Case Study 2: Precipitation on Injection – Problem Solving Failure

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Precipitation on Injection: Problem Statement

Clinical program halted

- Clinical dose escalation limited by injection site reaction
- Exposure not linear with increasing dose in human

Reformulate to proceed forward

- Significant work already done to evaluate improved formulations

Precipitation on Injection: Outstanding Questions

DRUG DELIVERY EXPERTS

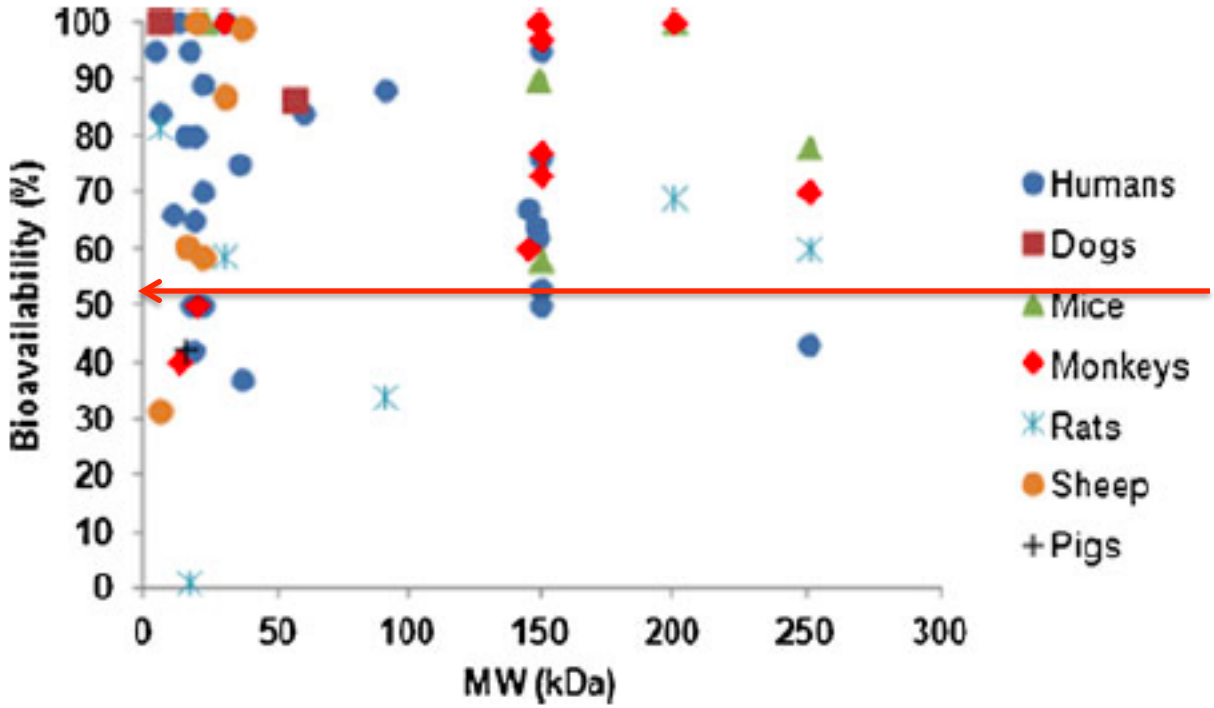
Bioavailability

- Not determined in humans
- Rodent study conducted to evaluate
  - Conducted and observed <10% bioavailability
  - Concentration effect on exposure

Reformulation work suggested an excipient that may help

- Concern for concentrations needed
- Concern over approvability of excipient – not in many formulations

Bioavailability for Most Biologics > 50%

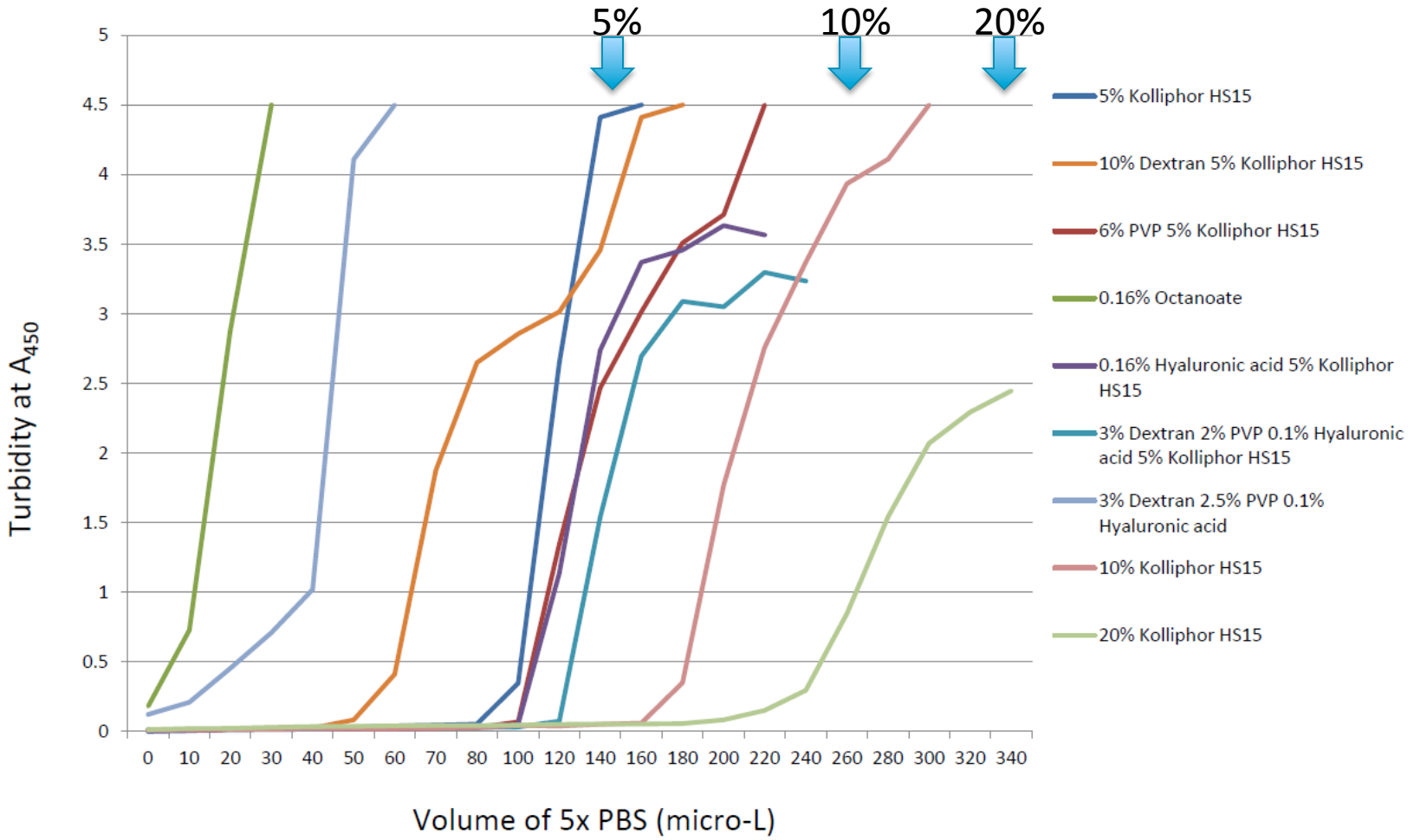


SC BA > 50%
For most drugs

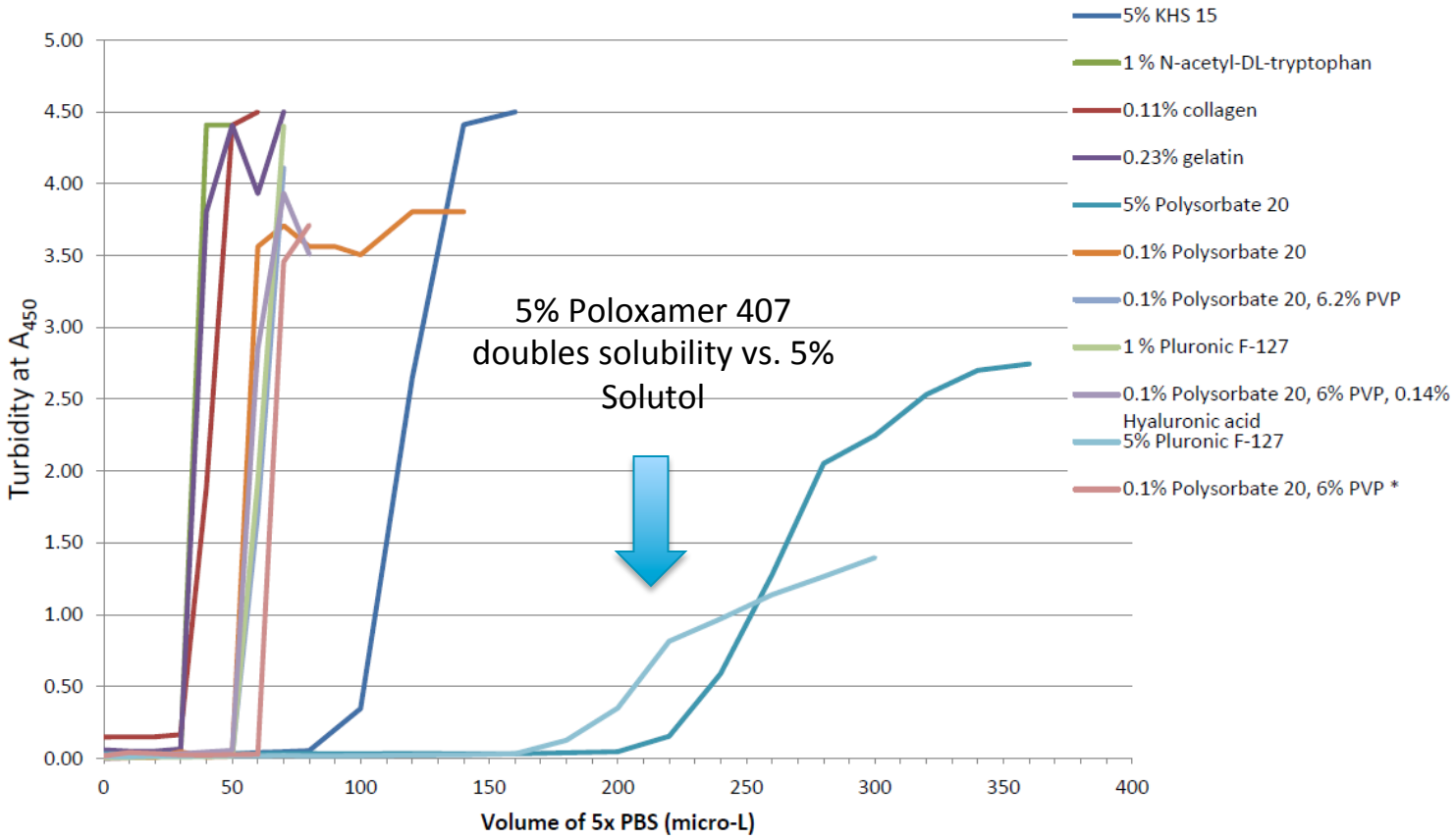
Fig. 3. Relationship between systemic availability of biotherapeutics and their molecular weight in various species. The data are provided in Tables I and II

WFRichter et al AAPS Journal 2012 14 (3) 559-570

Higher Levels of Excipient Improve Biocompatibility

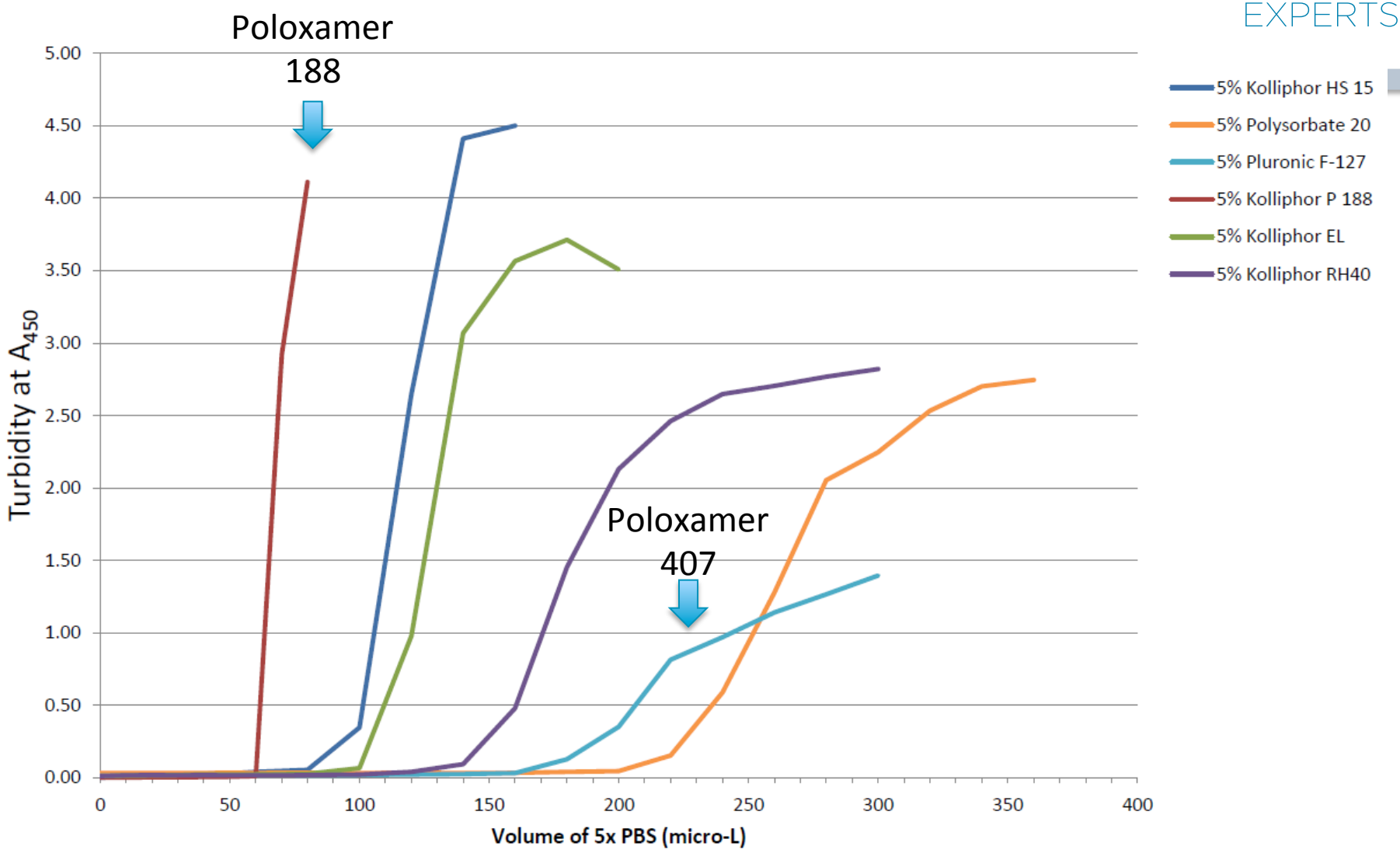


Poloxamer 407 has similar effect and is in commercial product



*has specific formulation: PVP mixed in acetic acid with peptide first, then spiked with polysorbate 20.
** All Polysorbate 20 formulations are based on volume percent not (weight/volume) percentage.

Poloxamer 188 also helps



Plasma Compatibility Useful for Screening Aqueous Miscible Formulations

In Vitro Turbidity Assay

Turbidity in in vitro biocompatibility assay

mg/mL	% solutol 2	% solutol 10	% solutol 20	% solutol 25	2% P407 PBS	2% P407 Plasma
2	0.7	0	0	0	0	0.7
4	1.2	0.7	0.3	0	0	1.1
8	1.7	0.9	0.3	0.4	0	1.4
10	1.9	1.1	0.5	0.5	0	1.4
12	1.9	1.9	1.1	0.8	0.7	1.6

Relative to current formulation:

- Better
- No improvement
- Worse

Clinical Formulation

Bioavailability in rat PK study at 10 mg/kg

mg/mL	% solutol 2	% solutol 10	% solutol 20	% solutol *25	2% P407
2	6%	8%			14%
4		5%		9%	
8		3%	4%	7%	5%
10				6%	
12			2%	4%	

In Vivo PK in Rodent

BA improved at 2 mg/ml

NOTE: *25% solutol solns showed reduced Peptide conc: 2.2, 5.3, 6.4, 7.3 mg/ml

Conclusion: Failure

Problem considered too difficult to solve in the short term

And may be insoluble or non-solvable

Program discontinued

References for solulibilization

Can be obtained on the BASF website:

Solubility Enhancement with BASF Pharma Polymers
Solubilizer Compendium
Thomas Reintjes
October 2011

Pharmaceutical Technology of BASF Excipients
Volker Buhler
June 2008

Solubilizing Excipients in Oral and Injectable Formulations
Strickley, Robert G
Pharmaceutical Research; Feb 2004; 21, 2; ProQuest Central
pg. 201

BACKUP SLIDES