Aggregation of therapeutic proteins after mixing with human plasma: implications for drug development

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- **Protein products designed to aggregate after in vivo administration in humans:**
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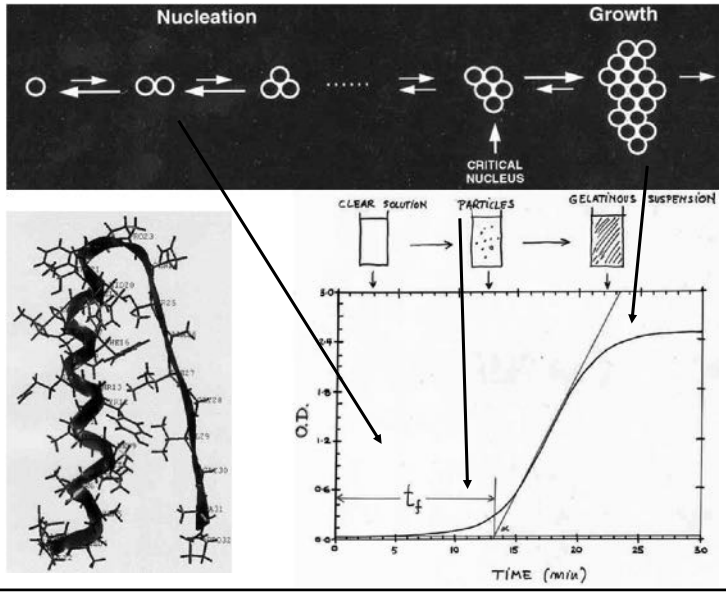
  - **Lantus insulin analogues**
- **Aggregation of antibody products in human plasma**
  - **Antibody candidate durin Ilaris development**
  - **Herceptin, Avastin, Remicade**
- **Therapeomic platform to optimize protein formulation based on studies of aggregation in human plasma**
  - **Therapeomic particle scanner imaging (PSI)**
  - **examples**

Arvinte, T., Cudd, A., Drake, A. (1993)
The Structure and Mechanism of Formation of Human Calcitonin Fibrils *J. Biol. Chem* . 286, 6415-6422



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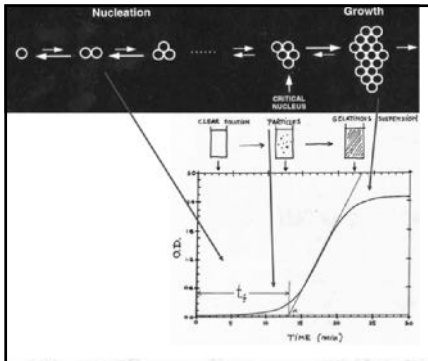
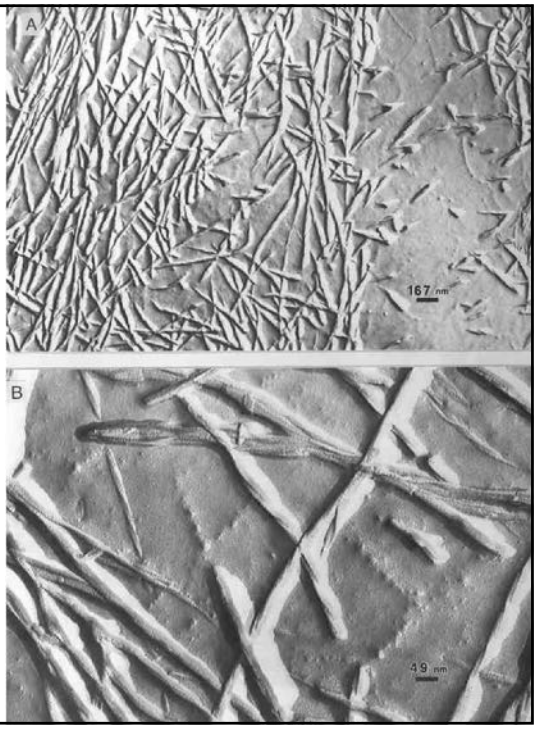


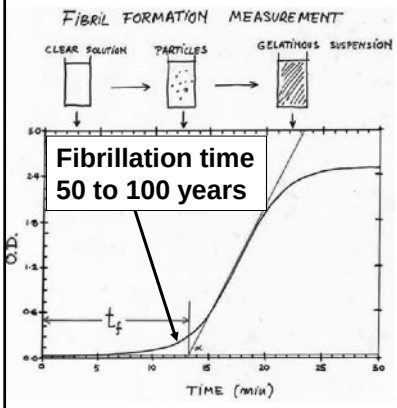
FIG. 6. **Freeze-fracture of hCT fibrils.** The samples, 100 mg/ml hCT, were incubated for 24 h at room temperature prior to the freeze-fracture.

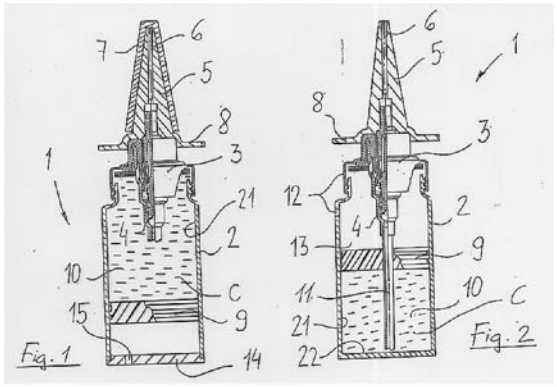


Arvinte, T., Cudd, A., Drake, A. (1993), The Structure and Mechanism of Formation of Human Calcitonin Fibrils *J. Biol. Chem* . 286, 6415-6422

4

1990-1997 Ciba-Geigy / Novartis: Development of stable, not aggregated hCT solutions by T. Arvinte. Nasal Human Calcitonin spray product



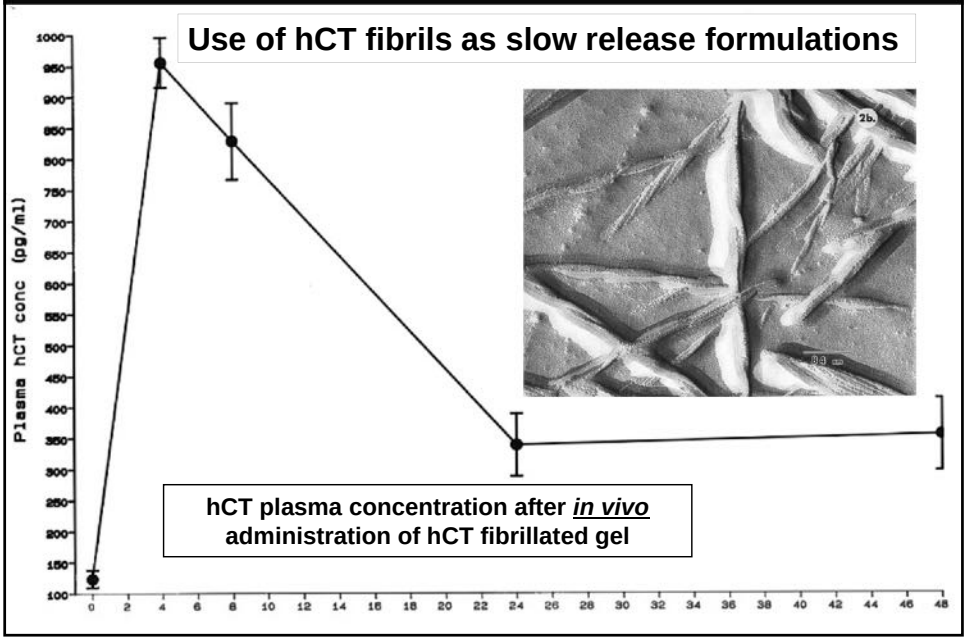


5

Galli, B., Arvinte, T. (1993) Contribution to the Ciba-Geigy patent on Human Calcitonin: Air-Tight Nasal Applicator, European Patent EP 0 531 257 A1

Arvinte, T., Cudd, A., Phillips, J. (1992). Use of Fibrillated Calcitonin in the Treatment of Calcium Deficiency Diseases. *European Patent*, Publication Number 0510549.

Use of hCT fibrils as slow release formulations



hCT plasma concentration after *in vivo* administration of hCT fibrillated gel

FERRING PHARMACEUTICALS

PEOPLE COME FIRST AT FERRING

Degarelix, a potent peptidic self-depoting GnRH receptor blocker

Grégoire Schwach
Ferring International PharmaScience Center,
Copenhagen, Denmark

60 YEARS FERRING 1950 - 2010

2010 PSWC AAPS annual meeting
New Orleans, 14-18 November 2010

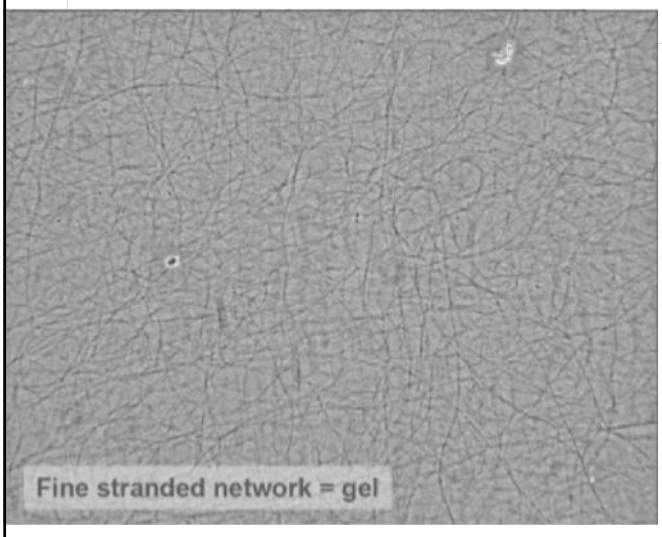
The Revival of Synthetic Peptides and Small Proteins in Biopharmaceuticals

Fibrillation induces depot formation in vivo

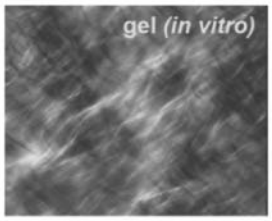
FERRING PHARMACEUTICALS

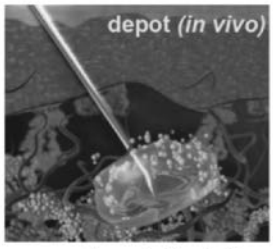
PEOPLE COME FIRST AT FERRING

Degarelix Gel



polarisation microscopy





schematic illustration

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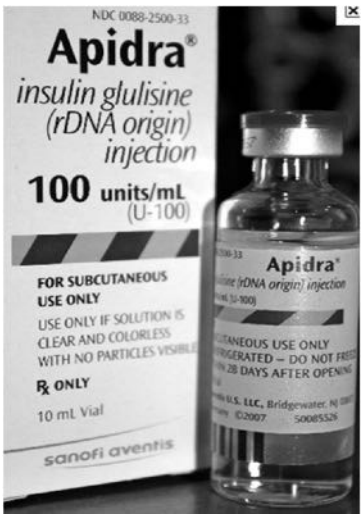
  - examples

Insulin analogs

Long-acting insulin analog

Precipitation of the protein after subcutaneous injection (formation of hexamers)

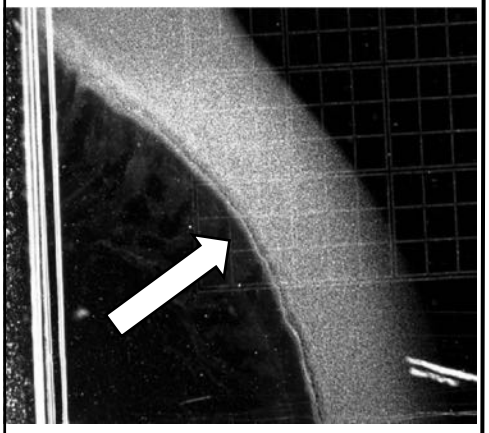
Fast-acting insulin analog



No precipitation of the protein after subcutaneous injection

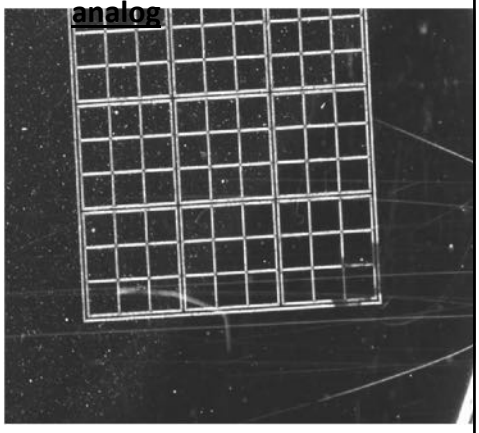
Interaction of insulin analogs with human plasma Light microscopy with phase contrast

Lantus: long-acting insulin analog



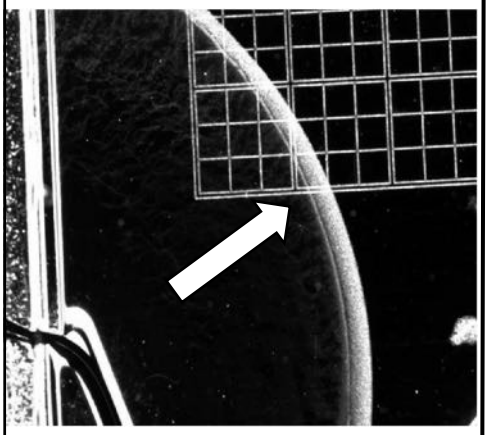
Precipitation at the interface Lantus - plasma

Apidra: fast-acting insulin analog



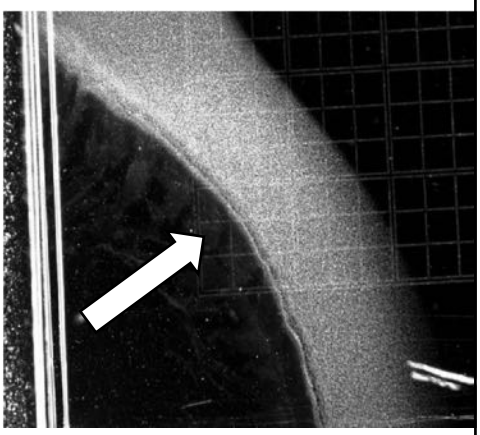
Comparison of aggregation in plasma with aggregation in PBS

Lantus added to PBS



Precipitation at the interface Lantus - PBS

Lantus added to human plasma



Precipitation at the interface Lantus - plasma

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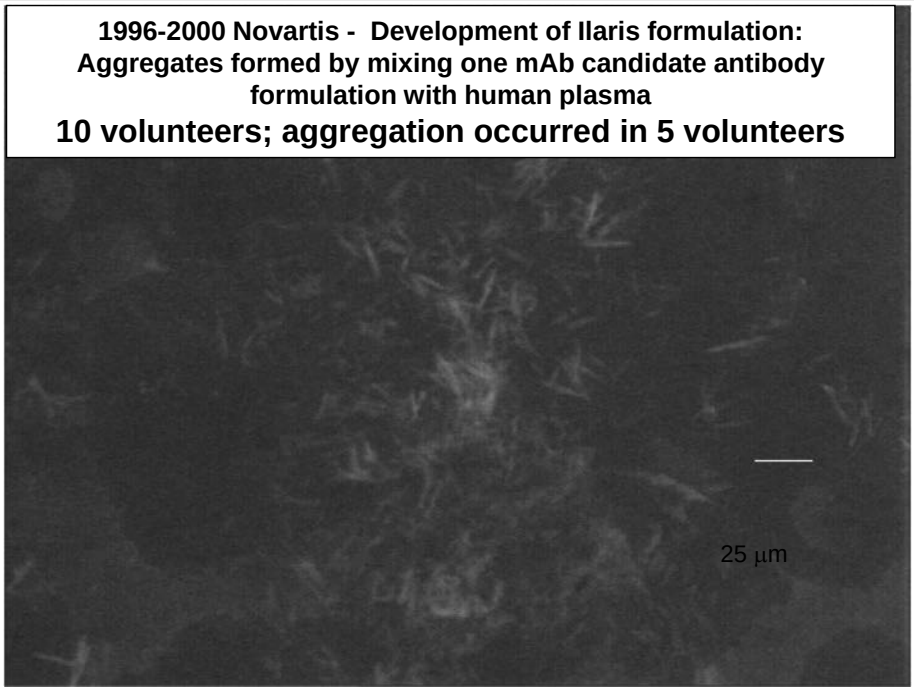
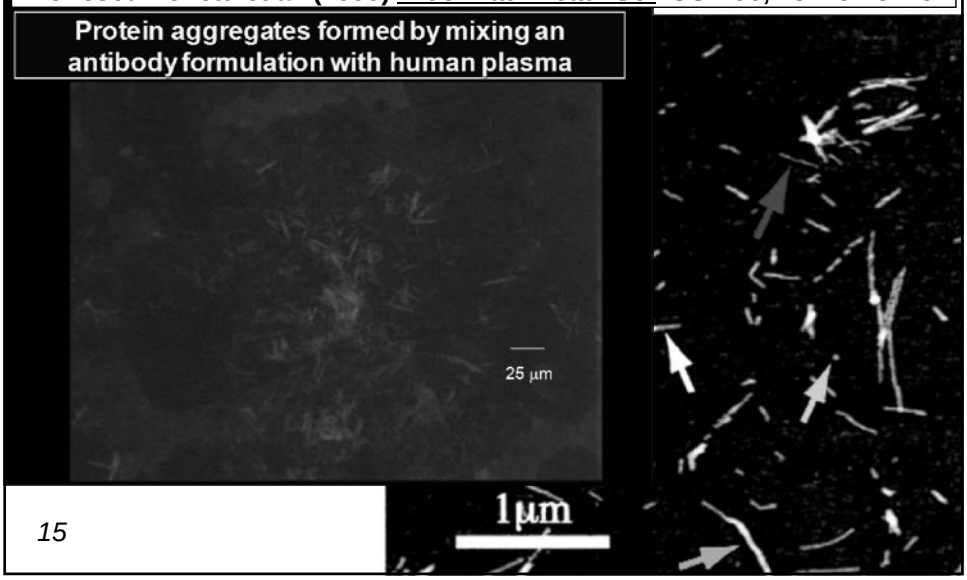
  - **examples**

1996-2000 Novartis - Development of Ilaris formulation: Aggregates formed by mixing one mAb candidate antibody formulation with human plasma

10 volunteers; aggregation occurred in 5 volunteers



Toxicity of Ig light-chain aggregates:
Atomic force microscopy of the initial structures observed during the formation of Ig light-chain amyloid fibrils.
Ionescu-Zenetti et al. (1999) *Proc. Natl. Acad. Sci*. USA 96, 13175-13179



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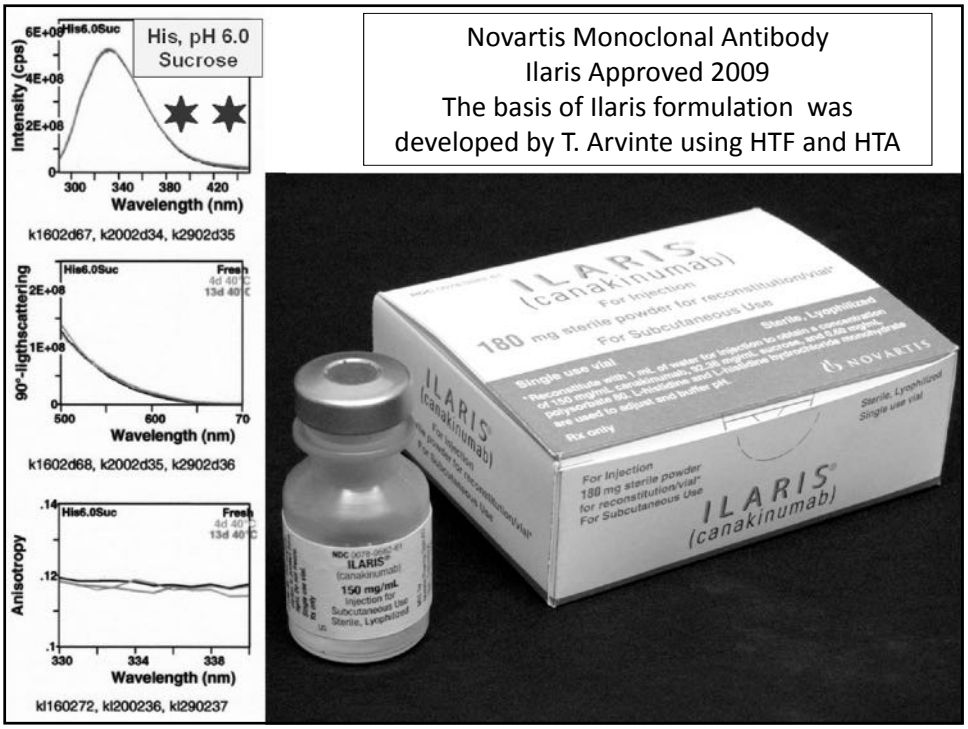

Novartis Monoclonal Antibody
Ilaris Approved 2009
The basis of Ilaris formulation was developed by T. Arvinte using HTF and HTA

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Herceptin® (trastuzumab)

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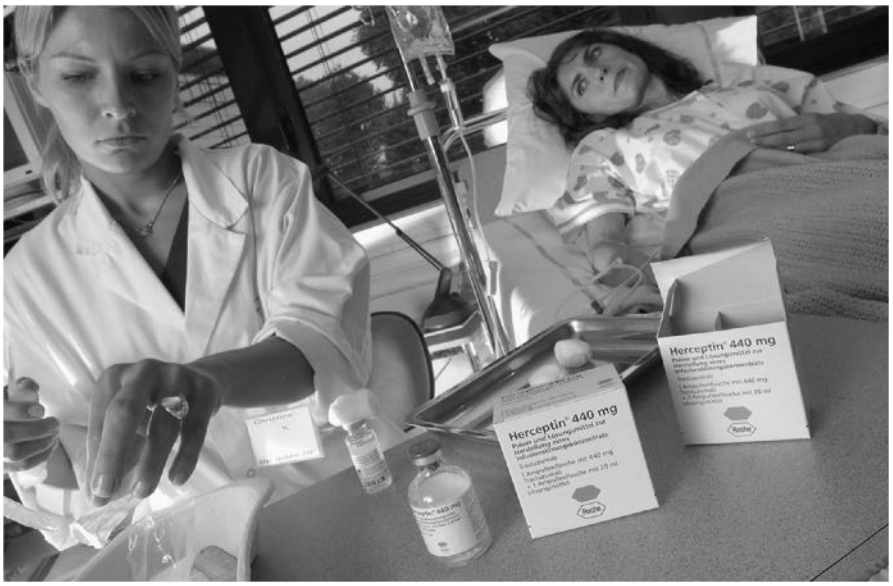
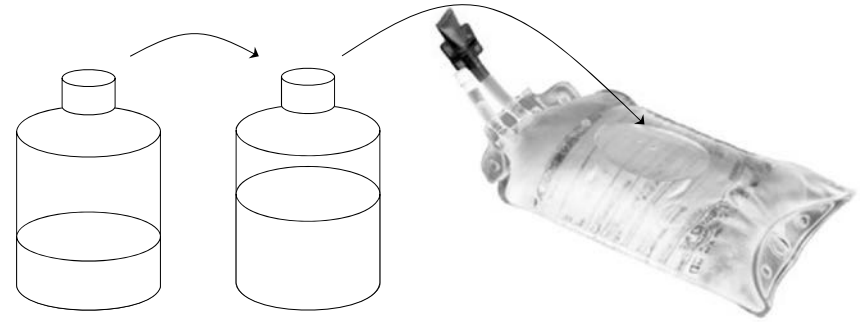


Herceptin® (trastuzumab)

Reconstitution with water (1.1% benzyl alcohol)

Dilution in an infusion bag Containing 0.9% NaCl



Lyophilized

21 mg/ml
Stable 28 days
at 2-8 ºC

0.2 – 1.3 mg/ml
Stable 24 hours
at 2-8 ºC

Herceptin® (trastuzumab): Package Insert

Use appropriate aseptic technique when performing the following reconstitution steps:

a. Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Trastuzumab. The stream of diluent should be directed into the lyophilized cake.

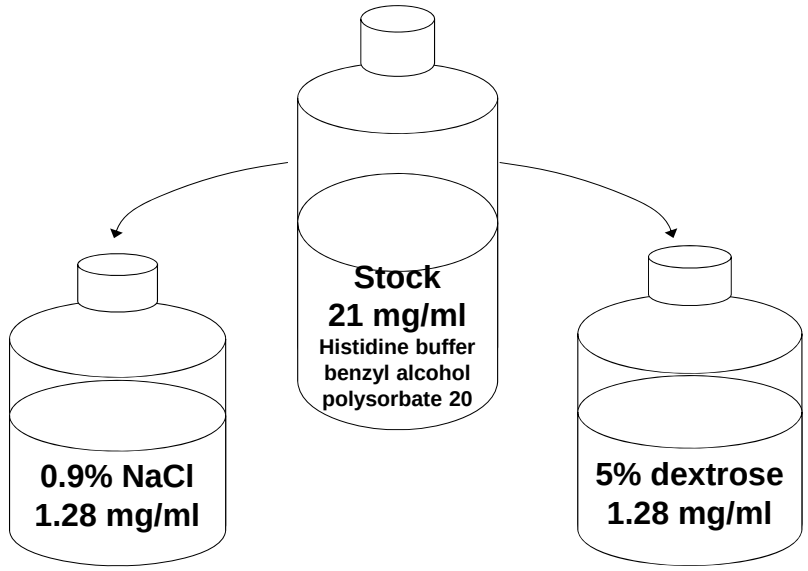
b. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. **DO NOT SHAKE**.

c. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent and colorless to pale yellow.

Determine the number of mg of Trastuzumab needed, based on a loading dose of 4 mg Trastuzumab/kg body weight or a maintenance dose of 2 mg Trastuzumab/kg body weight. Calculate the volume of 21 mg/mL Trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED**. Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

Medical proof of concept and the success of a protein drug depends on its formulation

Herceptin® (trastuzumab)



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[mAbs 1:2, 1-9; March/April 2009]; ©2009 Landes Bioscience

Report

New methods allowing the detection of protein aggregates

A case study on trastuzumab

Barthélemy Demeule,[1,†] Caroline Palais,[2] Gia Machaidze,[3] Robert Gurny[1] and Tudor Arvinte[1,*]

DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.

Demeule, B., Palais, C., Machaidze, G., Gurny, R, Arvinte, T, ***mAbs*** 1:2, 2009, 1-9

Case Study: Herceptin® (trastuzumab)

DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.

- **Standard analytical method do not detect Herceptin aggregation in 5% dextrose:**
- **Solution is perfect clear by eye**
- **No detectable changes in viscosity**
- **No aggregates by size exclusion chromatography (SEC)**
- **No aggregates by standard field flow fractionation (FFF)**

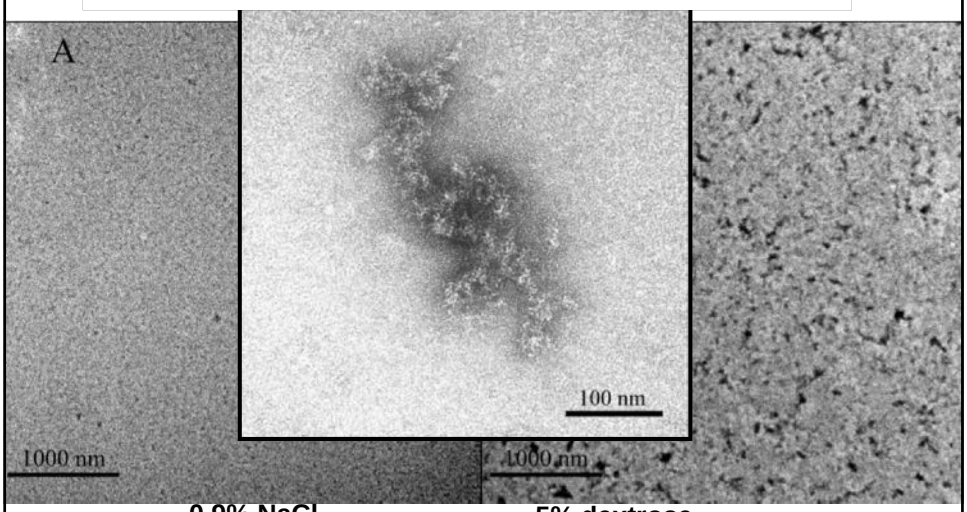
Case Study: Herceptin® (trastuzumab)

DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.

- **New methods developed by Therapeomic detected Herceptin aggregation in 5% dextrose:**
  - Intrinsic Trp fluorescence intensity
  - Intrinsic Trp fluorescence anisotropy
  - Intrinsic Trp fluorescence lifetime
  - 1,8-ANS fluorescence intensity
  - 1,8-ANS fluorescence anisotropy
  - 1,8-ANS fluorescence lifetime
  - Special Filed Flow Fractionation experiments
  - Nile red fluorescence microscopy
  - Electron microscopy

Electron Microscopy of Herceptin

Herceptin would have failed clinical trials if formulated in 5% dextrose instead of 0.9% NaCl



0.9% NaCl **5% dextrose**

Demeule, B., Palais, C., Machaidze, G., Gurny, R, Arvinte, T, *mAbs* 1:2, 2009, 1-9

REPORT

mAbs 5:3, 1–10; May/June 2013; © 2013 Landes Bioscience

Aggregation of biopharmaceuticals in human plasma and human serum

Implications for drug research and development

Tudor Arvinte,[1,2,*] Caroline Palais,[1] Erin Green-Trexler,[3] Sonia Gregory,[3] Henryk Mach,[3] Chakravarthy Narashimhan[3] and Mohammed Shameem[3]

[1]Therapeomic Inc.; Basel, Switzerland; [2]School of Pharmaceutical Sciences; University of Geneva; University of Lausanne; Geneva, Switzerland; [3]Merck Research Laboratories; Summit, NJ USA

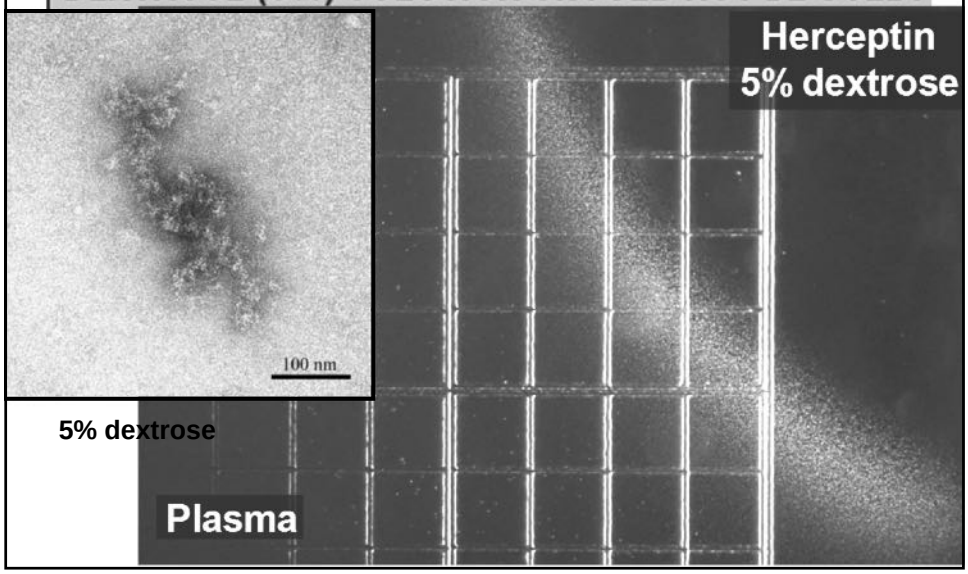
Keywords: aggregation, plasma, compatibility, biopharmaceuticals, administration

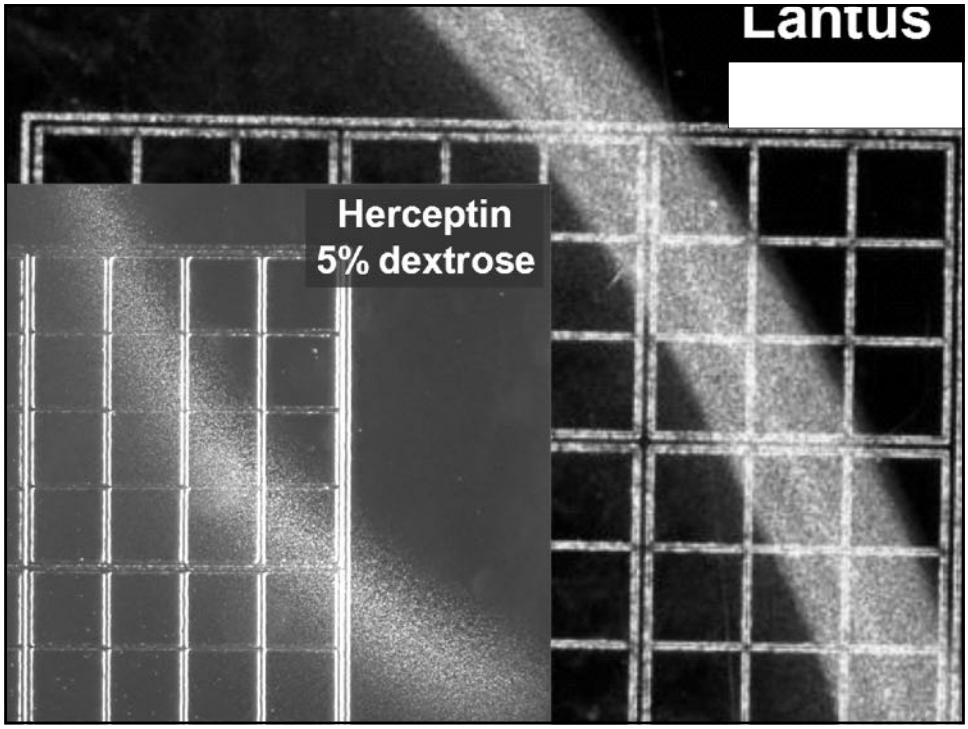
Abbreviations: SPR, surface plasmon resonance; mAb, monoclonal antibodies; NHS, *N*-hydroxysuccinimide; EDC, *N*-ethyl-*N*'-(3-diethylaminopropyl)carbodiimide

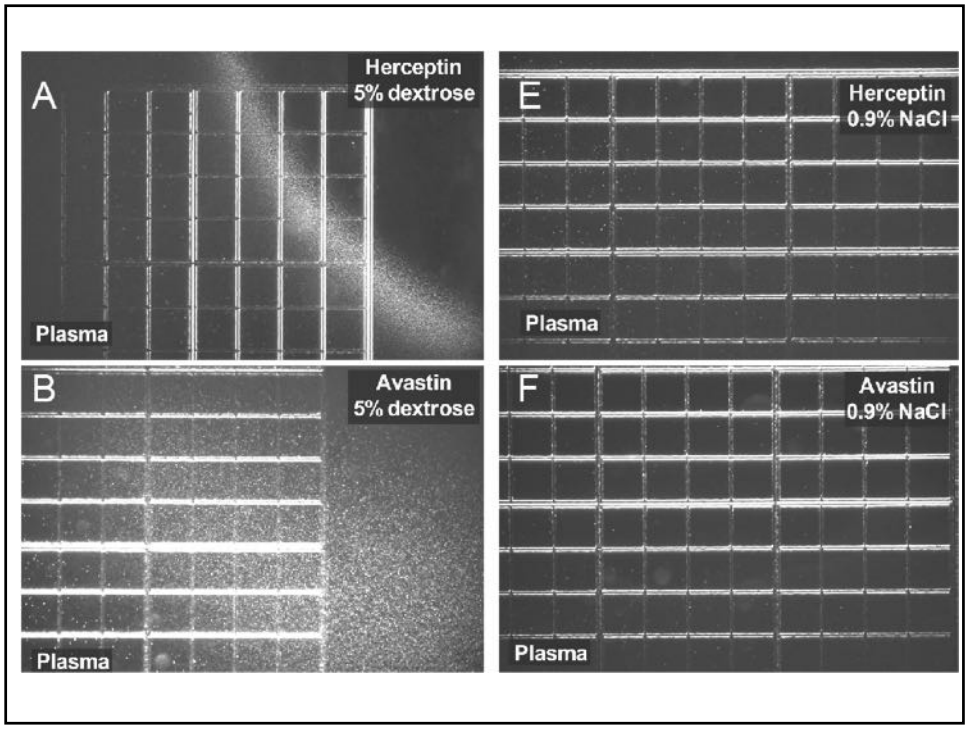
Analytical methods based on light microscopy, 90° light-scattering and surface plasmon resonance (SPR) allowed the characterization of aggregation that can occur when antibodies are mixed with human plasma. Light microscopy showed that aggregates formed when human plasma was mixed with 5% dextrose solutions of Herceptin® (trastuzumab) or Avastin® (bevacizumab) but not Remicade® (infliximab). The aggregates in the plasma-Herceptin-5% dextrose solution were globular, size range 0.5–9 μm, with a mean diameter of 4 μm. The aggregates in the plasma-Avastin®-5% dextrose samples had a mean size of 2 μm. No aggregation was observed when 0.9% NaCl solutions of Herceptin®, Avastin® and Remicade® were mixed with human plasma. 90° light scattering measurements showed that aggregates were still present 2.5 h after mixing Herceptin® or Avastin® with 5% dextrose-plasma solution. A SPR method was utilized to qualitatively describe the extent of interactions of surface-bound antibodies with undiluted human serum. Increased binding was observed in the case of Erbitux® (cetuximab), whereas no binding was measured for Humira® (adalimumab). The binding of sera components to 13 monoclonal antibodies was measured and correlated with known serum binding properties of the antibodies. The data presented in this paper provide analytical methods to study the intrinsic and buffer-dependent aggregation tendencies of therapeutic proteins when mixed with human plasma and serum.

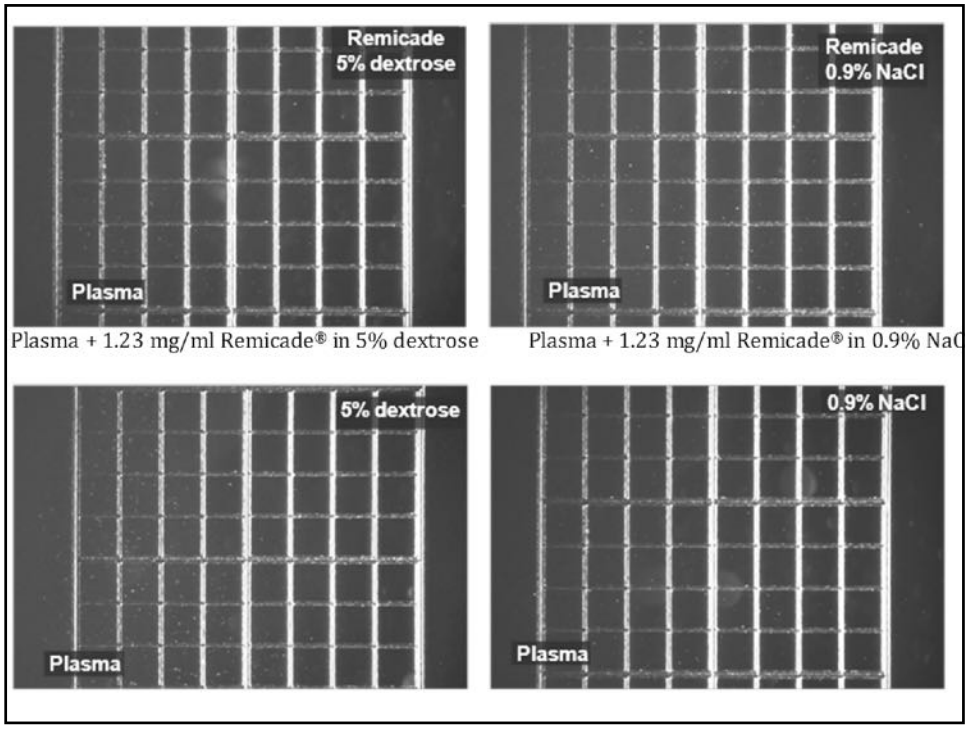
Case Study: Herceptin® (trastuzumab)

DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.



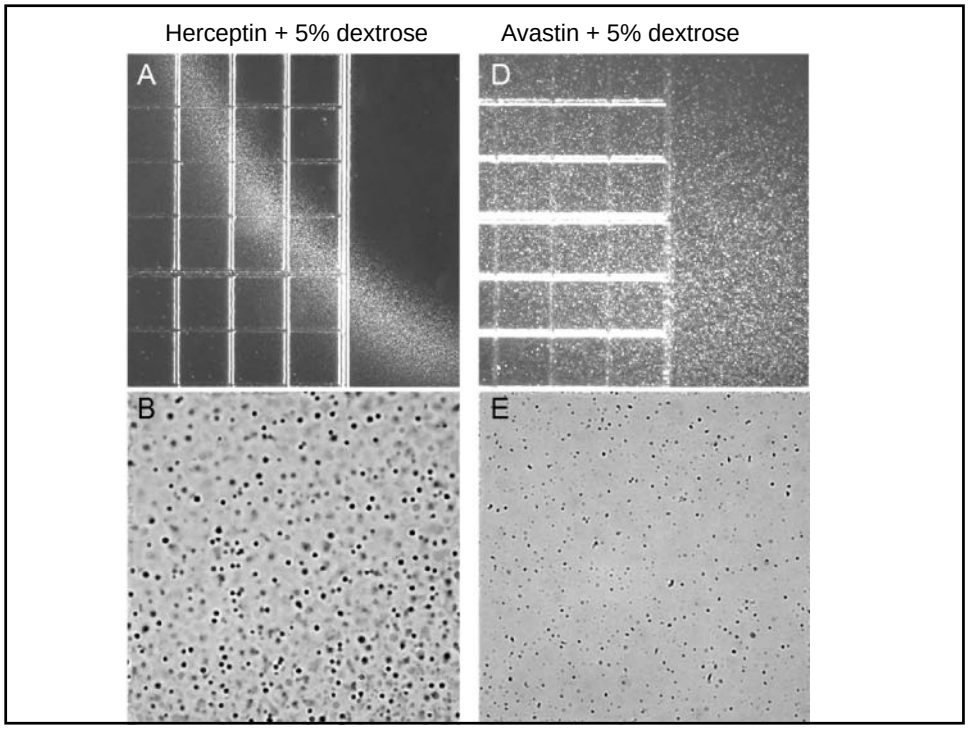

Lantus
Herceptin
5% dextrose

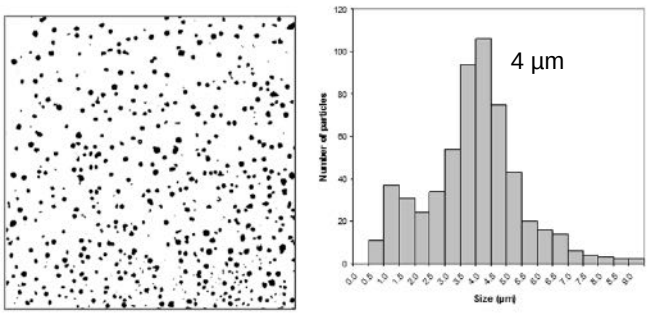

A
Herceptin
5% dextrose
Plasma
B
Avastin
5% dextrose
Plasma
E
Herceptin
0.9% NaCl
Plasma
F
Avastin
0.9% NaCl
Plasma



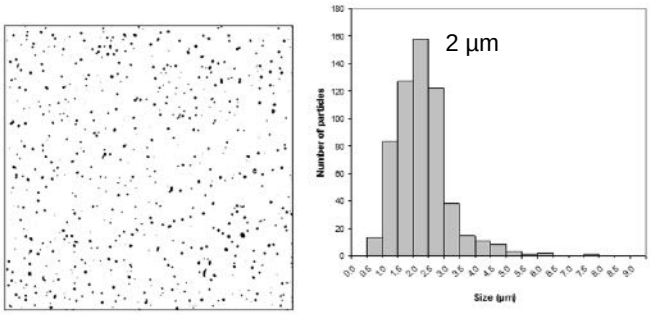
Plasma + 1.23 mg/ml Remicade® in 5% dextrose

Plasma + 1.23 mg/ml Remicade® in 0.9% NaC





577 particles; 250µm x 250µm ; 6.25nl Herceptin

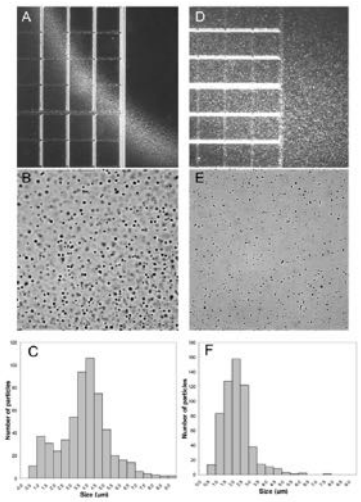


581 particles; 250µm x 250µm ; 6.25nl Avastin

Aggregation in contact with plasma

Herceptin+5%dextrose + human plasma

Avastin+5%dextrose + human plasma

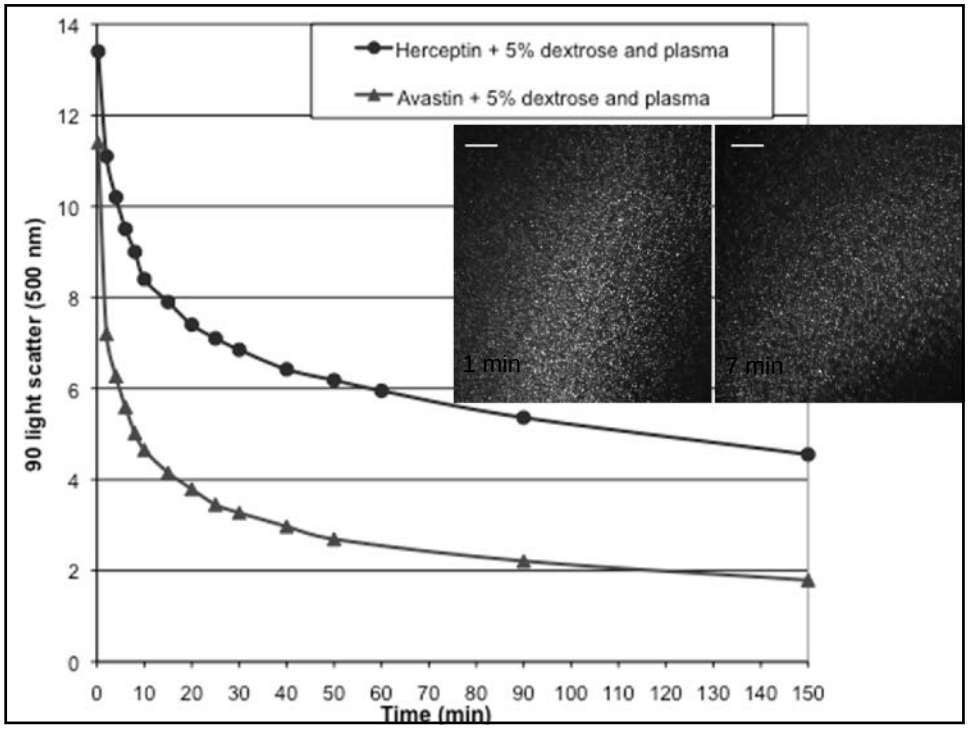


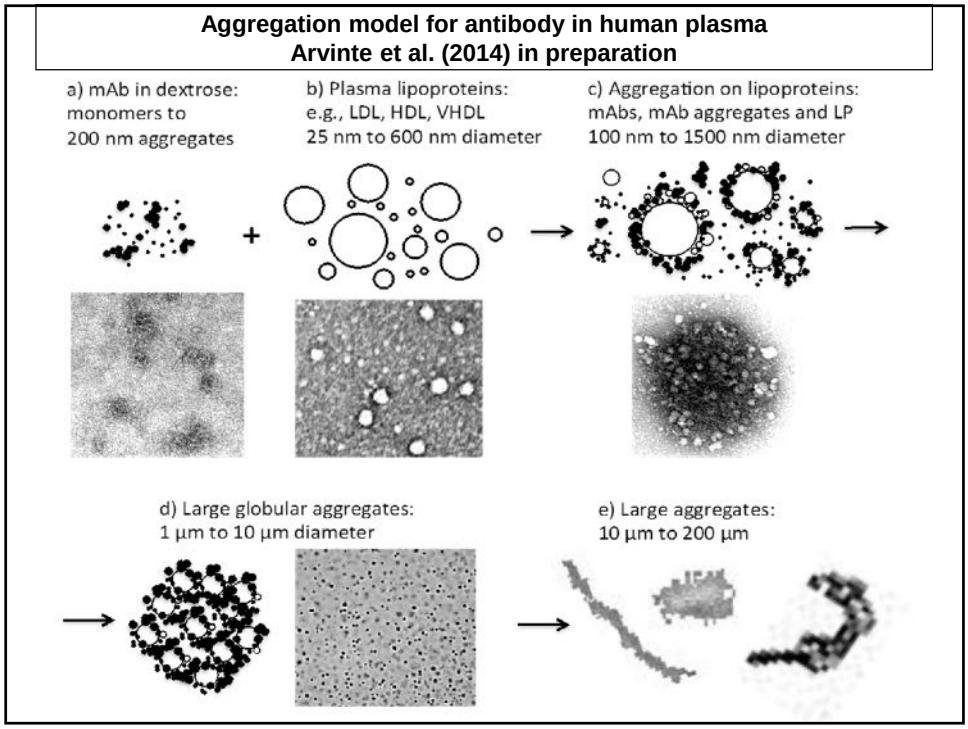
		Aggregation in contact with plasma	Size range µm	Mean diameter µm
5% dextrose	Herceptin	+	0.5 – 9	4
	Avastin	+	0.5 – 6	2
	Remicade	-		
0.9% NaCl	Herceptin	-		
	Avastin	-		
	Remicade	-		

Herceptin particle concentration ~10^8 particle/mL

Arvinte *et al*., *mAbs 2013,* 5:3, 1-10

Slide from: Dr. Ewa Marszal FDA / CBER PEGS Meeting Boston USA, May 2, 2013


Herceptin + 5% dextrose and plasma
Avastin + 5% dextrose and plasma
90 light scatter (500 nm)
Time (min)
1 min
7 min


Aggregation model for antibody in human plasma
Arvinte et al. (2014) in preparation
a) mAb in dextrose: monomers to 200 nm aggregates
b) Plasma lipoproteins: e.g., LDL, HDL, VHDL 25 nm to 600 nm diameter
c) Aggregation on lipoproteins: mAbs, mAb aggregates and LP 100 nm to 1500 nm diameter
d) Large globular aggregates: 1 µm to 10 µm diameter
e) Large aggregates: 10 µm to 200 µm

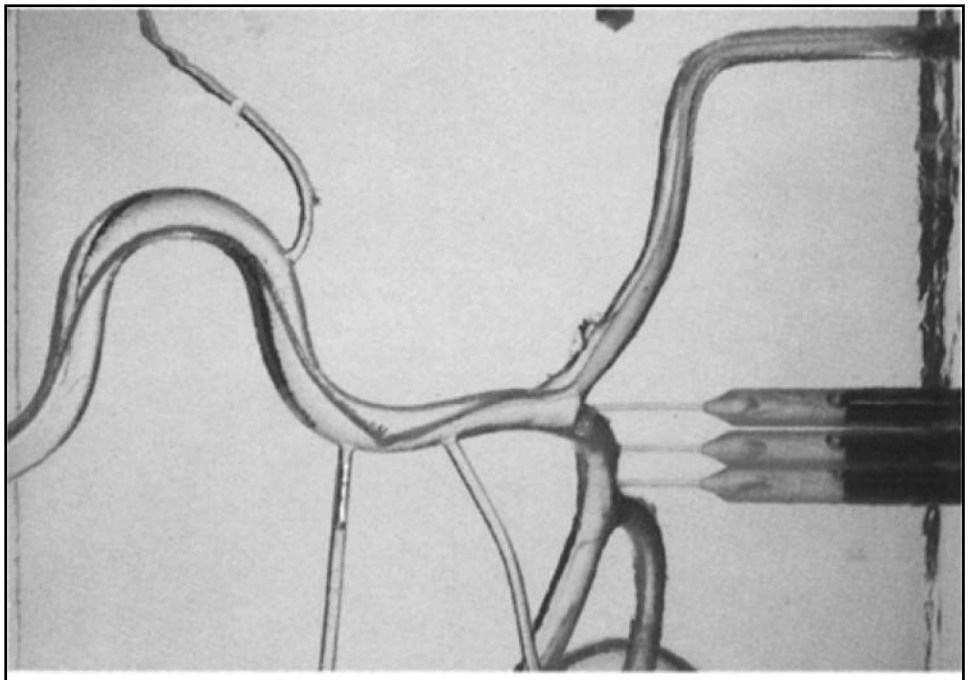
J Neurosurg 64:277–283, 1986

Mixing studies during intracarotid artery infusions in an *in vitro* model

ROBERT J. LUTZ, PH.D., ROBERT L. DEDRICK, PH.D., JOHN W. BORETOS, EDWARD H. OLDFIELD, M.D., J. BOB BLACKLOCK, M.D., AND JOHN L. DOPPMAN, M.D.

Biomedical Engineering and Instrumentation Branch, Division of Research Services; Department of Diagnostic Radiology, Clinical Center; and Clinical Neurosurgery Section, Surgical Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

Sporadic instances of retinal damage and of focal brain toxicity have been observed following intracarotid artery infusions of chemotherapeutic agents (such as BCNU and cis-platinum) for the treatment of glioblastomas. The episodic nature of these toxicities is consistent with the possibility that the drug solutions were streaming from the catheter tip and, therefore, were not well mixed or not uniformly distributed in all branches distal to the catheter tip location. To test this hypothesis, an *in vitro* system was fabricated which included a transparent model of the human carotid artery and its major branches. These were furnished with pulsatile flow of a blood simulant. Dye solutions infused at several infusion rates through various types of catheters in both supraophthalmic and infraophthalmic positions were monitored and recorded on videotape and photographic film. The effluent streams from distal branches of the model were collected, and the relative concentrations of dye in each branch were determined spectrophotometrically. The results indicate that infusate streaming occurs at low infusion rates. In some cases, the concentration in a given branch can be at least five times the expected concentration. Similar occurrences of streaming *in vivo* could cause focal toxicity. Methods to improve mixing should be used during intra-arterial administration of drugs; these include increasing the infusion rates and improving catheter tip design.



Lutz et al. 81986) J Neurosurg 64, 277

J Neurosurg 64:284–291, 1986

Drug streaming during intra-arterial chemotherapy

J. Bob Blacklock, M.D., Donald C. Wright, M.D., Robert L. Dedrick, Ph.D., Ronald G. Blasberg, M.D., Robert J. Lutz, Ph.D., John L. Doppman, M.D., and Edward H. Oldfield, M.D.

Clinical Neurosurgery Section, Surgical Neurology Branch, National Institute of Neurological and Communicative Disorders and Stroke; Biomedical Engineering and Instrumentation Branch, Division of Research Services; Nuclear Medicine Department, Clinical Center; and Department of Diagnostic Radiology, Clinical Center, National Institutes of Health, Bethesda, Maryland

Treatment of brain tumors by intra-arterial (IA) chemotherapy is occasionally complicated by sites of focal toxicity in the brain and retina. A possible cause of focal toxicity is non-uniform drug delivery due to intravascular drug streaming. To investigate this phenomenon *in vivo*, the authors examined the distribution of drug delivery after internal carotid artery (ICA) infusion in rhesus monkeys. Carbon-14 (^{14}C)-labeled iodoantipyrine was delivered into the ICA of eight monkeys at slow infusion rates (1% to 2% of ICA flow) or at fast infusion rates (20% of ICA flow) combined with additional techniques to promote mixing with ICA blood. Two monkeys received intravenous (IV) ^{14}C-antipyrine. Uniformity of delivery was assessed by comparing high-to-low ratios of isotope concentration in four brain regions evaluated by quantitative autoradiography.

There was striking non-uniformity of drug delivery in the slow IA infusion group, with as much as 13-fold differences in drug concentration in anatomically contiguous areas. The values of high-to-low concentration ratios (mean ± standard deviation) in individual autoradiographic planes were: 1) frontoparietal cortex: slow IA infusion 4.54 ± 2.07, fast IA infusion 1.71 ± 0.31, IV infusion 1.30 ± 0.174; 2) frontoparietal white matter: slow IA infusion 2.94 ± 1.45, fast IA infusion 1.59 ± 0.41, IV infusion 1.34 ± 0.21; 3) temporal cortex: slow IA infusion 5.43 ± 3.57, fast IA infusion 1.69 ± 0.24, IV infusion 1.67 ± 0.25; 4) basal ganglia: slow IA infusion 3.6 ± 2.9, fast IA infusion 1.18 ± 0.10, IV infusion 1.09 ± 0.04. Differences between concentration ratios after slow IA and fast IA infusion are significant ($p < 0.01$); those between fast IA and IV infusion are not significant.

Intra-arterial drug administration at infusion rates analogous to those currently used clinically results in drug streaming with markedly heterogeneous drug deposition in the perfused hemisphere. This may cause suboptimal drug levels in the tumor, and toxic levels at sites within the perfused hemisphere. This effect can be abrogated by techniques that eliminate drug streaming.

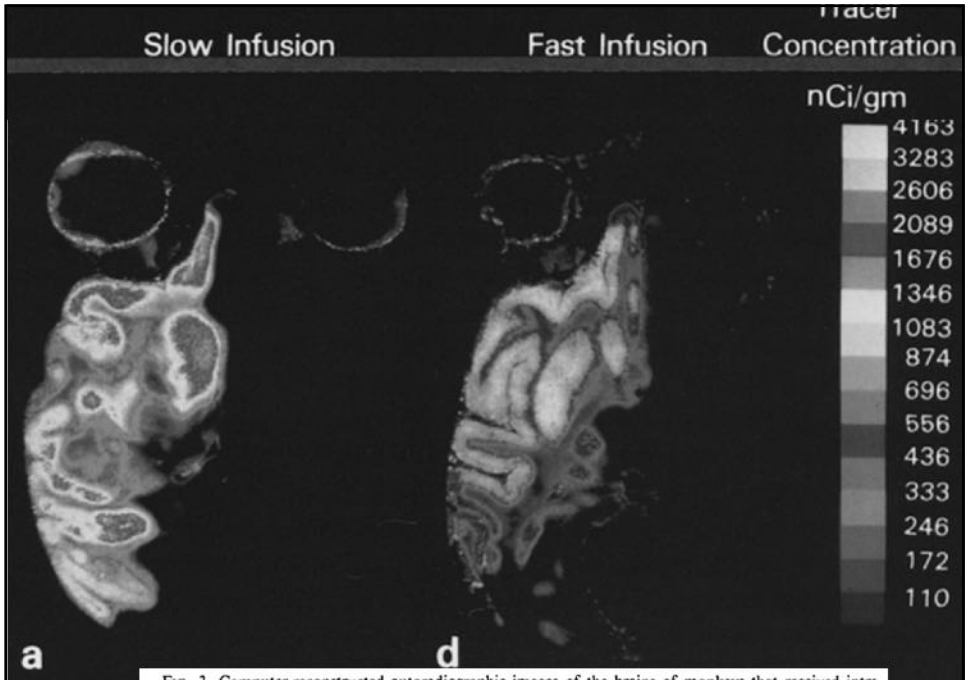


FIG. 3. Computer-reconstructed autoradiographic images of the brains of monkeys that received intra-arterial infusions of ^{14}C-iodoantipyrine at infusion rates equal to 1% to 2% (a, b, and c) or 20% (d, e, and f) of the estimated blood flow in the internal carotid artery.

Combination therapies which result in mixing of drugs and incompatible diluents may also be a source of formation of particulate aggregates. For example the chemotherapy agents Paraplatin (carboplatin) or Taxol (paclitaxel) can be administered either with 5% dextrose or 0,9% NaCl: these chemotherapy agents are often co-administered with Avastin. For another cytokine drug, Platinol® (cisplatin), it is recommended to pre-administer large volumes, i.e. 1 to 2 liters, of 5% dextrose containing saline and mannitol to the patient (Ref; FDA document).

Administration of Avastin® to these patients, even if administered in 0.9% NaCl, may result in aggregates formation since the patient has already large amounts of dextrose in his or her bloodstream.

Aggregates that form when human plasma is mixed with 5% dextrose-Avastin solutions could be one origin of the reported

"arterial thrombolytic events, including cerebral infarction, transient ischemic attacks, myocardial infarction and angina that occurred at a higher incidence in patients receiving Avastin in combination with chemotherapy as compared to those receiving chemotherapy alone" *

* **FDA"*Important Drug Warning" letter to Genentech on Avastin side effects, January 5, 2005**

Our finding that Avastin aggregates in human plasma in the presence of 5% dextrose, together with new studies of aggregation compatibility of Avastin with different chemotherapeutic agents, may be considered in the re-evaluation of patient data and may contribute to a better understanding of the origin of reported side effects .

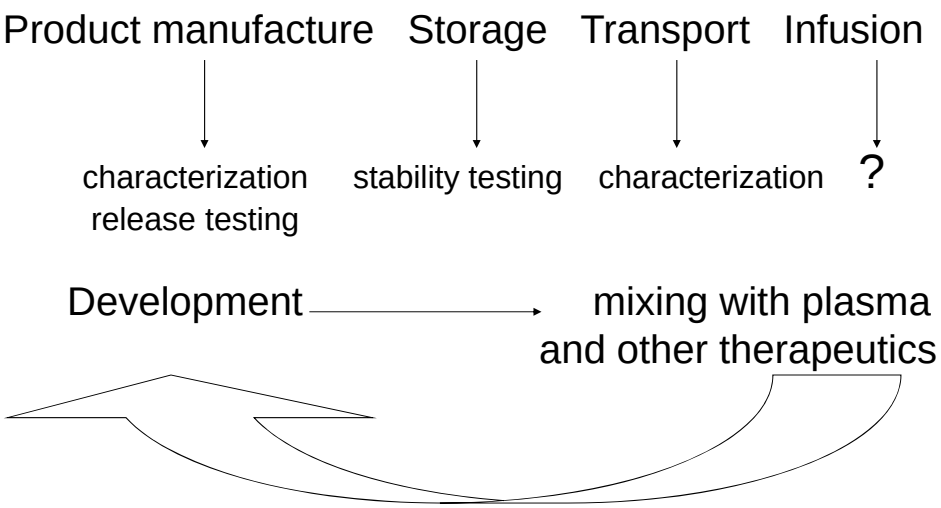
Risks related to drug co-administration

- Drugs that can be co-administered with Avastin
  - Paraplatin
    - Can be administered with 5% dextrose
    - Pre-administered with 1-2 L of 5% dextrose containing saline and mannitol
  - Taxol
    - Can be administered with 5% dextrose
- Some data suggested increased rate of arterial thrombolytic events in patients receiving Avastin® in combination with chemotherapy treatment as compared to those receiving chemotherapy alone – should these data be reconsidered?

Arvinte *et al*. *mAbs* 2013, 5:3, 1-10

Slide from: Dr. Ewa Marszal FDA / CBER PEGS Meeting Boston USA, May 2, 2013

Sources of protein aggregates



Slide from: Dr. Ewa Marszal FDA / CBER PEGS Meeting Boston USA, May 2, 2013

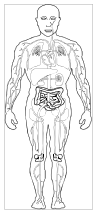
Aggregation of therapeutic proteins after mixing with human plasma: implications for drug development

- **Protein products designed to aggregate after in vivo administration in humans:**
  - **Human calcitonin, Degarelix**
  - **Lantus insulin analogues**
- **Aggregation of antibody products in human plasma**
  - **Antibody candidate during Ilaris development**
  - **Herceptin, Avastin, Remicade**
- **<u>Therapeomic platform to optimize protein formulation based on studies of aggregation in human plasma</u>**
  - **Therapeomic particle scanner imaging (PSI)**
  - **examples**

THERAPEOMIC
Bio Park Rosental WRO-1055, Mattenstrasse 22
CH-4002 Basel, Switzerland
Our laboratories and offices are on the 4th floor of the WRO-1055 building.

Therapeomics: the next Step in the Development of New Therapies based on Genomics and Proteomics

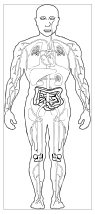
Genomics



- Resolve human genome
- Find differences in *genes* due to disease

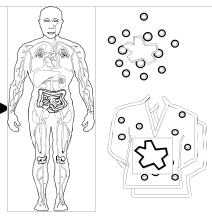
Proteomics

Functional genomics
Pharmacogenomics
Biomimetics



- Find differences in *proteins* due to disease
- Determine protein structure and function
- Find new drugs: s.m.w. and proteins

Therapeomics



Develop therapies

- Characterize protein (drug) biochemical & biophysical properties
- Characterization of structure-function*: in vitro* and *in vivo*
- Develop drug formulations and treatments

Therapeomic expertise in characterization, formulation and product development of biopharmaceuticals

- **Monoclonal antibodies (mAbs)**
  - Canakinumab (Ilaris®)
  - Omalizumab (Xolair®)
  - Trastuzumab (Herceptin®)
  - Bevacizumab (Avastin®)
  - Infliximab (Remicade®)
  - More than 20 other mAbs
- **Bispecific mAbs and fragments**
  - BlyMat Eurostars with Merus B.V.
  - More than 20 others
- **Proteins**
  - Hirudin (Revasc®)
  - BMP-2 (InductOs®)
  - Human growth hormone
  - Amylin
  - Transforming growth factor beta 3
  - More than 25 other proteins
- **Bio-similars**
  - 3 proteins
- **Peptides**
  - Salmon calcitonin (Miacalcin®)
  - Human calcitonin (Cibacalcin®)
    - Insulin glulisine (Apidra®)
    - Insulin glargine (Lantus®)
  - Somatuline autogel (Lanreotide®)
    - Starch-peptide conjugates
  - More than 20 other peptides
- **Vaccines**
  - Seasonal influenza vaccines: Inflexal®, Agrippal®, Influvac®, Mutagrip®, Fluarix®
  - Therapeutic cancer, prophylactic, multivalent, polysaccharide-conjugate vaccines
  - Virosomes, Virus-like particles
  - Natural extract allergy treatments
    - Developed vaccines with improved in vivo potency
    - More than 30 vaccines

48

Therapeomic expertise in formulation and product development of biopharmaceuticals

- **Formulation of protein drugs on the market** **3**
- Contribution to solving issues of protein drugs on the market 4
- Contribution to launch of protein drugs on the market 5
- **Stable formulations used in Phase III human studies** **3**
- **Stable formulations used in Phase II human studies** **3**
- Contribution to formulations and solving issues of protein drugs in Phase III and Phase II human studies 4
- **Stable Formulations used in Phase I human studies** **7**
- Contribution to formulations and solving issues of protein drugs in Phase I human studies 10

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Aggregation of therapeutic proteins after mixing with human plasma: implications for drug development

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  - **Human calcitonin, Degarelix**
  - **Lantus insulin analogues**
- **Aggregation of antibody products in human plasma**
  - **Antibody candidate during Ilaris development**
  - **Herceptin, Avastin, Remicade**
- **<u>Therapeomic platform to optimize protein formulation based on studies of aggregation in human plasma</u>**
  - **<u>Therapeomic particle scanner imaging (PSI)</u>**
  - **<u>examples</u>**

Therapeomic Scanner

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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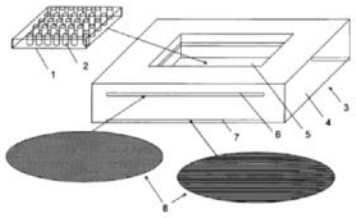
(54) Title: METHOD AND APPARATUS FOR EVALUATING SAMPLES



(57) Abstract: For detecting and storing information on optical properties analytical samples are digitally scanned with filters put in front of and behind the samples. A device for performing this method has means for putting filters on each side of the analytical samples. The filters may be polarizers, fluorescence filters etc.

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(71) Applicant: **ARVINTE, Tudor** [RO/CH]; Tiefweg 50, CH-4125 Riehen (CH).

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Published:
— *with international search report*

(54) Title: METHOD AND APPARATUS FOR DETECTING AND REGISTERING PROPERTIES OF SAMPLES

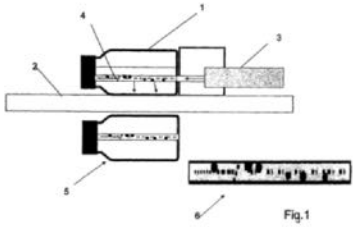

Fig.1

(57) Abstract: A laser beam (4) is guided onto or through a sample (1) which while exposed to the laser is scanned by means of a digital scanner (2). The apparatus for performing this method comprises a laser light source (3) and a digital scanner (2).

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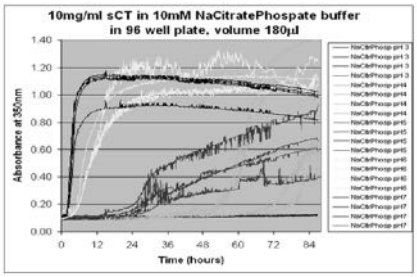
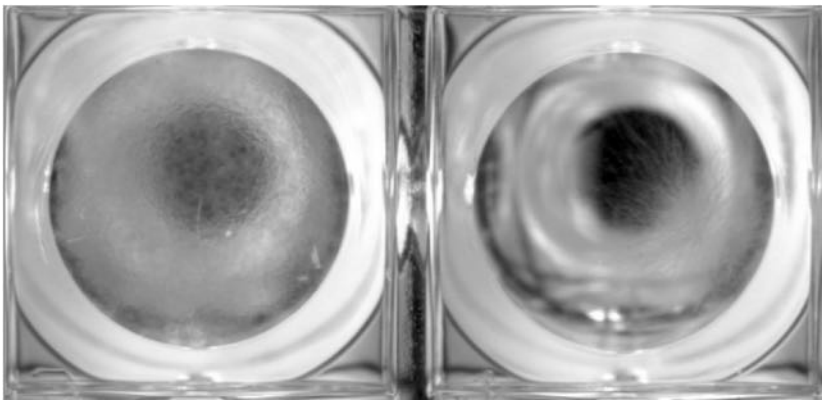
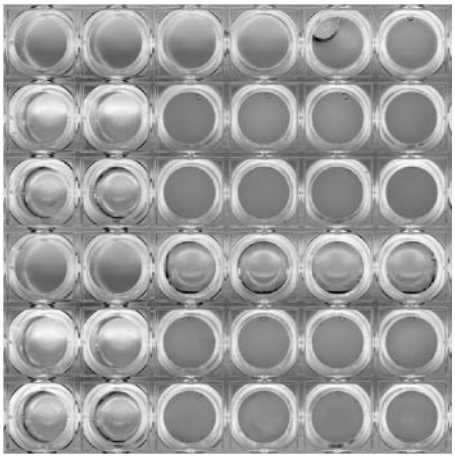
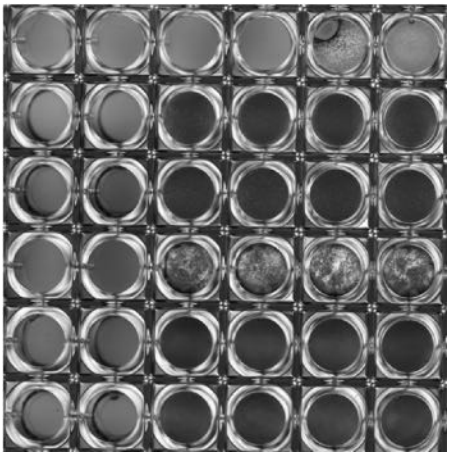
c)



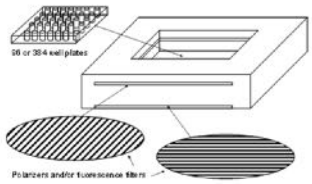


Therapeomic Scanner: Studies of drug-plasma interaction





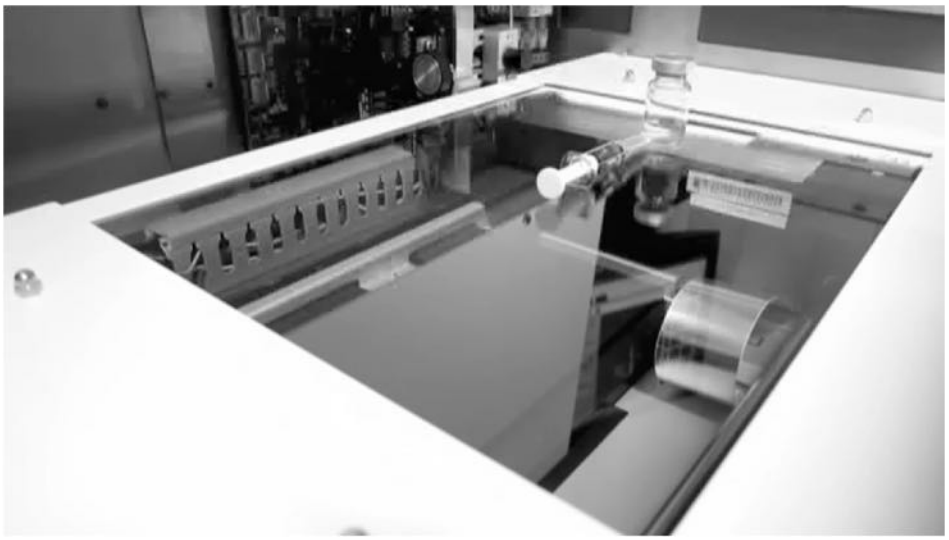
No polarizer



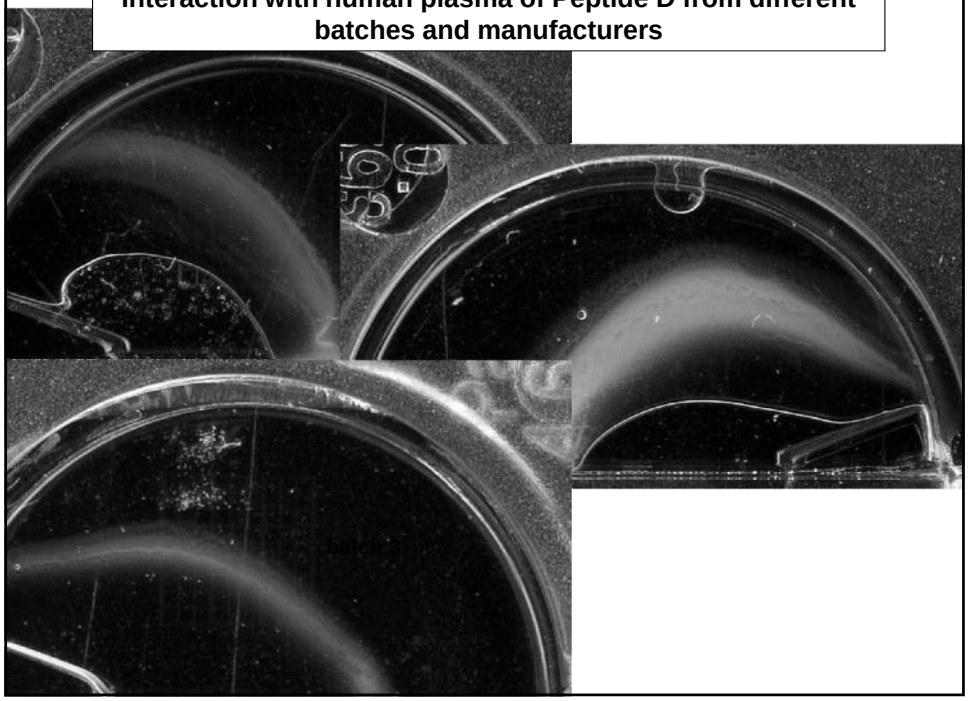
With polarizer

53

Occhio Therapeomic Scanner
To be launched in 2014



Interaction with human plasma of Peptide D from different batches and manufacturers



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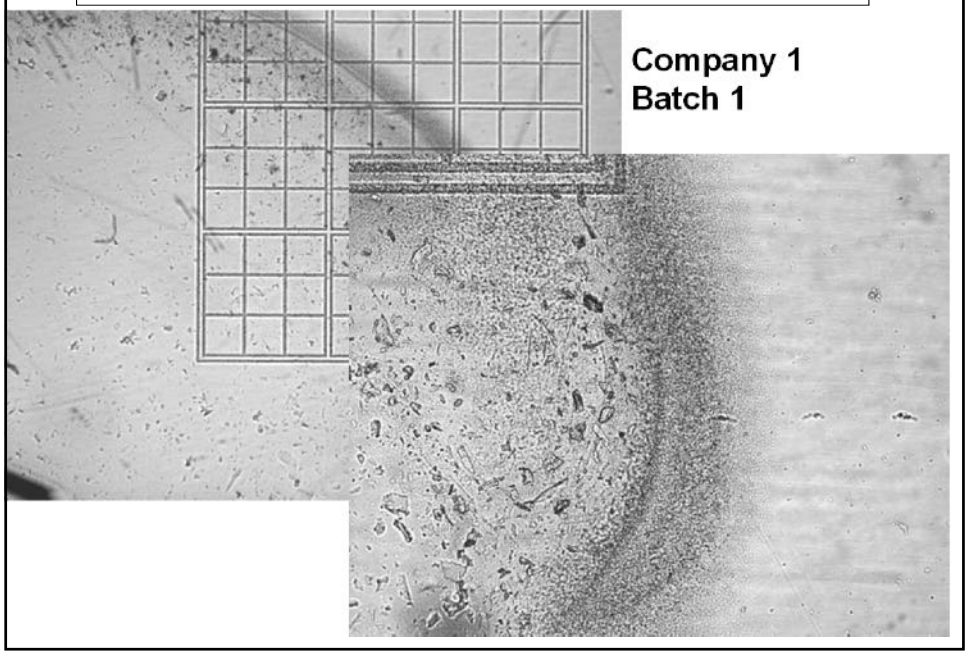

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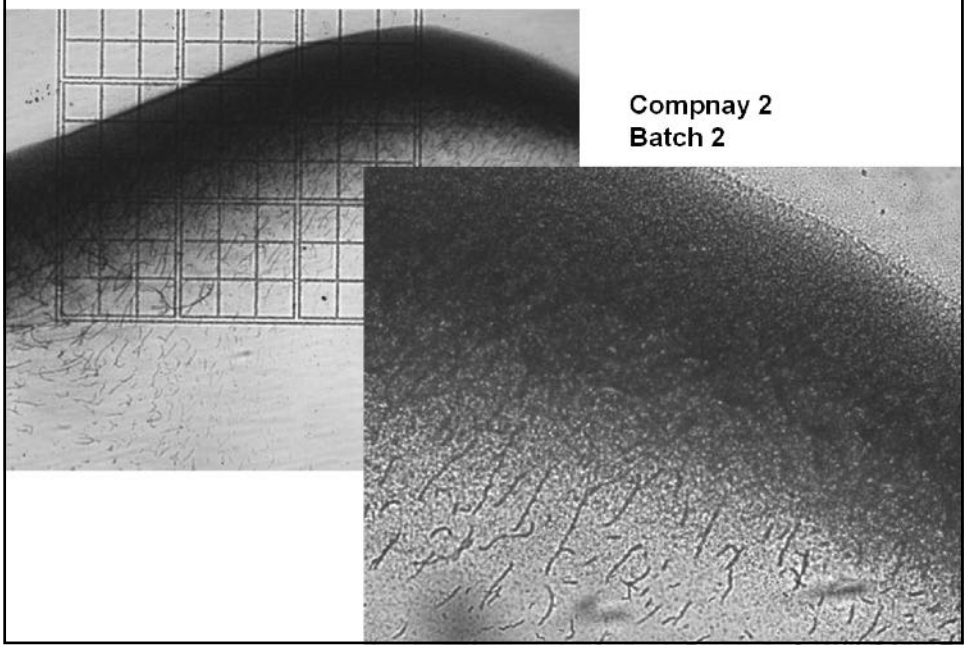

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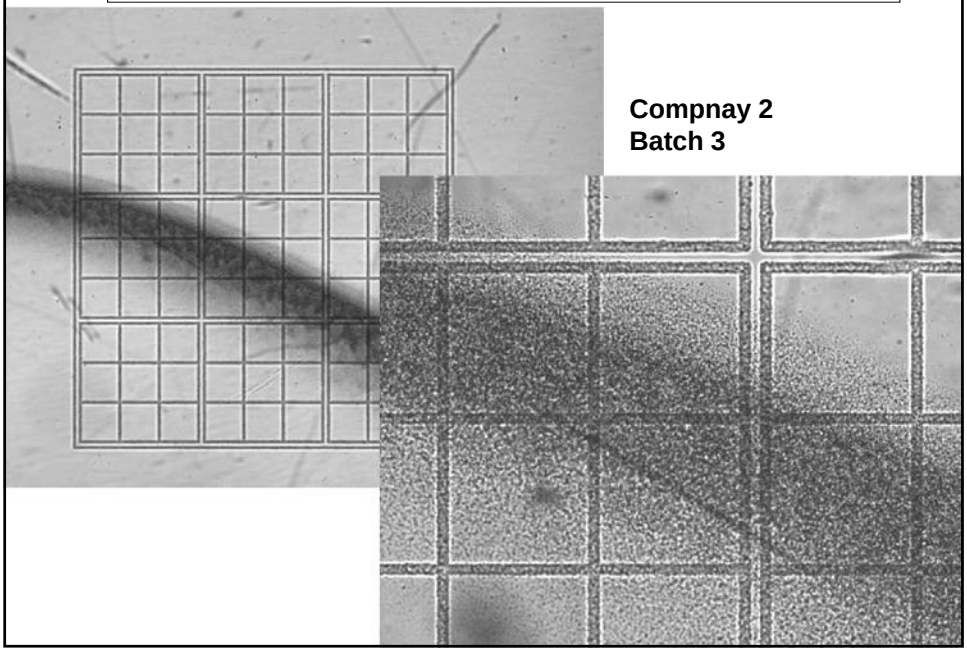
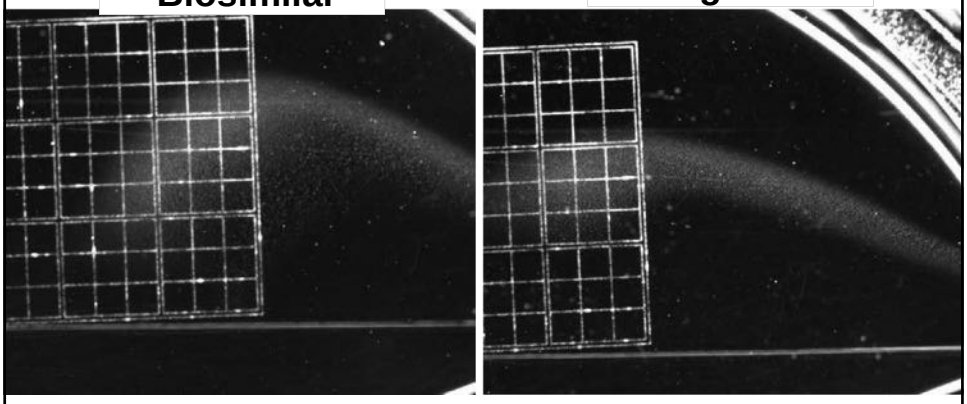


Studies of the interaction of different formulation with human plasma, serum and blood

Biosimilar **Originator**



Sources of protein aggregates

Product manufacture → characterization, release testing

Storage → stability testing

Transport → characterization

Infusion → ?

Development → mixing with plasma and other therapeutics

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Slide from: Dr. Ewa Marszal FDA / CBER PEGS Meeting Boston USA, May 2, 2013