 100 \text{ kDa}$

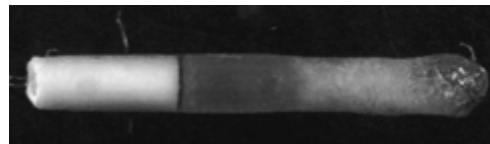
- Advantages

- wide range of properties
- ease of processing
- predictable *in vivo* degradation kinetics
- FDA approval for use in humans
- No daily injections
- Control release rate
- Lower systemic toxicity
- Reduce booster doses (vaccines)

- Major configurations of injectable devices



microspheres (1 - 100 μm)



millicylinders ($\varnothing = 0.8\text{-}1.5 \text{ mm}$)



in-situ forming implants

Top FDA approved PLGA LAR products

Name	Drug	Company	Dosing	Indication	Sales
Risperdal Consta	Resperidone	Janssen Alkermes	1 mo	Schizophrenia Bipolar	1.4 B
Sandostatin LAR	Octreotide	Novartis	1 mo	Acromegaly	1.5 B
Zoladex	Goserelin	AstaZeneca	1, 3 mo	Prostate Cancer	1.1 B
Lupron Depot	Leuprolide	Takeda/ Abbott	1, 3, 4, 6 mo	Prostate Cancer	600 M
Decapeptyl/ Telstar/ Pamorelin	Triptorelin	Ipsen/ Watson/ Reddy Debiopharm	1 mo 3 mo 6 mo	Prostate Cancer	500 M
Profact Depot	Buserelin	Aventis	2-3 mo	Prostate Cancer	500 M
Bydureon	Exenatide	Amylin/BMS Alkermes	1 wk	Type 2 Diabetes	350 M
Eligard	Leuprolide	QLT	1, 3, 4, 6 mo	Prostate Cancer	300 M

Generic LAR product approval has been slow

- Complex processes, specialized equipment, specialized plants
- Small process and raw material changes could result in significant product changes
- No standard *in vitro* drug release assay predictive of *in vivo* changes exists – different assays = variable results
- Few models correlating *in vitro* drug release with *in vivo* pharmacokinetics (efficacy and safety) available

Research is needed to: 1) fill the scientific gaps, 2) aid in FDA regulation development for LAR and 3) publish data to guide generic product development.

Processes for leuprolide solution and Lupron Depot®

Leuprolide solution process

1. Dissolve peptide and excipients
2. Filter and 3. Fill vials

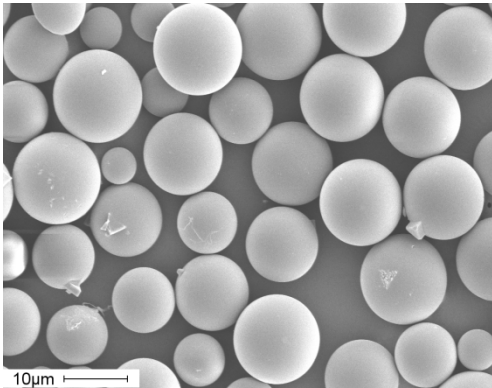
Lupron Depot® process

1. Dissolve peptide and excipients
2. Dissolve and 3. Filter polymer
4. Homogenize for w/o emulsion
5. Cool and mix with PVA water
6. In flow homogenize for w/o/w
7. Stir, 8. Filter and 9. Centrifuge
10. Disperse in water and 11. Sieve
11. Add excipients and 12. Lyophilize
13. Prepare diluent
14. Fill dual-chamber syringes

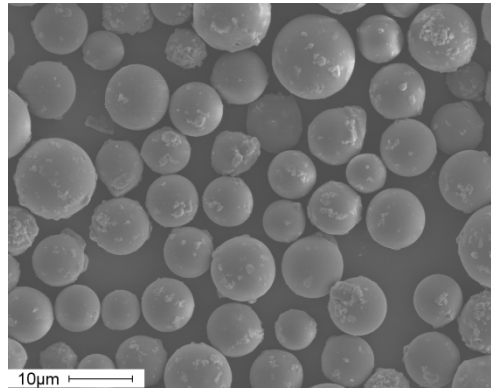
Lupron Depot® process ~ 14 steps
Leuprolide Solution ~ 3 steps

**Many more process variables
could affect Lupron Depot®
performance *in vivo***

Equivalent formulations made by different processes can result in drug release differences



O/W



S/O/W

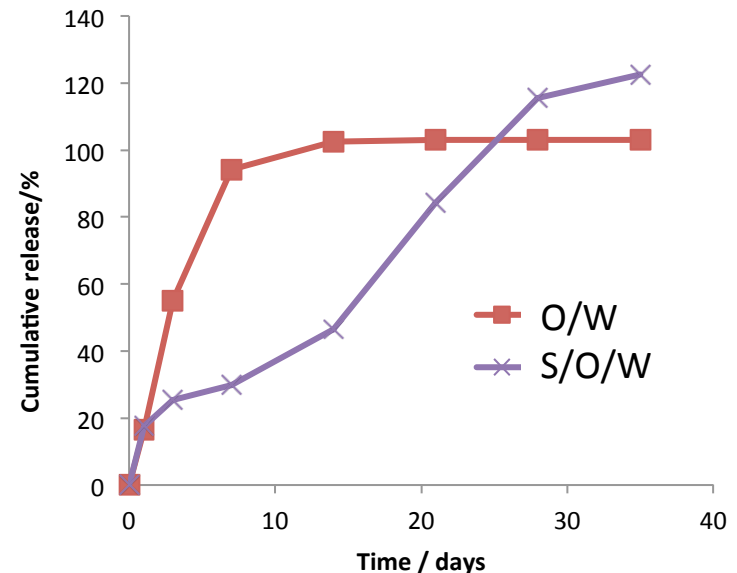
Two equivalent Q1/Q2 formulations of triamcinolone acetonide in PLGA

Process 1: oil-in-water emulsion (O/W)

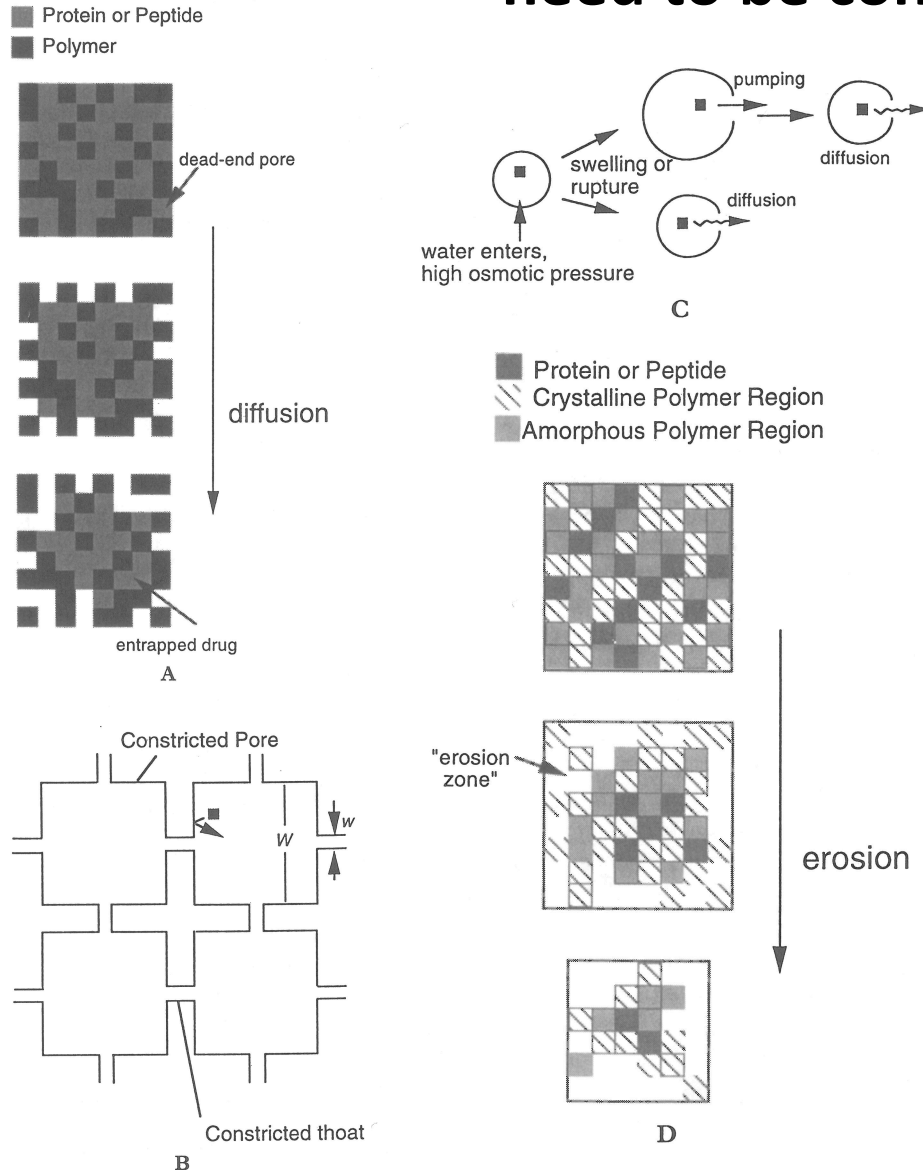
Process 2: solid-in-oil-water suspension-emulsion (S/O/W)

Process differences result in drug release differences

Release differences will likely result in *in vivo* PK, efficacy and toxicity differences



Multiple mechanisms of release from PLGA need to be considered



Physical principles that govern release of peptides and proteins from polymers.

A: Diffusion through percolating clusters.

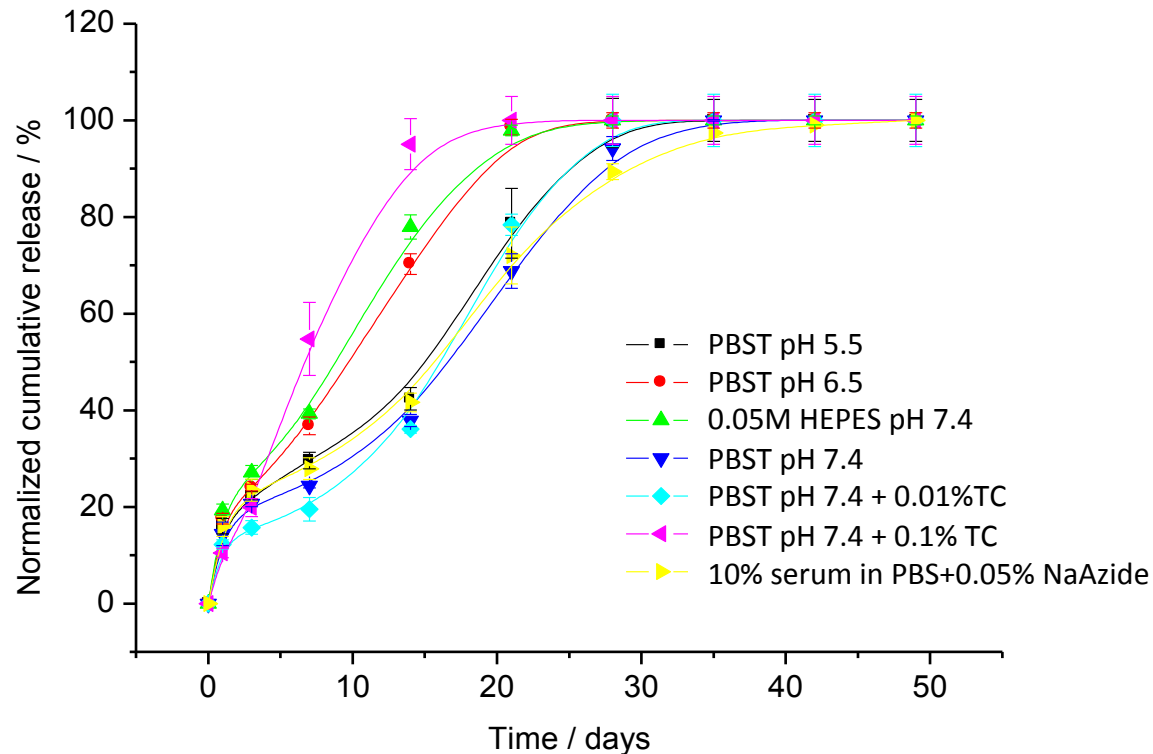
B: Diffusion out of a "trap" created by constrictions between pores.

C: Osmotically induced mass transfer or new pore formation.

D: Erosion of the biodegradable polymer.

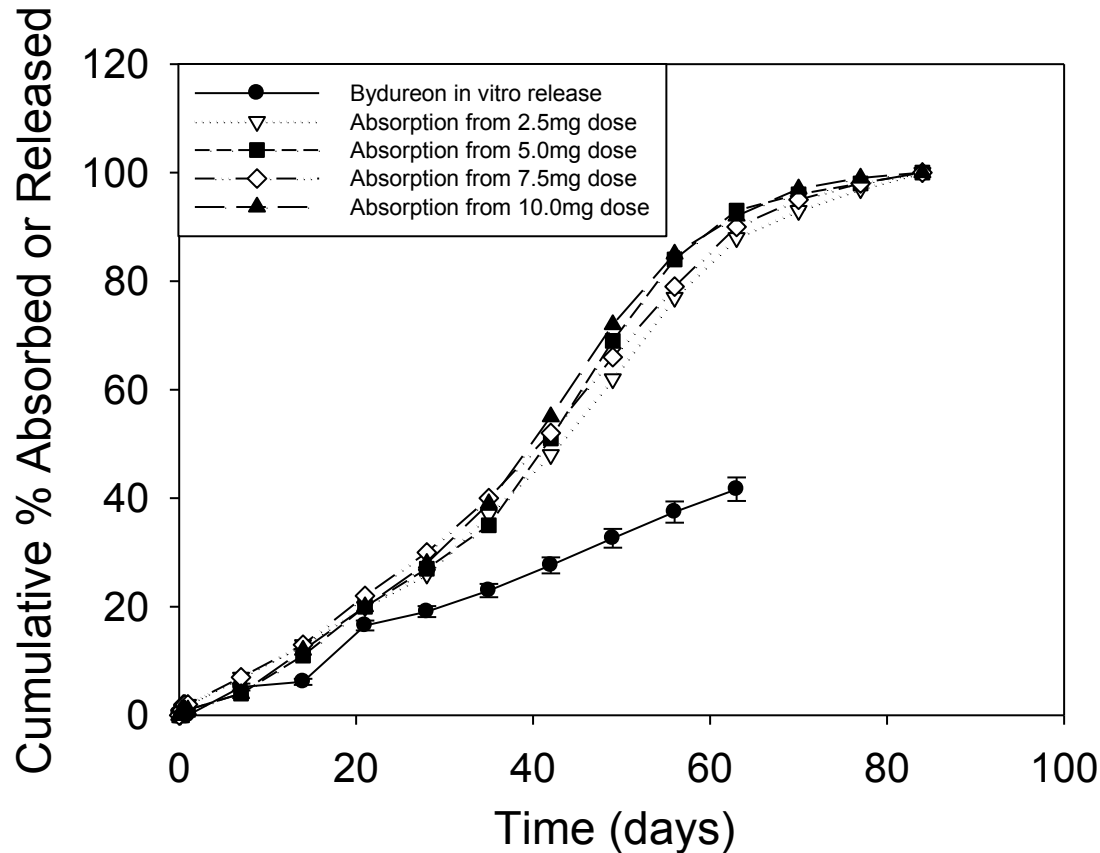
From: Schwendeman et al., in *Controlled Drug Delivery Challenges and Strategies*, Park (ed), ACS: Washington DC, 1997.

Different release conditions = Different results



- Selection of drug release conditions that are predictive of *in vivo* release is needed
- Drug properties (solubility, size) and mechanism of release (diffusion, erosion) need to be considered for assay development

Human PK used to predict exenatide *in vivo* release and compare it with *in vitro* release



In vitro release from Bydureon® microspheres compared with calculated cumulative absorption by the Wagner-Nelson method and human PK data. A first step for *in vivo/in vitro* correlation (IVIVC) development.

In vitro/in vivo correlation model

Table 5

Correlation coefficients between in vitro dissolution and in vivo pharmacokinetic parameters

In vitro parameter	In vivo parameter	R^2	Slope	Intercept
MDT ^a	MRT ^b	0.983	1.0224	- 1.7477
$T_{63.2\%}$ ^c	MRT	0.9863	0.9318	- 1.888
$T_{50\%}$ ^d	AUC _{0-24 h} ^e	0.9993	- 2.0299	19.914
$D_{48 h}$ ^f	C_{max} ^g	0.9774	0.8354	- 8.3737

^a Mean dissolution time.

^b Mean residence time.

^c Time required to dissolve 63.2% of drug.

^d Time required to dissolve 50% of drug.

^e Area under the serum concentration-time curve from zero time to 48 h.

^f Percentage of drug dissolved after 48 h.

^g Maximum serum concentration.

Levels B & C

Level A →

G. Schliecker et al. / Journal of Controlled Release 94 (2004) 25-37

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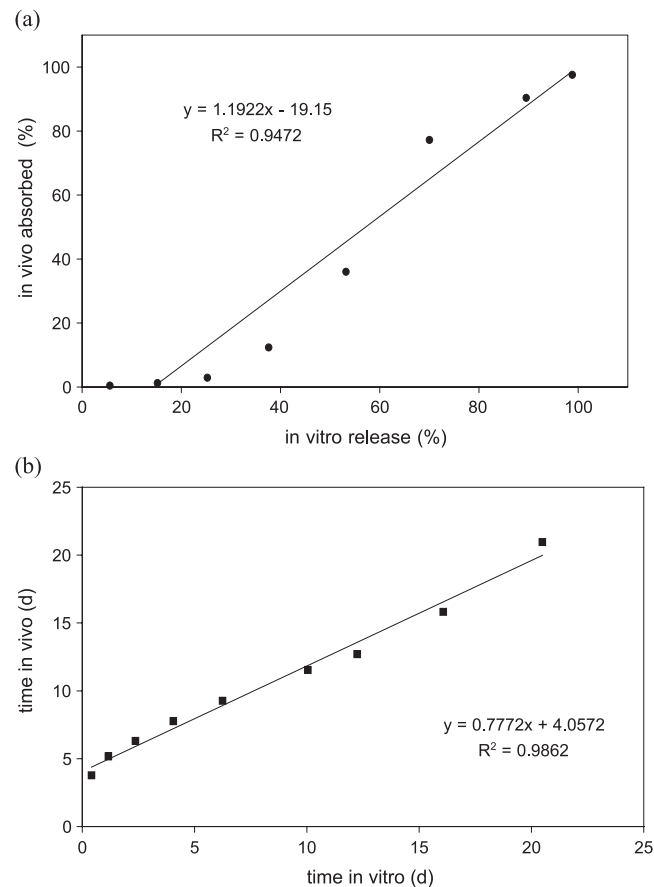


Fig. 4. Plot of percentage of dose absorbed in vivo versus percent released in vitro (a) and Levy plot obtained from times for 0-90% buserelin released in vitro and absorbed in vivo (b).

Summary

- Despite the large health economic need there are no generic long-acting-release (LAR) products approved in the USA currently
- LAR product complexities make it difficult for generic companies to produce, and for FDA to regulate, LAR products
- Process changes can result in markedly different performance or Q1/Q2 equivalent LAR products
- Research in regulatory sciences on how process changes affect LAR products, development of predictive in vitro release assays, and IVIVC models will greatly help approval of generic products and further LAR development
- FDA sponsored research will increase the body of scientific knowledge about LAR formulations and will guide development and approval of safe and efficacious LAR drug products

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