DRUG DELIVERY EXPERTS

Peptide Preformulation: Physicochemical Properties Evaluation

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Peptide Preformulation Outline

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Peptide Physicochemical Properties

What Do We Need to Know and Why?

Tools for Evaluation of Solubility and Stability

Modifying Peptide Properties

Pharmaceutical Development Roadmap

Peptide Physicochemical Properties

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Common Solids Properties

- Amorphous powder - isolated by lyophilization
- Poor powder flow properties
- Bulk density is low - can be compacted easily
- Hygroscopic
- Stable frozen at -20C or -80C in most cases

Common Solution Properties

- Unstable in water and pH > 8 or pH < 4
- Solubility is pH, buffer and salt concentration dependent
- Physical precipitation over time as fibrils, particles, etc…
- Stable frozen or at 2-8C

What Do We Need to Know and Why?

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How will solid drug substance be handled?

- Research lab and in scale-up
- Transfer processes for poorly flowing solid
- Bulk storage condition and as useful aliquots
- Special humidity controls needed for weighing
- Will solids be weighed in a glove box?
- Often stored in plastic bag / drum liner / fiber drum at -20C or -80C

What Do We Need to Know and Why?

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What do we need to know for formulation?

- Dose or dose range for animal and human
- Injection route (IM, SC, IV)
  - Dictates volume per dose and excipients
  - Direct injection IV or diluted into infusion bag
- Bioavailability and PK profile
  - Often a diagnostic for injection site precipitation
- Exposure desired – immediate release or sustained exposure?
- Storage often 2-8C, sometimes frozen

Contraints for Injectables

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What is the volume limitation for SC Injection?

For IM Injection?

For IV Injection?

Osmolarity?

Pharmaceutical Development of an IV Injection Formulation

Current clinical formulation for phase 1 study IV injection

- 15 mg/ml in phosphate buffer with tonicity modifiter
- Dilution into IV bag from a smaller volume (5 to 15 ml)
- Potential for SC injection?

Human Dose mg/kg	DP Volume 15 mg/ml	DP Volume 50 mg/ml	DP Volume 100 mg/ml
0.1	0.4	0.13	0.065
0.3	1.3	0.39	0.195
1.0	4.3	1.3	0.65
3.0	13.0	3.9	1.95
8.0	34.7	10.4	5.2
10.0	43.3	13	6.5

Based on 65 kg human

Dose fits in 5 ml vial

New formulation target is ~50 mg/ml due to aqueous solubility constraints
Vial size will be 5, 10, or 20 mL depending on effective dose

Tools for Physicochemical Properties Evaluation

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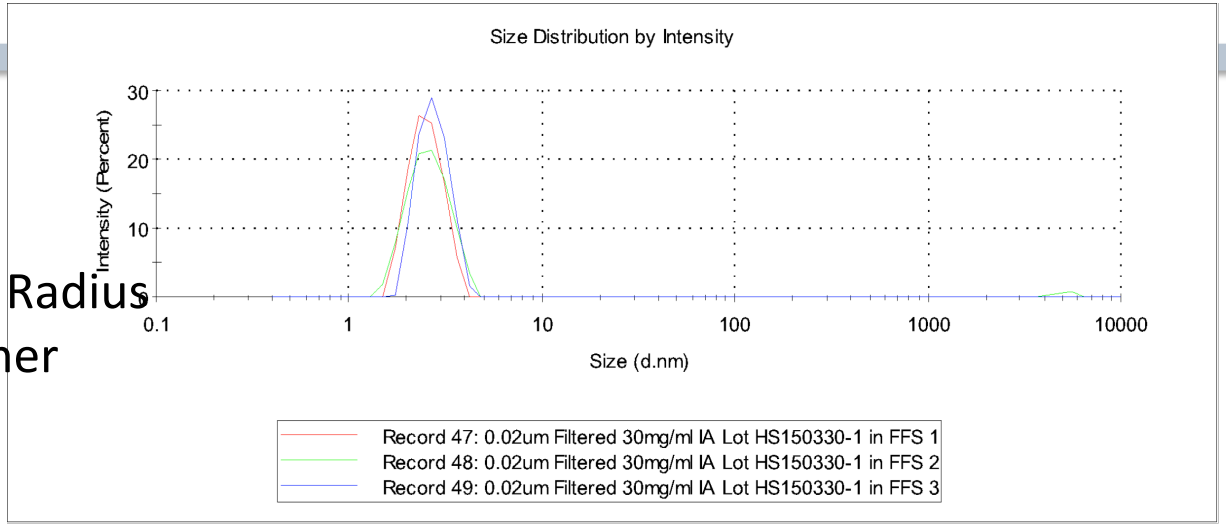
- Solubility at solution saturation
  - Water (determine the pH)
  - Phosphate buffered saline with pH adjusted to 7.4
  - pH solubility profile (make sure you adjust pH)
- Solubility determination
  - Visual / nominal screen for gross observations
  - UV or HPLC concentration after filtration
- Solubility in blood / injection site?

What is the nature of the peptide in solution?

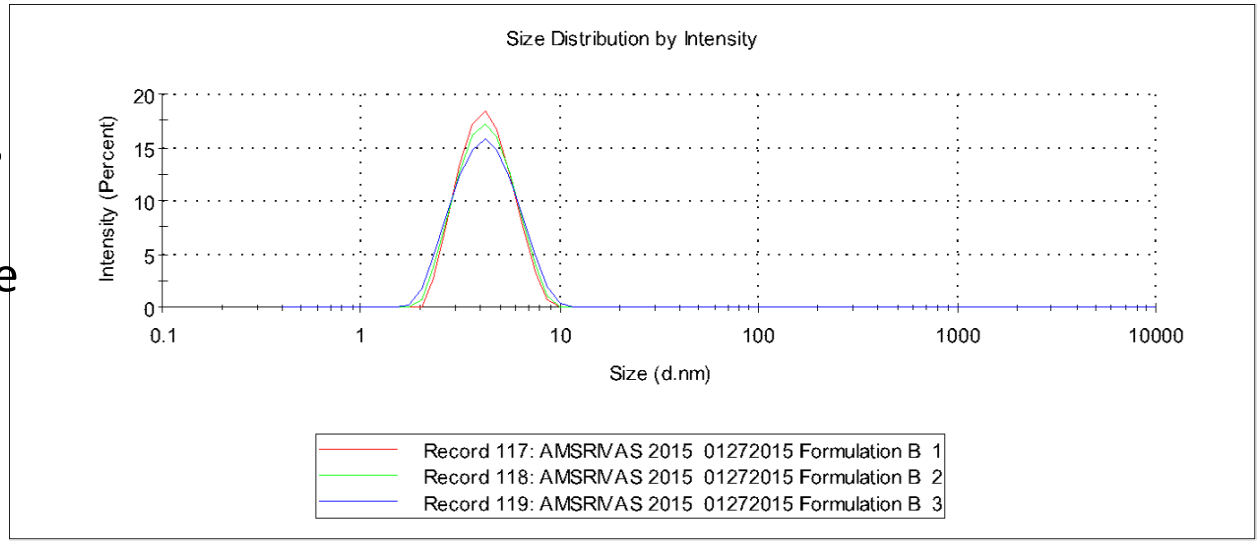
- Dynamic light scattering
- Observation of solution monomer or higher order structures
- Higher order structures can be on the path to agglomeration, aggregation, precipitation, fibril formation
- Higher order structure may be purposeful to enhance PK properties (lipidated peptides)

Dynamic Light Scattering

Hydrodynamic Radius
Typical Monomer
1 to 2 nm



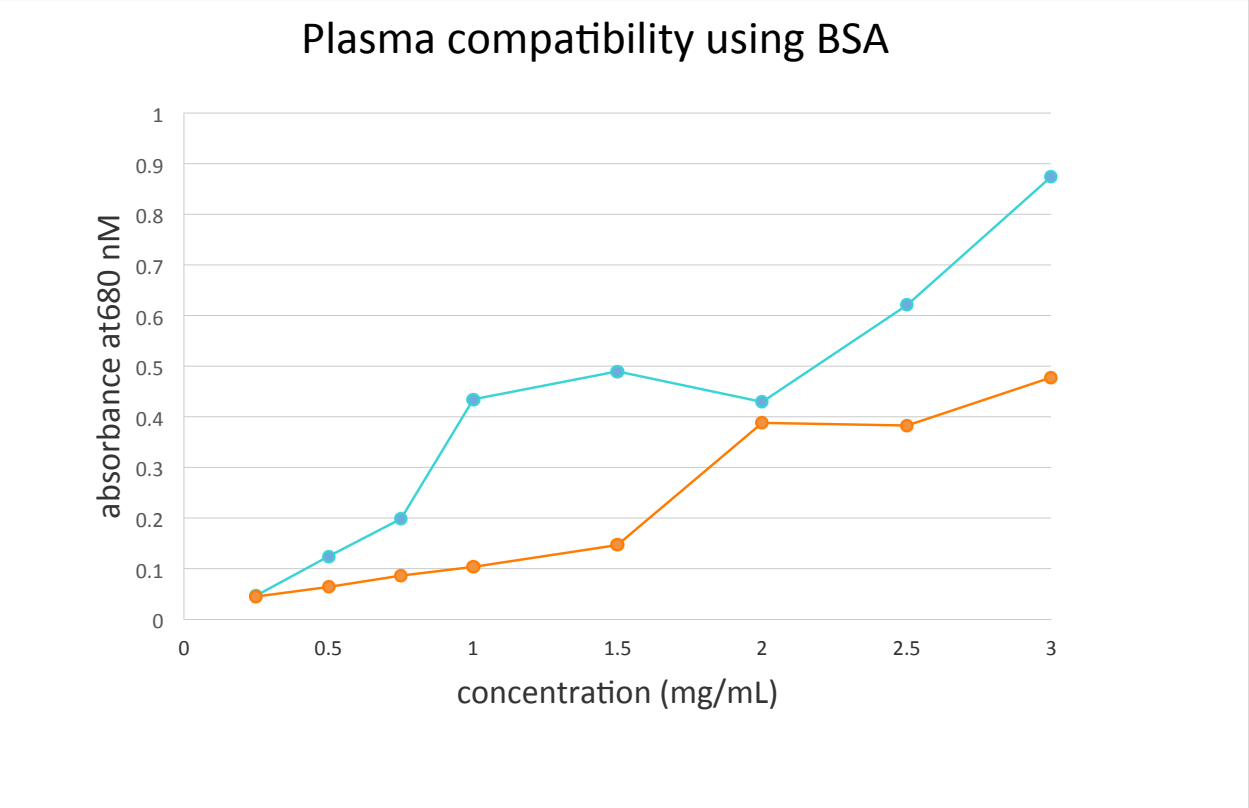
Hydrodynamic Radius
5 to 7 nm:
Higher order structure
5 to 7 peptides



What happens on injection?

- Is the peptide precipitating at the inject site?
  - Plasma compatibility assay mimics
- Nephelometric analysis
  - Precipitation
- UV / Vis plate reader assay
  - Precipitation observation at 600 nm
  - Formulations added to PBS, PBS w/ HSA, or plasma

Precipitation on injection prediction



Comparative precipitation with different formulation excipients

Drug Substance Modification

Salt preparation

- TFA or acetate salt is typically isolated in peptide synthesis
- Evaluate the usefulness of other salts for varying solubility
- Or for ease of dissolution in formulating drug product
- Small scale titration of an insoluble acid with base is easy
- Difficult on a 100 to 1 kg scale – example

Modifying Properties

- Modify the solubility of peptide for suspension formulation
- Or for solubilization in alternate formulations (non-aqueous)

Pharmaceutical Development

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Pre-formulation

- pH solubility profile (is the drug soluble where it is stable?
- pH stability and buffer selection at 0.1 or 1 mg/ml

Co-solvent solubility

- Commonly used parenteral co-solvents screening for solubilization
- Additive to prevent precipitation on stability at high concentration

Formulation optimization

- Final screening at selected pH range, at concentration
- Prototypes (3-4) on stability (5, 25, 40C) for 3 months

Pharmaceutical Development

Vial and syringe for early development

- Dosing flexibility and manufacturer availability

Pre-filled syringe attractive for larger volumes (1-2 ml)

- Need to know the dose so often challenging to use in early development

Pen injection / cartridge

– may be attractive for later development and commercialization

Pharmaceutical Development Roadmap: Preformulation and Early Formulation

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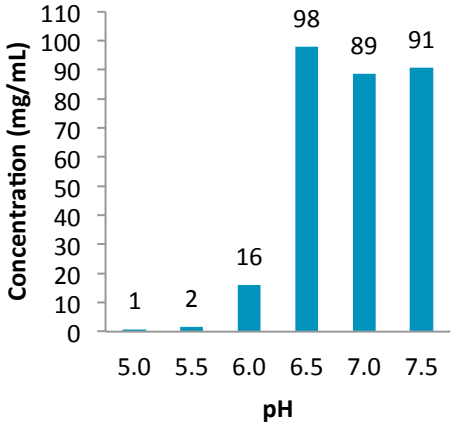
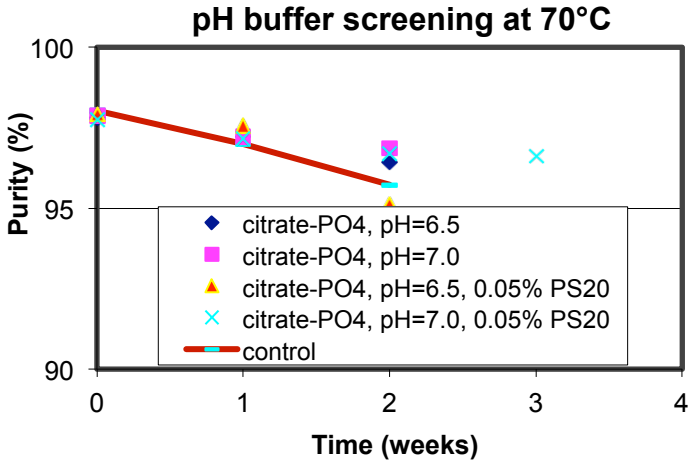
Preformulation → **Formulation**

pH Solubility Profile	pH Buffer Stability	Solubility in Co-Solvent	High Conc Stability	3 Months Stability
1. High solubility at pH > 6.5 2. Buffer strength affects solubility	Best stability at pH~7 (1 mg/ml)	High solubility in NMP, DMSO, DMA	Excipient screen (50 mg/ml)	3-4 Candidates on stability, Na Salt vs Acid





pH 7 citrate-PO4 best
> clinical pH 7.5 (control)
> Phosphate pH 7
>> pH 8 or no buffer

Peptide Preformulation

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Understand Basic Peptide Physicochemical Properties

Carefully consider what Do We Need to Know and Why?

Simple Tools for Evaluation of Solubility and Stability

Will Peptide Structure be Modified? Is a Salt Needed

Outline Pharmaceutical Development Roadmap

BACKUP SLIDES