Drug Delivery of Biologics: A Controlled Release Strategy

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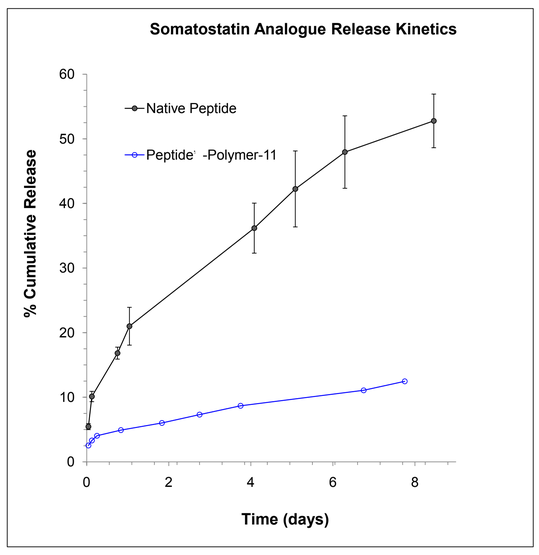
Abstract

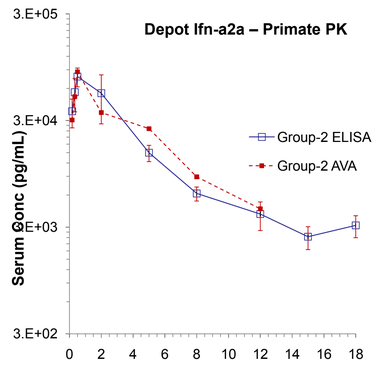
DURECT reports here a novel drug delivery technology strategy for creating controlled release injectable depots for a variety of biotechnology drugs from peptides to proteins. This technology is based on novel proprietary bioerodible structures that are designed to complex with various drug entities to yield proprietary depot products. As examples, several drug candidates such as somatostatin analogue, nucleoside analogue pro-drug, GLP-1 analogues, interferon-a2a, human growth hormone and anti-TNFa [IgG] were formulated by this drug-complexation technique. These drug-complexes were lyophilized to dry powders and subsequently suspended either in a purely aqueous vehicle or non-aqueous vehicles (DURECT depot technology). Such suspension formulations were evaluated for physical (e.g., injectability) and chemical stability after a range of *γ*-irradiation, and for controlled release properties *in vitro*. In addition, PK studies were conducted in different animal models for various depot formulations. We are reporting here animal PK data as well as stability of the DURECT injectable depot formulations and conclude that either aqueous or non-aqueous formulations based on API-complex technology can be manufactured for the proteins and peptides economically to yield controlled delivery depot products using Durect's biodegradable polymers.

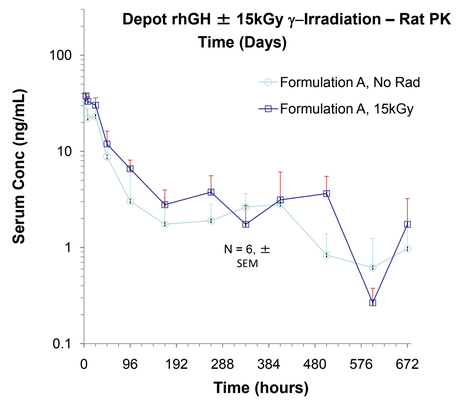
DURECT Depot Technology - Somatostatin Analogue (M_W ~ 1100Da)



- We have prepared API-complex of Somatostatin analogue and complexable polymer (11) and compared the *in vitro* release kinetics with native somatostatin analogue nanotube-formulation in water (>100mM)
- The release of somatostatin analogue from API-polymer complex was better controlled than the marketed reference product

DURECT Depot Technology - IFN-a2a and rhGH (M_Ws ~ 20kDa)





- Suspending an IFN-polymer complex in a low-viscosity organic vehicle, we were able to control the delivery over 18 days in cynomolgus monkeys (C_{Max}/C_{Last} ~ 25) until the appearance of neutralizing antibodies. The anti-viral activity assay (AVA) results indicate delivery of active protein
- We developed similar formulations for rhGH, and achieved 28 day delivery (~constant over days 7-21) with C_{Max}/C_{Last} ~ 20 in immune-suppressed rats
- Stability against sterilizing dose of γ-radiation was quite good

γRadiation Dose (kGy)	% Purity		
	T_0	T_{1wk}	T_{4wks}
0	100		96
3.8	97	97	
9.6	96		
14.5	96		95
23.4	95		93

Range of Applications of DURECT Depot Technology

Small Peptide/Nucleoside
(e.g., Somatostatin analogue, Nucleoside analogue pro-drug)

Medium Peptide
(e.g., GLP-1 analogues)

LACTEL Absorbable Polymers

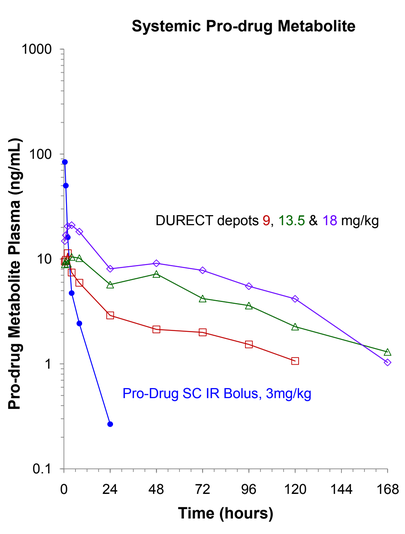
- Dedicated labs for custom polymer synthesis / process development
- Custom designed clean rooms for polymer production

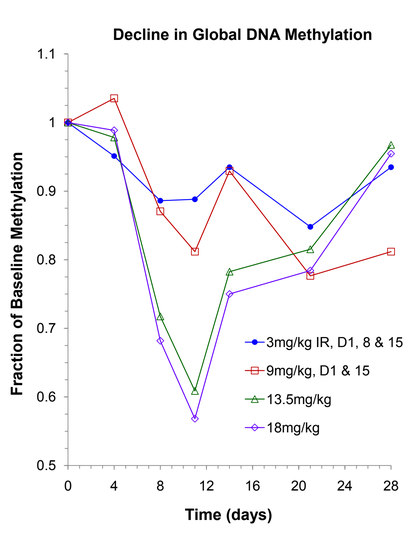
1. **API-Complex** (Proprietary complexable agents)
2. **Organic or Aqueous Vehicle**

Large Protein
(e.g., Anti-TNFa, Ab)

Medium Protein
(e.g., rhGH, Interferon-a2a)

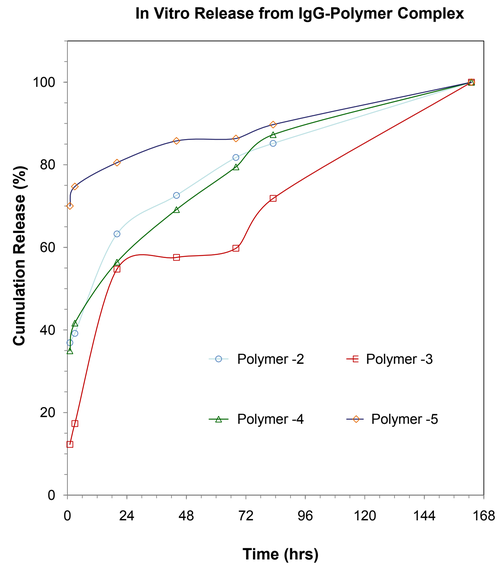
DURECT Depot Technology - Nucleoside Analogue Pro-drug





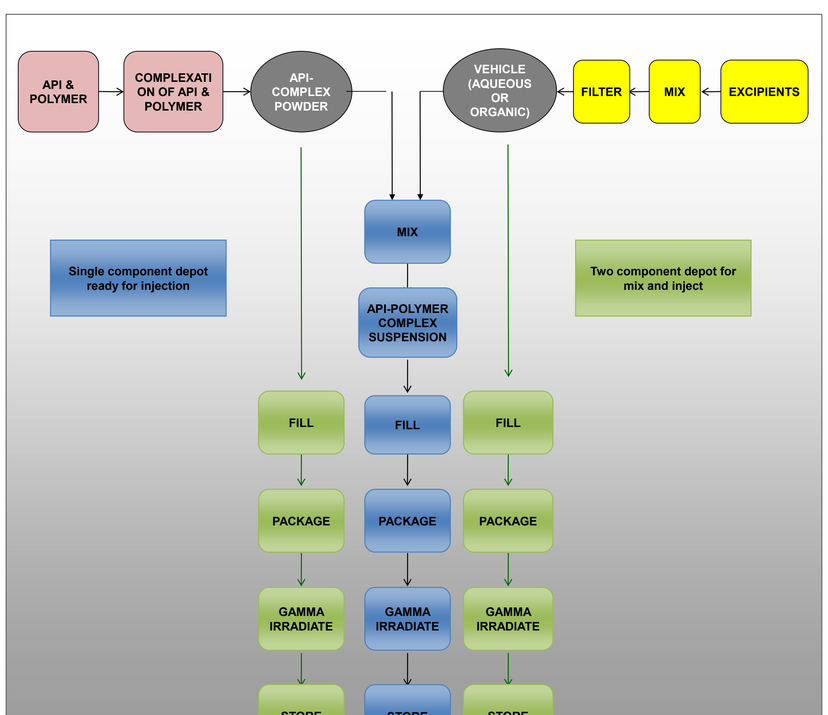
- We have incorporated a nucleoside analogue pro-drug-complex in non-aqueous vehicle for controlled release of the API from a subcutaneous injection in cynomolgus monkeys
- The pro-drug depot formulation delivered pro-drug metabolite for a week(PK)
- The pro-drug metabolite levels induced demethylation of DNA over 28 days (PD)

DURECT Depot Technology - anti-TNFα [IgG] Ab (M_W ~150kDa)

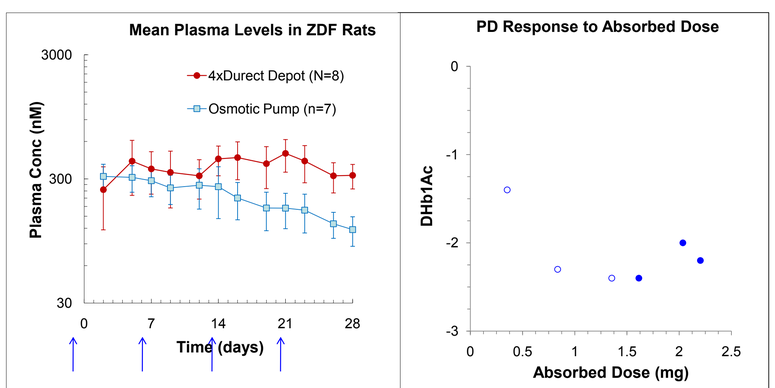


- Results of in vitro release rate measurements for IgG-polymer complexes in PBS
- From an initial screening of complexing polymers, we found a range of release kinetics

Manufacturing Process – DURECT Depot Technology



DURECT Depot Technology - GLP-1 Analogue (~ 4kDa M_W) PK/PD



- Plasma levels from a DURECT depot (3.8 mg API/week) and an implanted 28-day osmotic pump (1.23 mg/week) are plotted at left
- The DURECT depot, dosed on days 0, 7, 14, and 21, produced notably flat plasma levels
- The observed PD effect (% reduction in glycated hemoglobin) is plotted as a function of the cumulative dose absorbed from the pumps and depot formulations into the systemic circulation
- The PD effect displayed saturation: No further reduction in Hb1Ac was observed beyond ~ 1mg of GLP-1 analogue absorbed

Summary / Conclusions

- DURECT depot technologies enable the use of aqueous or non-aqueous suspension of API-complex for the controlled drug delivery over the periods ranging from days to weeks
- Our preclinical studies in animals such as rats, rabbits, minipigs, dogs and primates exhibited minimal to moderate injection site reactions comparable to that of other commercially available injectable depot products (data not shown in here)
- The stabilization and long term controlled delivery of fragile and reactive biologics such as peptides, proteins and antibodies have been achieved by DURECT depot technologies based on API-complex
- The manufacturing steps of DURECT depot products based on the API-complex of peptides, proteins and antibodies have proven to be cost effective and is based on off the shelf equipment, resulting in the low cost of goods (COGS)

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