Biopharmaceutics of Subcutaneous Drug delivery:

“Development and Delivery Challenges of Highly Concentrated and large volume formulations”

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Seminar Presented in the school of Pharmacy

Temple University

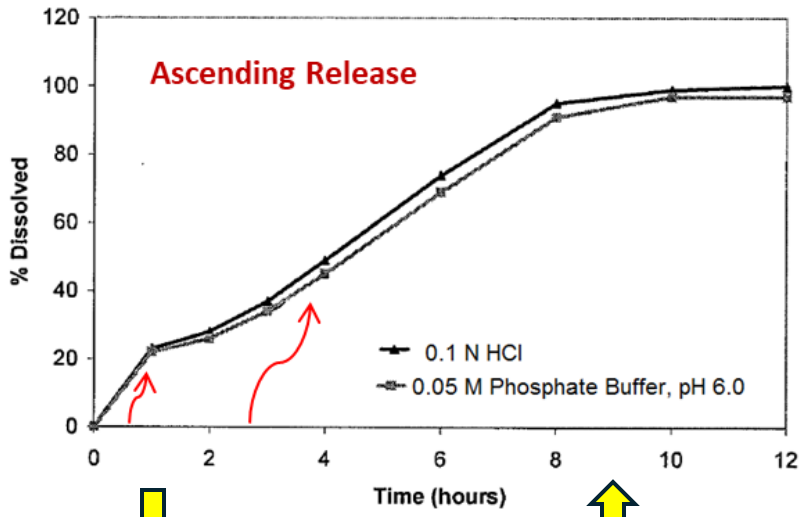
11/15/2024

What is the meaning of Biopharmaceutics?

- Biopharmaceutics is a scientific discipline that examines the interrelationship of the physicochemical properties of the drug, the drug delivery system in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption.
- Consequently, one of the primary concern in biopharmaceutics is to improve the bioavailability of drugs.
- Biopharmaceutics also plays a significant role in evaluation of bioequivalence between generic and innovator drug products.
- Biopharmaceutics is relevant to scientists working in the R&D department, preclinical and regulatory affairs.
- It aims to enhance the therapeutic activity, improve patient compliance and safety by optimizing drug delivery rate to control absorption into systemic circulation from any extravascular site (i.e.; Oral, Subcutaneous, IM, Lung, Skin etc.).

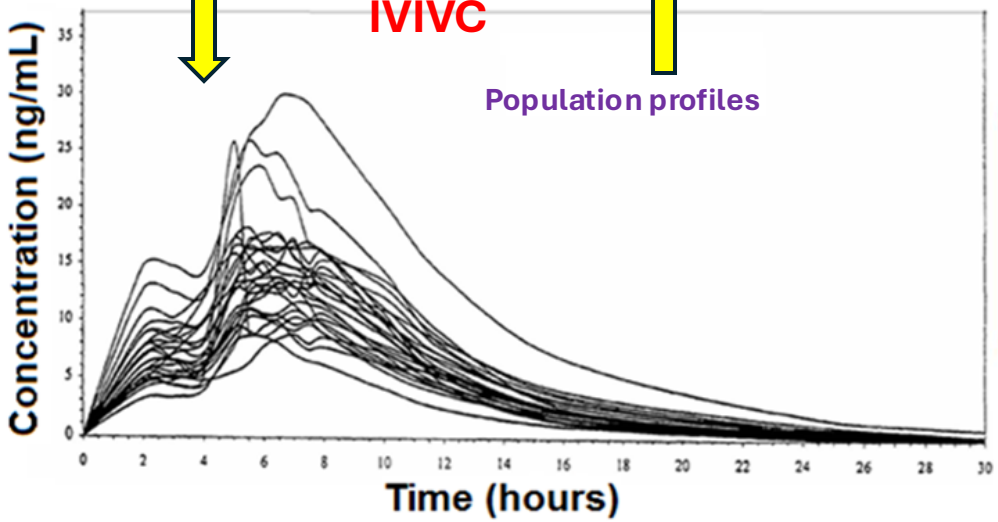
- Oral administration: The rate of drug release in-vitro and at the absorption site (In-vivo).
- The systemic absorption of the drug and its BA.
- Establishing "In-vitro - In-vivo" correlations.

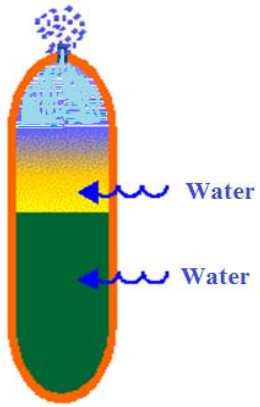
Concerta™
Methylphenidate-XR



IVIVC

Population profiles





R. FASSIHI & W. A. RITSCHEL; Journal of Pharmaceutical Sciences Vol. 82, No. 7, July 1993

Extravascular: Subcutaneous Drug Delivery (SC)

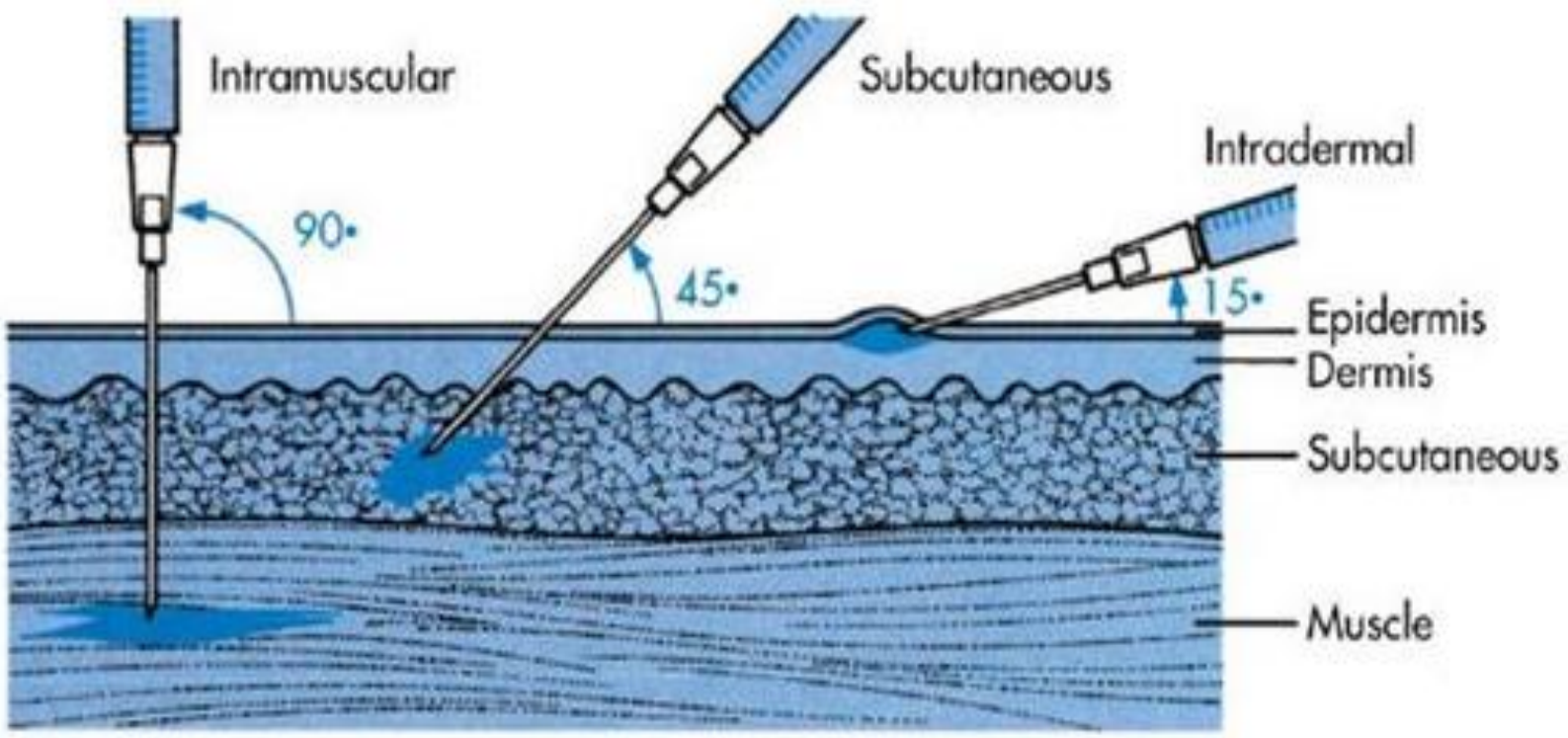
- Subcutaneous injections are widely utilized as a delivery route for different types of compounds with limited oral bioavailability or to modify the release profile.
- In recent years, there is a shift from IV to SC administration as a preferable route for certain chronic conditions.
- The SC route is becoming popular as product development has continued to shift towards **patient centricity** by enabling self-administration and ease of use for patients, improving compliance, reducing cost and reducing the burden on healthcare systems.
- Further advantages include SC local delivery, targeted delivery to the lymphatics, and prolonged systemic exposure.
- To date, SC administration continues to be challenged with **knowledge gaps** in formulation-related issues, immunogenicity, variable and (or) low bioavailability and unpredictable PK, etc.

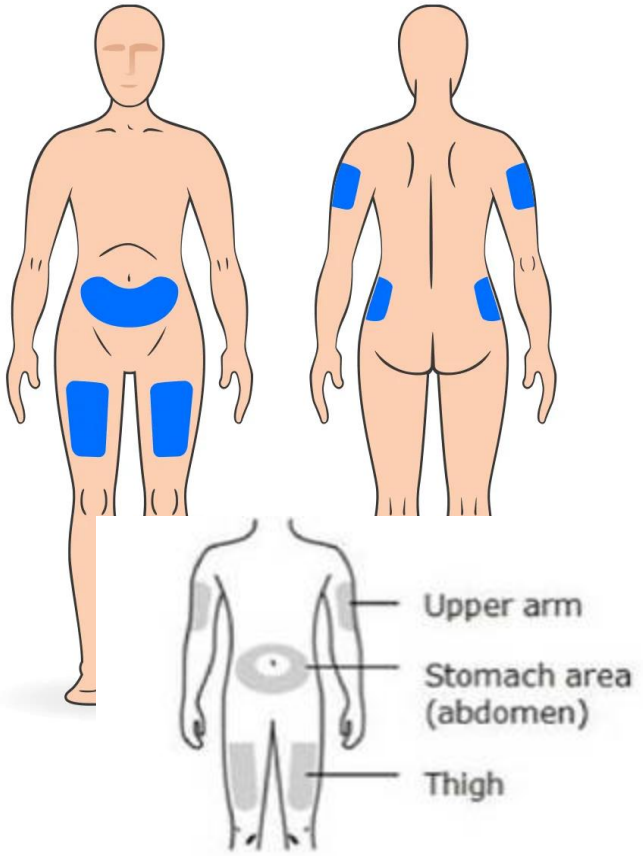
Extravascular: Subcutaneous Drug Delivery (SC)

- Major Concerns with SC administration include:
- The sensation of pain at the injection site might reduce patient compliance.
- Other issues-
  - Direct effect of the drug itself on tissues & sensation of pain
  - Needle features, injection site, injection speed,
  - Osmolality, viscosity and pH of formulation,
  - Excipients employed, including buffers and preservatives.
- Large subcutaneous injection volumes are associated with pain.
- Types of compounds often used include vaccines, insulin, growth hormone, hematopoietic growth factors, interferons, monoclonal antibodies, small drug molecules etc.,

- **SC products are typically self-administered and show significant dosing variability, with < 2-3 mL being the predominant volume range, although for some drugs typically we require large doses and volumes in the range of ~5 mL to 20 mL.**

- **A systematic understanding of dose volumes and frequencies for large-volume (>5.0 mL) SC biopharmaceuticals (LVSCs) is lacking.**





Typical example:

SC formulation of Rituximab has shown that SC administration of this antibody is a valid alternative to IV.

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen.

Rituximab has an approximate molecular weight of 145 kD.

(375 mg/m^2 IV once weekly x 4-8 doses) followed by retreatment.

Comparison between rituximab intravenous (IV) and rituximab SC

Characteristics	Rituximab IV	Rituximab SC
Administration	IV infusion over 1.5 to 2.5 hours	SC injection over 5 minutes
Rituximab Concentration	10 mg/mL	120 mg/mL
Co-formulation	none	Hyaluronidase
Dosing regimen	Body surface area - based	Fixed
Doses	375 mg/m^2 → 1400 mg 500 mg/m^2 → 1600 mg	

Use of hyaluronidase to facilitate drug absorption

(Rituximab is indicated for the treatment of adult patients with Non-Hodgkin's Lymphoma (NHL) and Rheumatoid Arthritis).

Subcutaneous Physiology and Absorption Mechanisms

Subcutaneous injection targets the fibrous hyaluronic acid (HA)/collagen matrix within the subcutaneous tissue, which is bathed in interstitial fluid (ISF).

ISF is an ultrafiltrate of the plasma. It has the same pH (pH 7.4) and electrolyte composition. It is however acellular and has a lower protein concentration (albumin concentration is ~7.36 g/L, only ~15% of that in plasma). Bicarbonate concentration is typically maintained at 25 mM.

In addition to connective tissue, lymphatic capillaries, (which collect ISF and return it, via lymphatic ducts), the subcutaneous layer also contains adipocytes (fat cells), which can act as a reservoir for lipophilic compounds. These adipocytes are surrounded by the extracellular matrix (ECM).

The subcutaneous tissue is perfused with a network of blood capillaries; however, the lymphatic route is the predominant route of absorption for larger molecules.

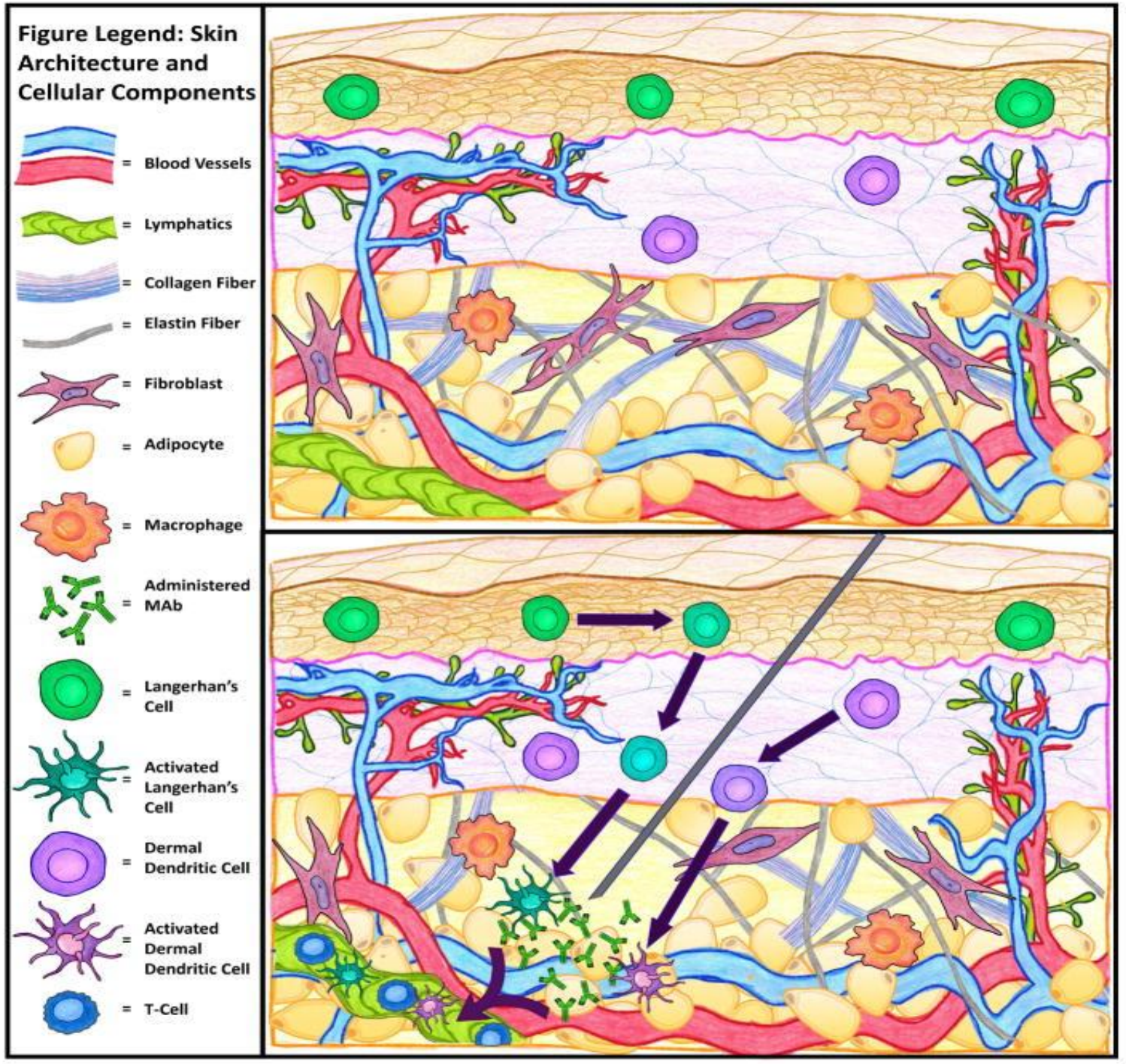
Composition of ISF

Cation	Concentration (Eq/L)	Anion	Concentration (Eq/L)
Na^+	0.137	Cl^-	0.111
K^+	0.003	HCO_3^-	0.031
Mg^{2+}	0.002	SO_4^{2-}	0.001
Ca^{2+}	0.001	CO_3^{2-}	0.000045
Total cations	**0.143**	**Total anions**	**0.143**

Kinnunen, H.M. and Mrsny, R.J. (2014). *J. Control. Release* **182**: 22–32.

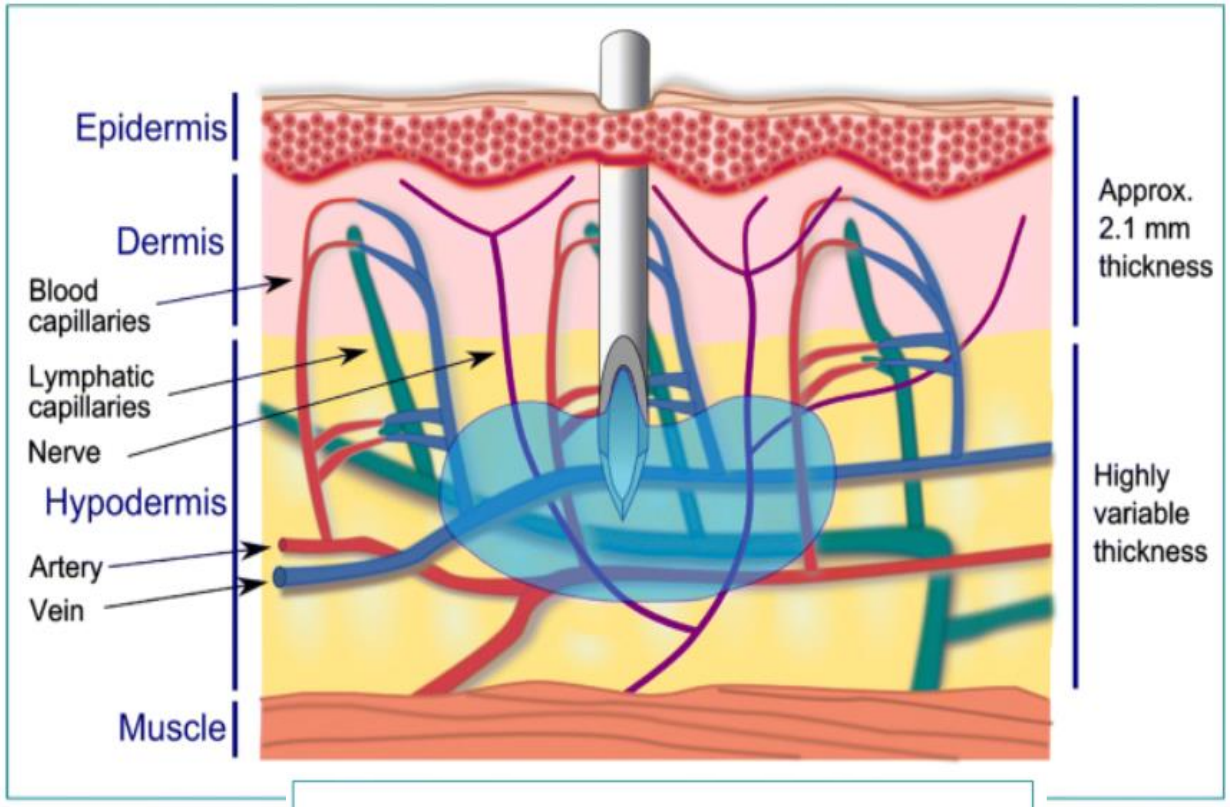
A glance at the Heterogeneous nature of SC tissues

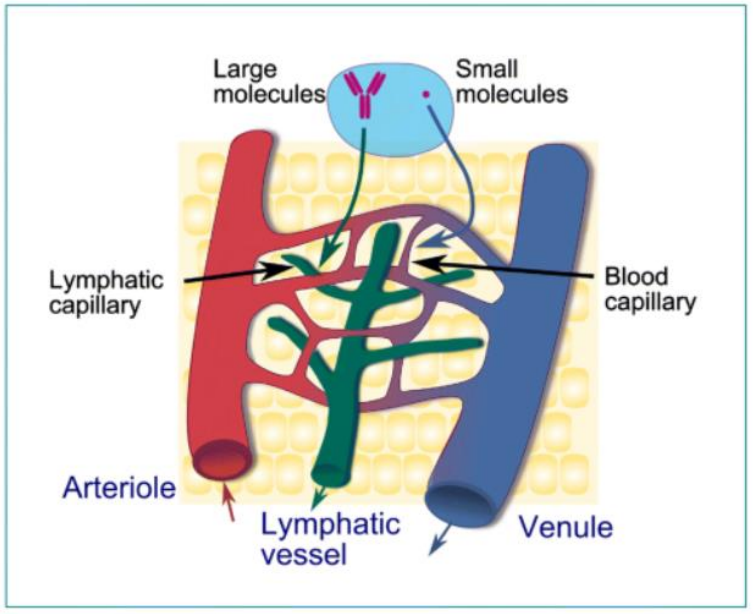
The physiological makeup of the extracellular matrix (ECM) is a subject that has not been sufficiently explored for drug absorption, especially for protein pharmaceuticals that undergo specific uptake pathways and have an inherent risk for aggregation in environments they were not specifically designed to endure. A general depiction of the anatomy and physiology of the skin is presented in the figure.



J Pharm Sci. 2018 May; 107(5): 1247–1260.

Physiology of the SC tissues



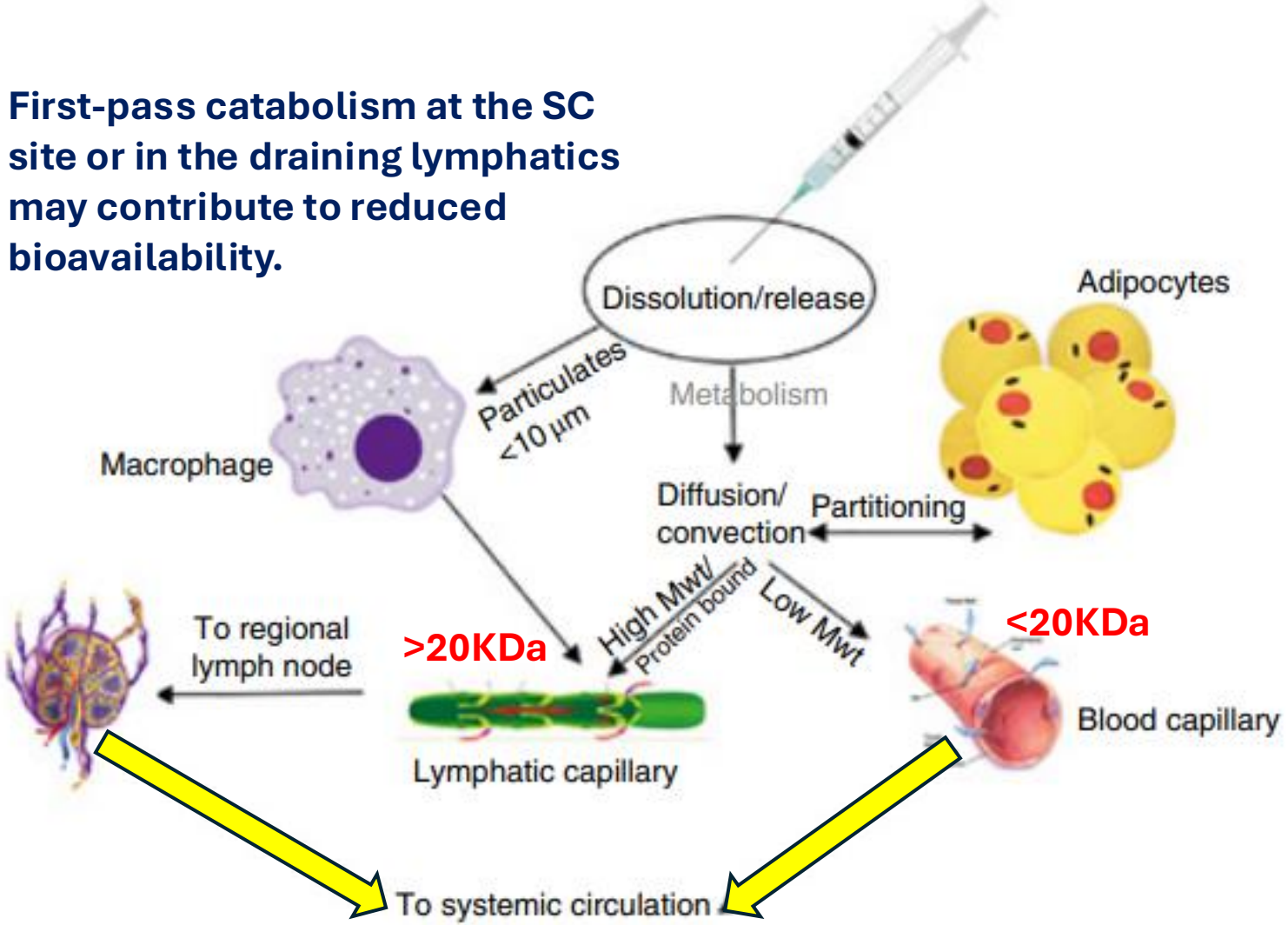


- SC tissue, is heterogeneous and consists of adipose tissue, cells (e.g., fibroblast, adipocyte), vessels (e.g., blood and lymph capillaries), proteins (e.g., collagen, elastin), as well as glycosaminoglycans (e.g., hyaluronic acid, chondroitin sulfate), etc.
- The properties of extracellular matrix (ECM) and capillaries (blood and lymphatic) profoundly impact drug migration and uptake from the injection site.
- Many injectable formulations are of high concentration, likely susceptible to aggregation in the interstitium and “first-pass catabolism”.
- For a mAb, recycling by the neonatal Fc receptor (FcRn) is known to mitigate the lysosomal degradation and thus affect its circulating half-life.

Adv Ther (2019) 36:2986–2996

Formulation Factors & SC Absorption

First-pass catabolism at the SC site or in the draining lymphatics may contribute to reduced bioavailability.



Factors affecting SC absorption

- Physchem
  - Solubility
  - Particle size/dissolution rate
  - Lipophilicity
  - Protein binding
  - Size
  - Charge

  Current assay cascade appropriate
- Physiological
  - Lymph/blood flow
  - Interstitial pressure
  - Local metabolic stability
  - Immune response
- Formulation
  - Vehicle And viscosity
  - Injection force/volume
  - Tonicity
  - Concentration
  - **Aggregation and Stability**

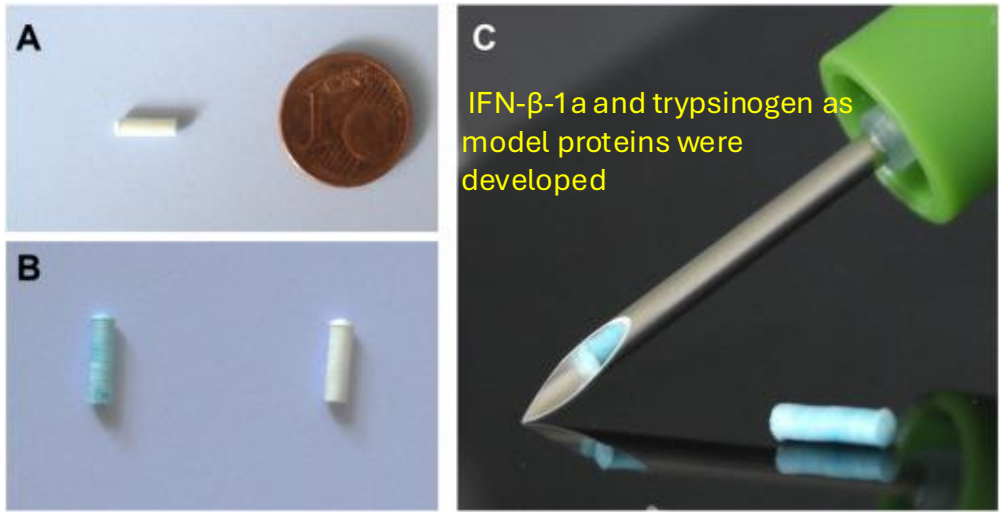
Additional uptake mechanism for mAbs in the form of FcRn-mediated transcytosis from the interstitium to the blood.

Wang w. Lee, Claire M. Patterson 2022 John Wiley & Sons Ltd.https://doi.org/10.1002/9781119678366.ch15

Types of SC Delivery Systems (implants)

- **M Danckwerts and Reza Fassihi (1991); Drug Development and Industrial Pharmacy ; "Implantable Controlled Release Drug Delivery Systems" Volume 17, 1991 - Issue 11 .. Pages 1465-1502 | Published online: 20 Oct 2008.**
- Norplant implant- development process that brought Norplant onto the world market began in the mid-1960s with FDA approval in Dec. 1990.

The rhetoric of population control in the 1960s, when the pill and IUD were introduced was very different from the language of individual choice that dominated in the 1990s, the era of Norplant.



Uses Silastic tubing

The implants were obtained by compression at 1.5 Nm of the lyophilizates into a cylindrical shape with a diameter of 2 mm, a length of 8 mm and a weight of approximately 30 mg. S. Beyer et al. / Journal of Controlled Release 235 (2016) 352–364

Marketed long-acting injectable solid implants.

Product Name	API	Dose	Dimensions	Duration	Biodegradable
Norplant®	Levonorgestrel	36 mg × 6	2.4 × 34 mm	5 years	No
Jadelle®	Levonorgestrel	75 mg × 2	2.5 × 43 mm	5 years	No
Levoplant®	Levonorgestrel	75 mg × 2	2.5 × 43 mm	3 years	No
Implanon®	Etonogestrel	68 mg	2 × 40 mm	3 years	No
Vantas®	Histrelin acetate	50 mg	3 × 3.5 mm	1 year	No
Ozurdex®	Dexamethasone	0.7 mg	0.46 × 6 mm	6 months	Yes
Zoladex®	Goserelin	10.8 mg	1.5 × 17 mm	3 months	Yes
Scenesse®	Afamelanotide	16 mg	1.45 × 17 mm	2 months	Yes
Viadur®	Leuprolide acetate	72 mg	4 × 45 mm	1 year	No

Uses Silastic tubing

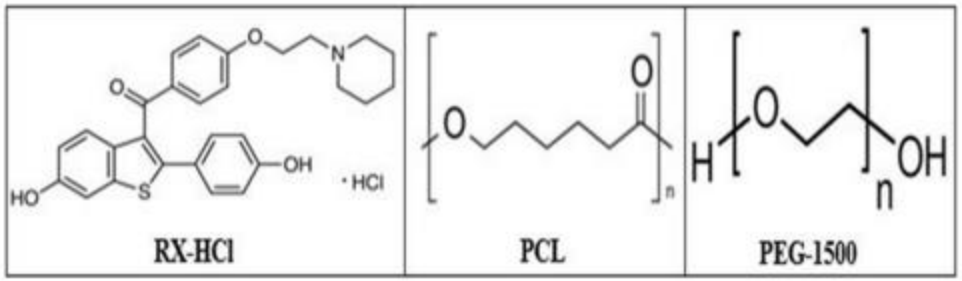
D,L-lactic and glycolic acids copolymer

phototoxicity

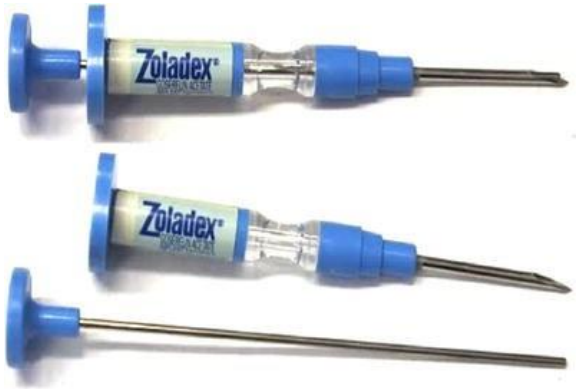
osmotically driven miniaturized implant

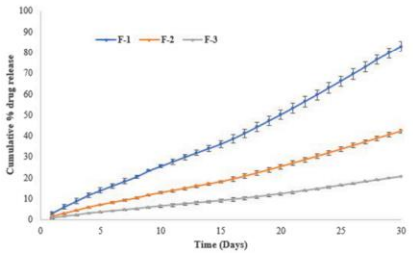
Dissolution rate determination cumbersome??

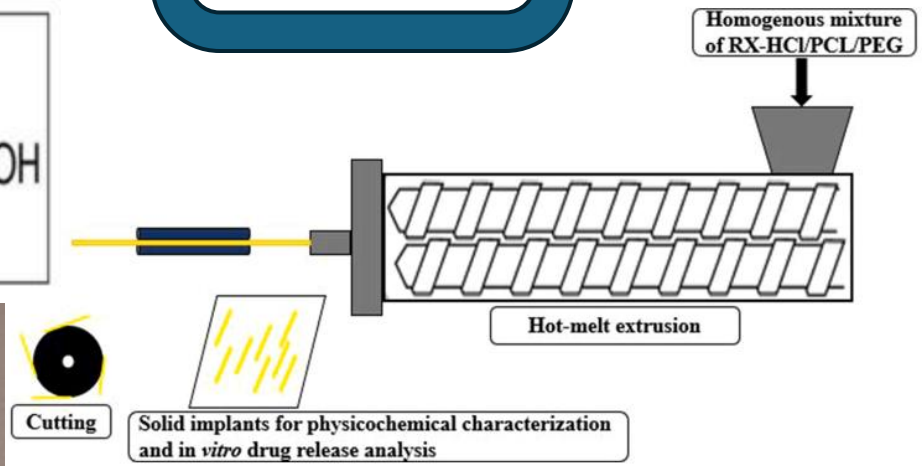
Raloxifene-HCl, Polycaprolactone PEG-1500



Zoladex—Uses PLGA







Development and evaluation of raloxifene hydrochloride-loaded subdermal implants using hot-melt extrusion technology (used in osteoporosis).

International Journal of Pharmaceutics 622 (2022) 121834

JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Research Paper

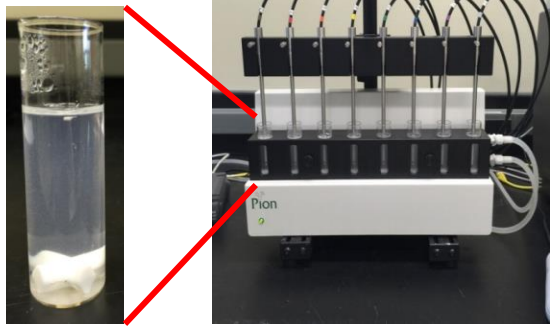
PLGA based Implants for:
1-SR Naltrexone Implant 1000mg
2-SR buprenorphine

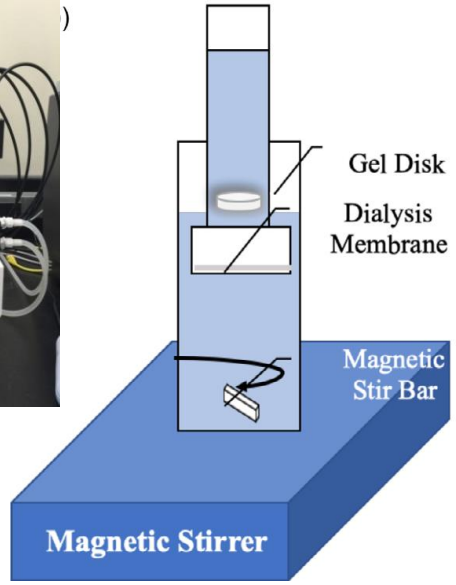
Release rate determination from in situ gel forming PLGA implant: a novel 'shape-controlled basket in tube' method

Qiangnan Zhang and Reza Fassihi

Department of Pharmaceutical Sciences, School of Pharmacy, Temple University, Philadelphia, PA, USA

20mL





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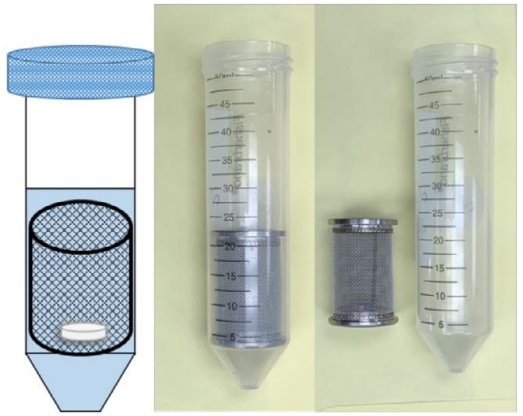
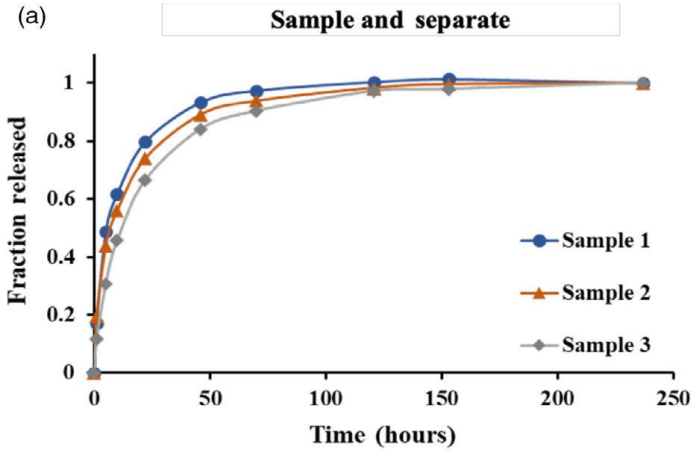
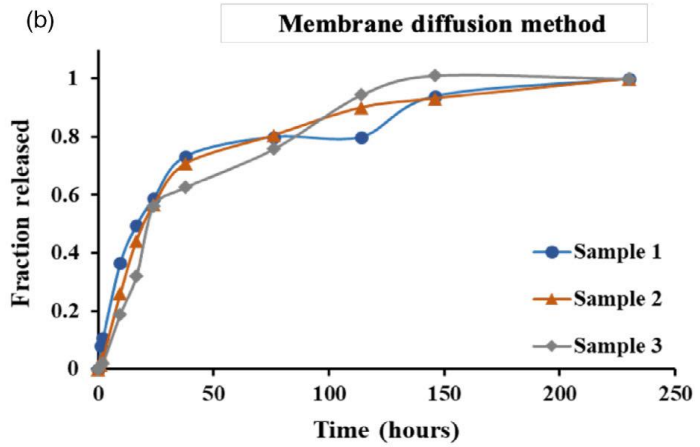
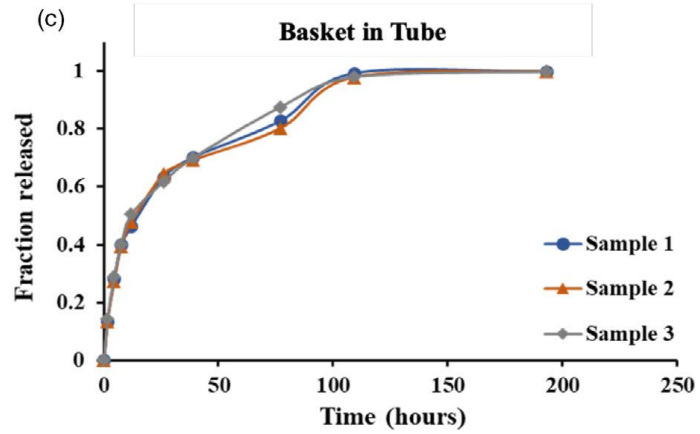


Micro-dissolution

Simplified and More Relevant Dissolution Rate Determination







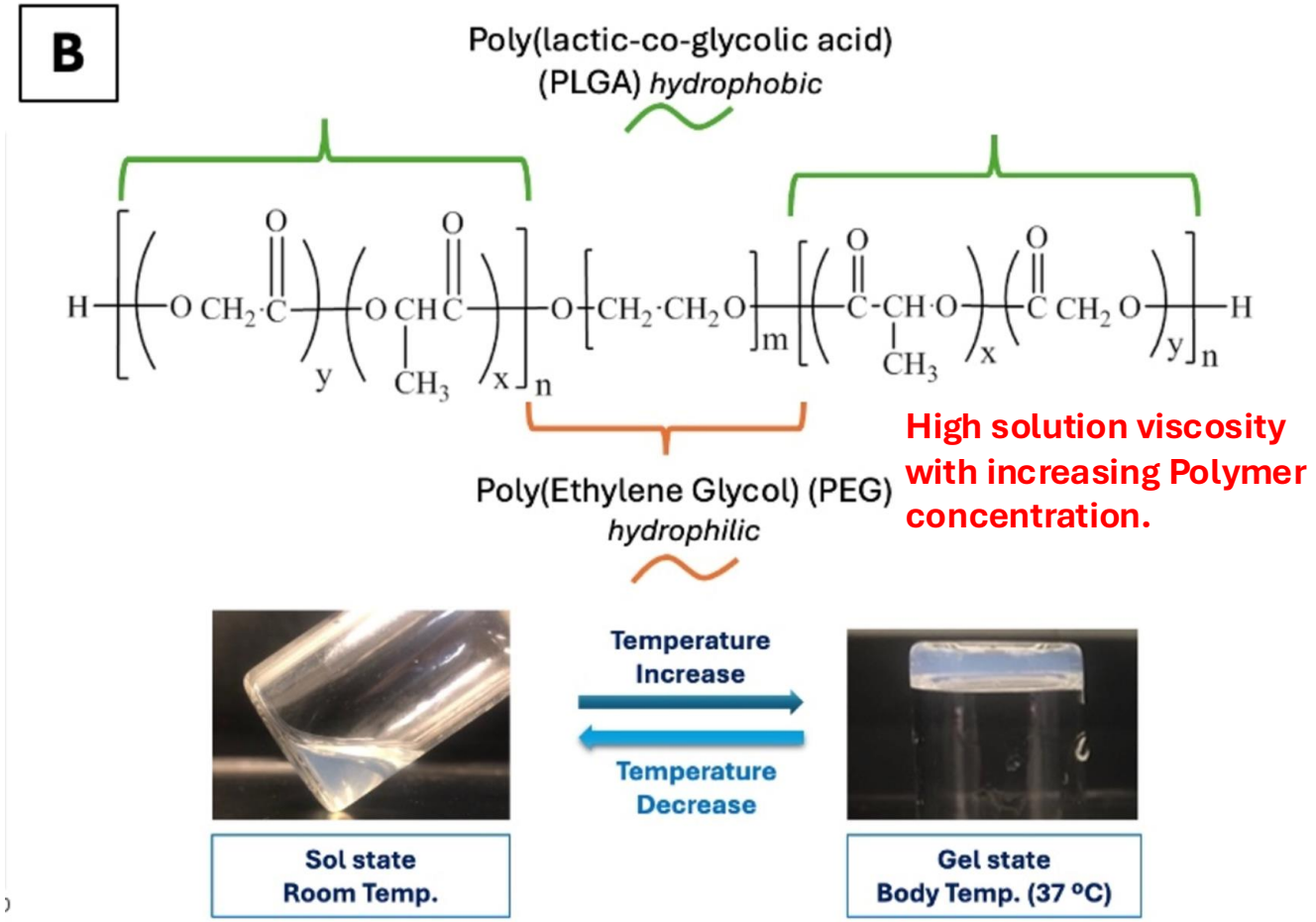
Zhang and Fassihi; Journal of Pharmacy and Pharmacology, 72 (2020), pp. 1038–1048

INTRAVITREAL DELIVERY OF PIRFENIDONE AN ANTIFIBROTIC AGENT

- in situ cross-linked polymer systems
- in situ solidifying organogels and
- in situ phase separation systems.

In-situ forming mechanisms trigger via:
pH
Solvent exchange
Temperature increase

The FDA recently approved several intravitreal products:
Susvimo - age-related macular degeneration (AMD)
Izervay
This treatment for geographic atrophy (GA) secondary to AMD was approved in 2023.
Yesafili and Opuviz
These are interchangeable biosimilars to Eylea
Annual Cost Per Eye ($) for Eylea and Lucentis is 10000 to 19000 for 7 injection and 12 injection per year.

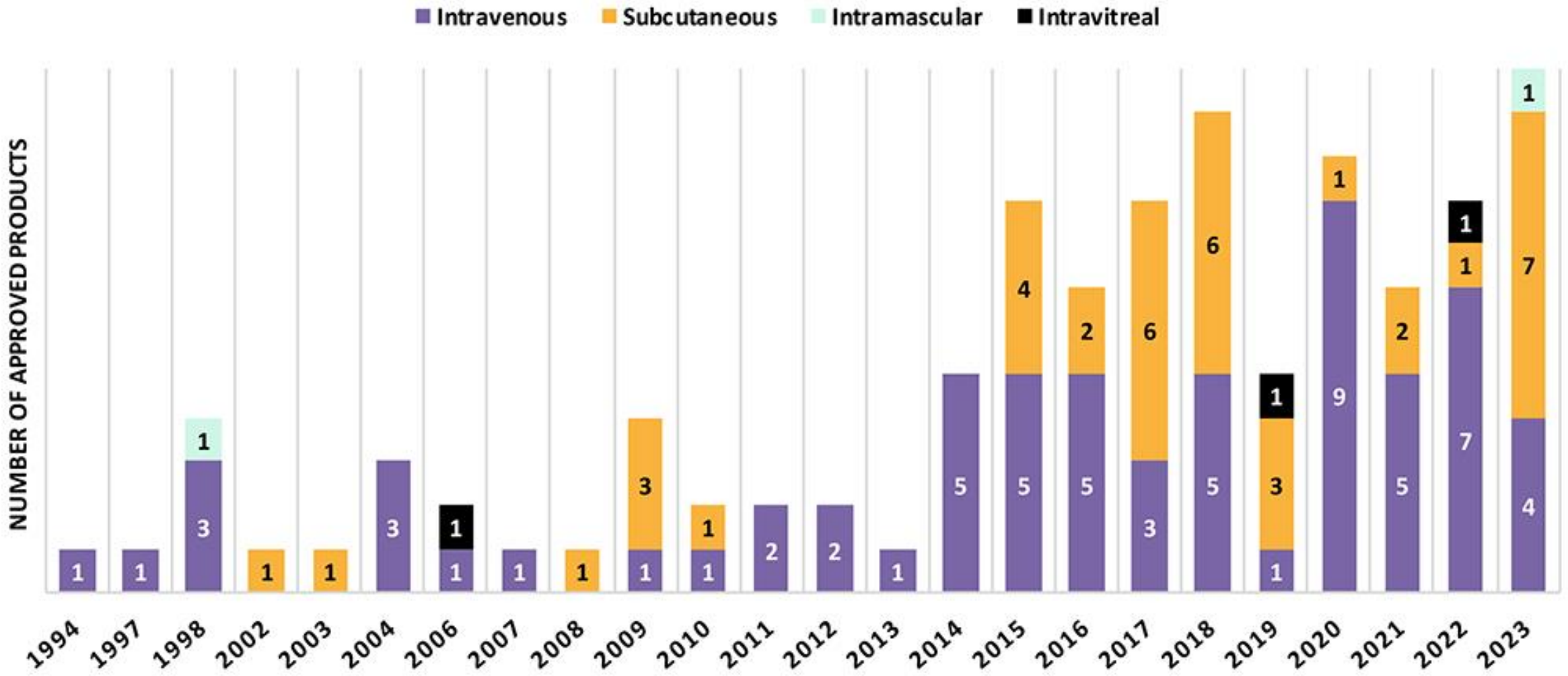


B. Alshahrouri, B. Blass and R. Fassihi, AAPS, Annual meeting October (2024) Salt Lake -Utah "poster presentation".

Biologics in 20th century and Shift to SC injection

- In the 20th century the formal recognition and distinction of biologics emerged, which led to the enactment of the Biologics Control Act by the United States Congress in 1902.
- The advent of genetic engineering in the late 1970s and early 1980s enabled scientists to modify genetic sequences, enhancing the stability , safety, and efficacy of existing agents while broadening their applications, notably seen in the enhanced targeting abilities of antibodies.
- Biologics research surged post-1980s, contributing to the development of innovative therapeutic strategies for various therapeutic areas.
- **Today Monoclonal antibodies (mAbs) represent nearly one-fifth of all recent approvals by the US Food and Drug Administration (FDA).**

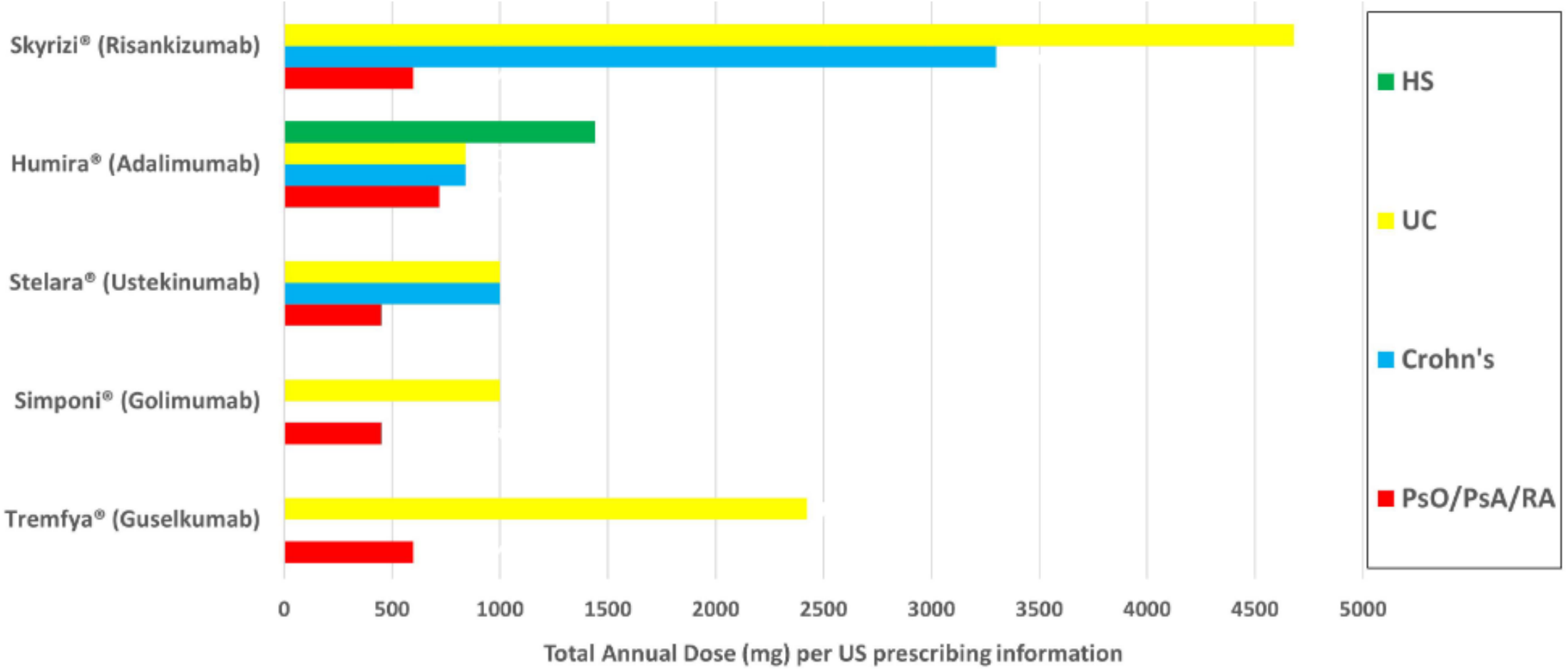
Route of administration of FDA-approved monoclonal antibody products



About 79 mAb products, excluding antibody-drug conjugates (ADCs), were approved between 2015 and 2023.

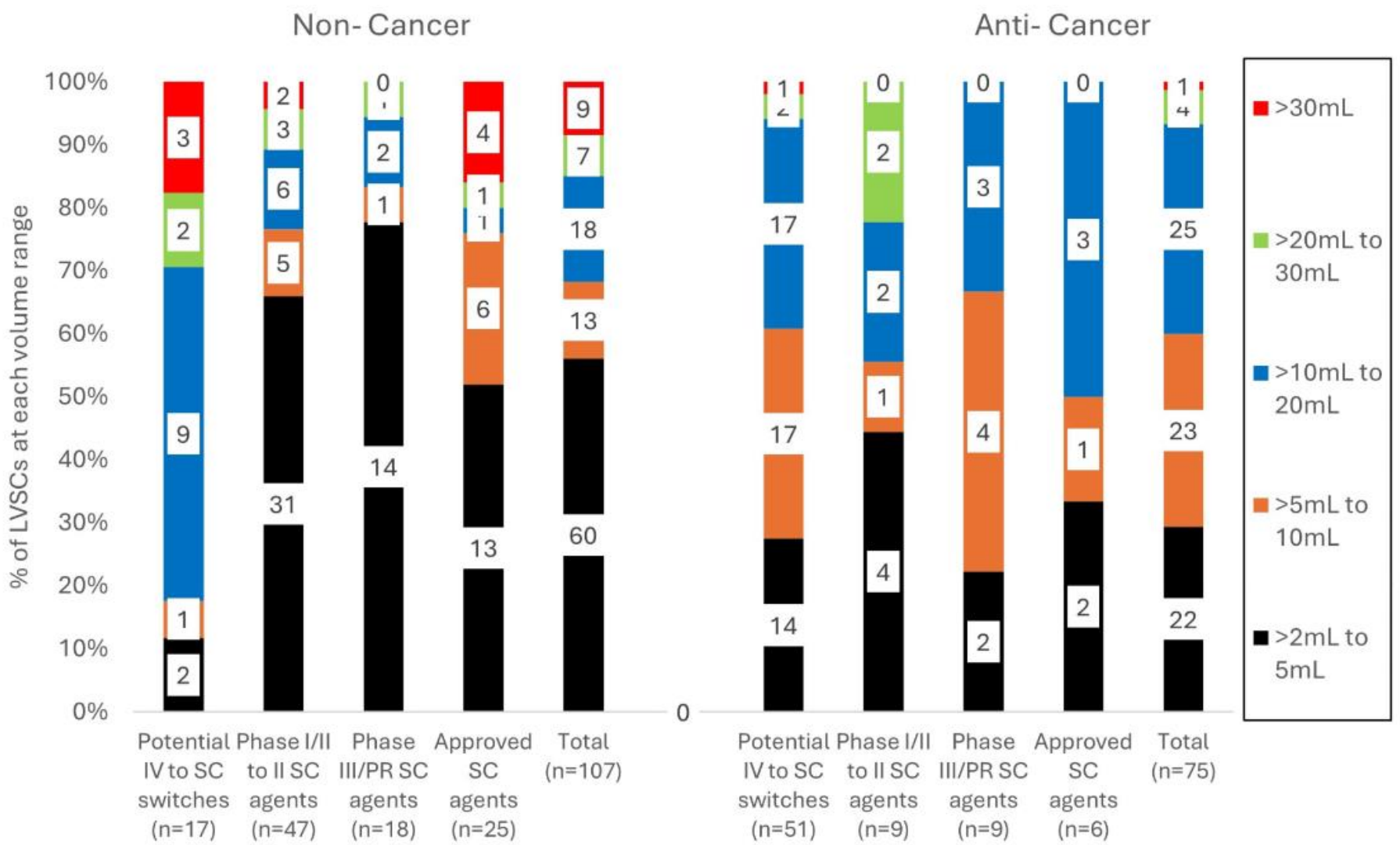
Compiled by ten23 health.

Annual SC dose per patient for selected mAbs



Autoimmune indications: **UC, Ulcerative Colitis; Crohn's, Crohn's Disease; RA, rheumatoid arthritis; PsA, Psoriatic Arthritis, PsO, Psoriasis, HS, Hidradenitis suppurativa** (also known as acne inversa).

Dose volume ranges for all IV-to-SC switching candidates



Dose volume ranges for all IV-to-SC switching candidates, SC clinical-stage assets, and approved LVSCs (N = 182).

Green. P. et.al. MABS-2024, VOL. 16, NO. 1

Table 2. High-volume mAb formulations for SC delivery.

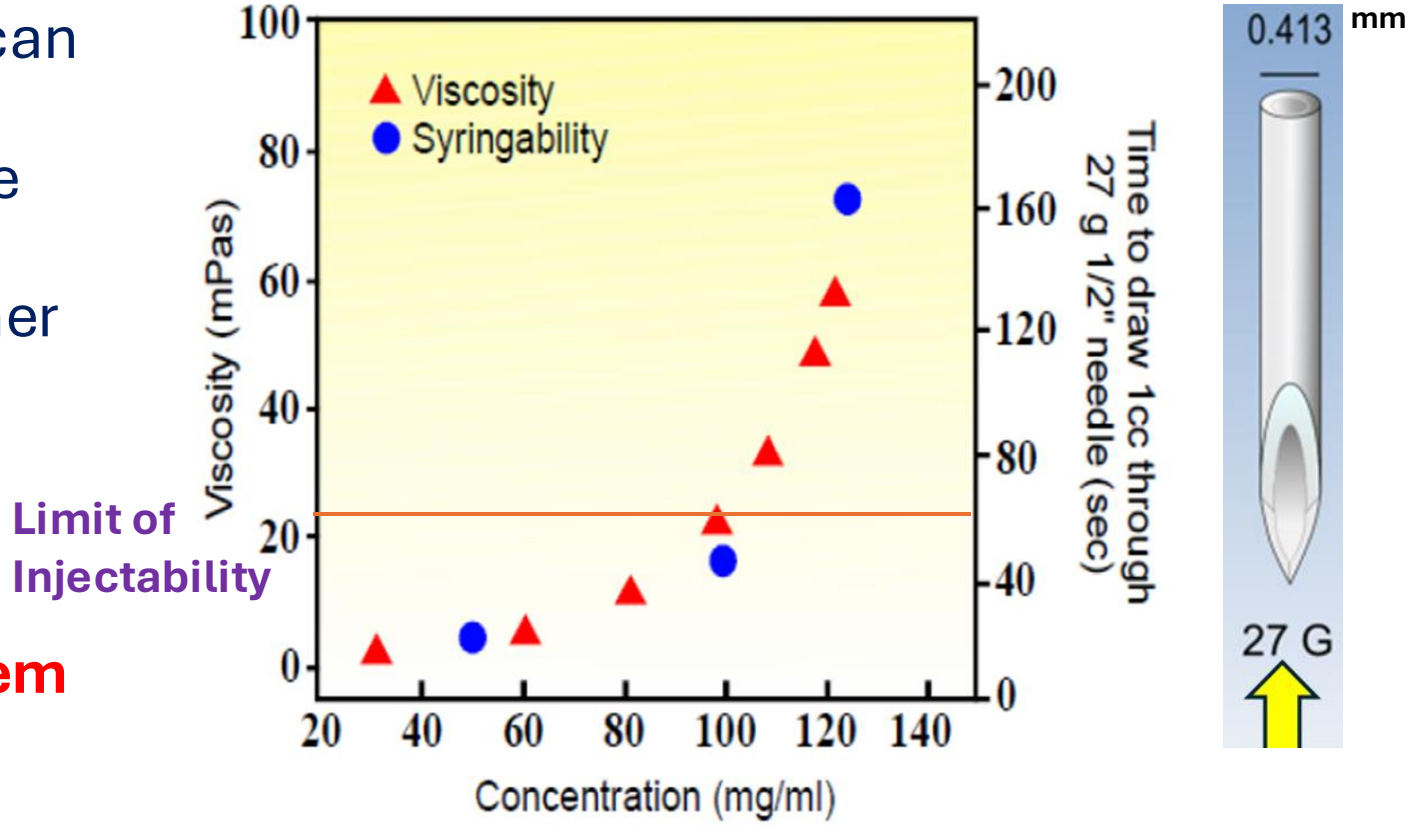
Company	Brand Name	Drug Name	Approval Year	Delivery Method	Needle Gauge	Volume and Time	Concentration
CSL Behring	HIZENTRA®	Immune globulin infusion 20% (human)	2010	SC syringe pump	24 or lower	Volumes vary by disease and weight and may be up to 100 mL	200 mg/mL
CSL Behring	HYQVIA®	Immune globulin infusion 10% (human) with hyaluronidase	2014	Peristaltic pump or syringe pump	24	1–2 mL per minute for up to 3 hours (median 2 hours)	100 mg/mL
Amgen	Repatha®	Evolocumab	2016	OBDS	29	3.5 mL over 5 mins	120 mg/mL
Genentech	RITUXAN HYCELA®	Rituximab/hyaluronidase	2017	Syringe	25	11.7 mL over ~5 mins; 13.4 mL over ~7 mins	120 mg/mL
Genentech	Herceptin HYLECTA®	Trastuzumab/hyaluronidase	2019	Syringe	25	5 mL over 2–5 mins	120 mg/mL
Genentech	PHESGO®	Pertuzumab/trastuzumab/ hyaluronidase	2020	Syringe	25	10 mL over 5 mins; 15 mL over 8 mins	120 mg/mL
Janssen	DARZALEX FASPRO®	Daratumumab/hyaluronidase	2020	Syringe	23	15 mL over 3–5 mins	120 mg/mL
Apellis	EMPAVELI®	Pegcetacoplan	2021	OBDS or SC syringe pump	29	20 mL over 20 mins	54 mg/mL
Alexion/ AstraZeneca	ULTOMIRIS® SC	Ravulizumab	2022	OBDS	29	7 mL over 10 mins	70 mg/mL
UCB	RYSTIGGO®	Rozanolixizumab	2023	SC syringe pump	26	3–6 mL – infusion pump over 9–18 minutes	140 mg/mL
Argenx	VYVGART HYTRULO®	Efgartigimod/hyaluronidase	2023	Syringe	25	5.6 mL over 1.5 minutes	180 mg/mL

Abbreviations: OBDS, on-body delivery system; PFS, prefilled syringe; SC, subcutaneous.

Friday, Sep 13, 2024- FDA Approves Ocrevus Zunovo™ Twice-A-Year 10-Minute SC Injection for People With Relapsing and Progressive Multiple Sclerosis. The recommended **dosage is (920 mg ocrelizumab and 23,000 units of hyaluronidase)** administered as a **single 23 mL SC** injection.

Protein self-association can have a major impact on important pharmaceutical properties

- The high mg/mL concentrations typical of very large molecules can result in injectable product viscosities high enough to cause problems for device designers, manufacturers, primary container suppliers, and patients.



- **Injectability becomes a problem**

- Manufacturing and stability is also a concern.

JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 94, NO. 9, SEPTEMBER 2005

AAPS PharmSciTech, Vol. 19, No. 4, May 2018 (© 2018)
DOI: 10.1208/s12249-018-0963-x

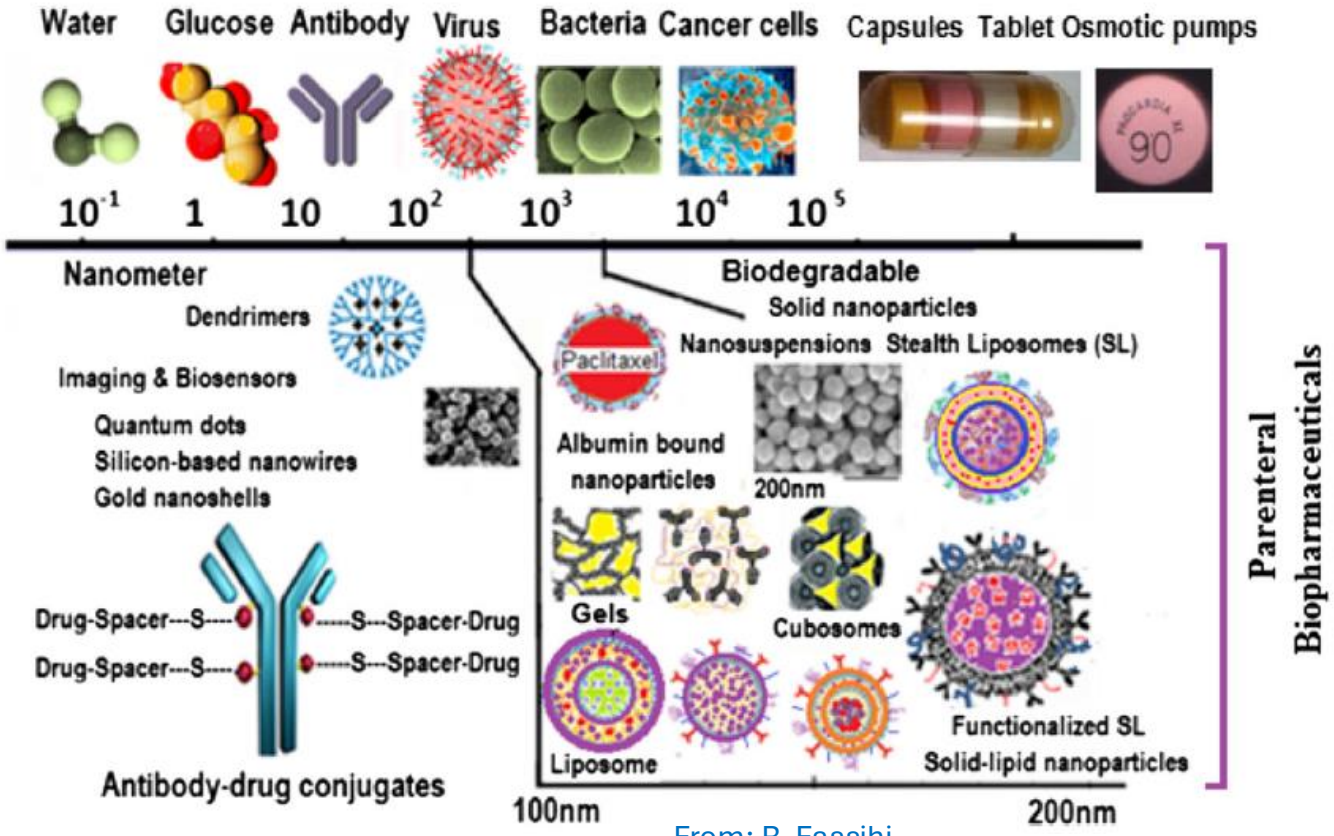
Research Article

Delivery Considerations of Highly Viscous Polymeric Fluids Mimicking Concentrated Biopharmaceuticals: Assessment of Injectability *via* Measurement of Total Work Done "W_T"

Qiangnan Zhang,[1] Mona A. Fassihi,[2] and Reza Fassihi[1,3]

Received 25 August 2017; accepted 23 January 2018; publ

Typically, viscosities of liquids range from one to several thousand centipoise (cPs). For example, viscosity of:
water is ~ 1–5 cP,
blood is 10 cP,
corn syrup 50–100 cP,
maple syrup 150–200 cP,
and many concentrated biologicals have viscosities >20–200 cPs.



From: R. Fassihi

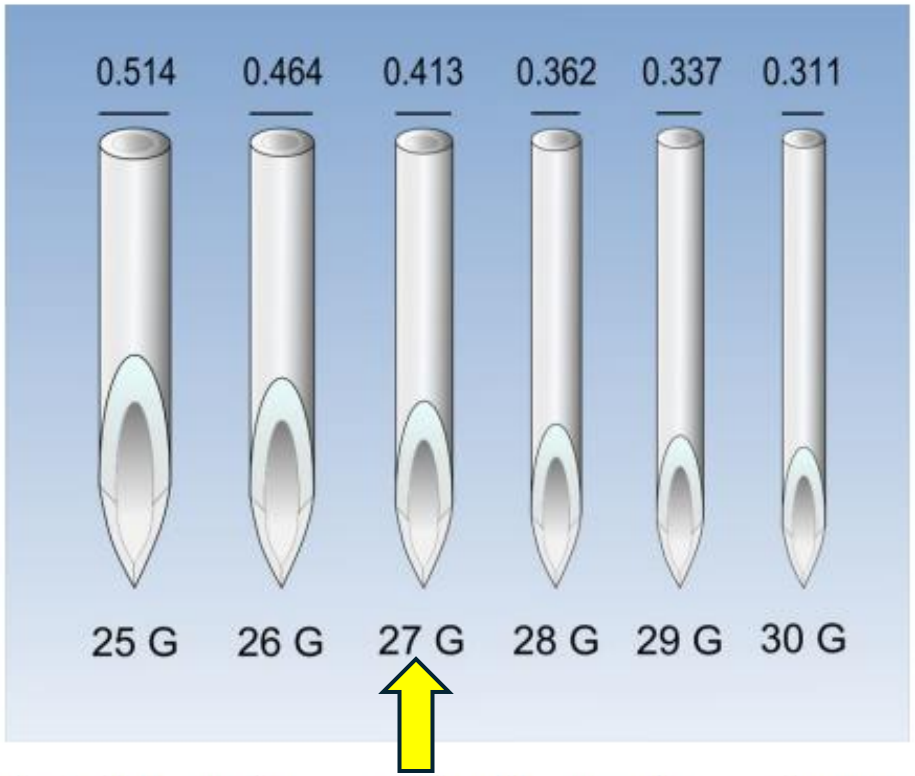
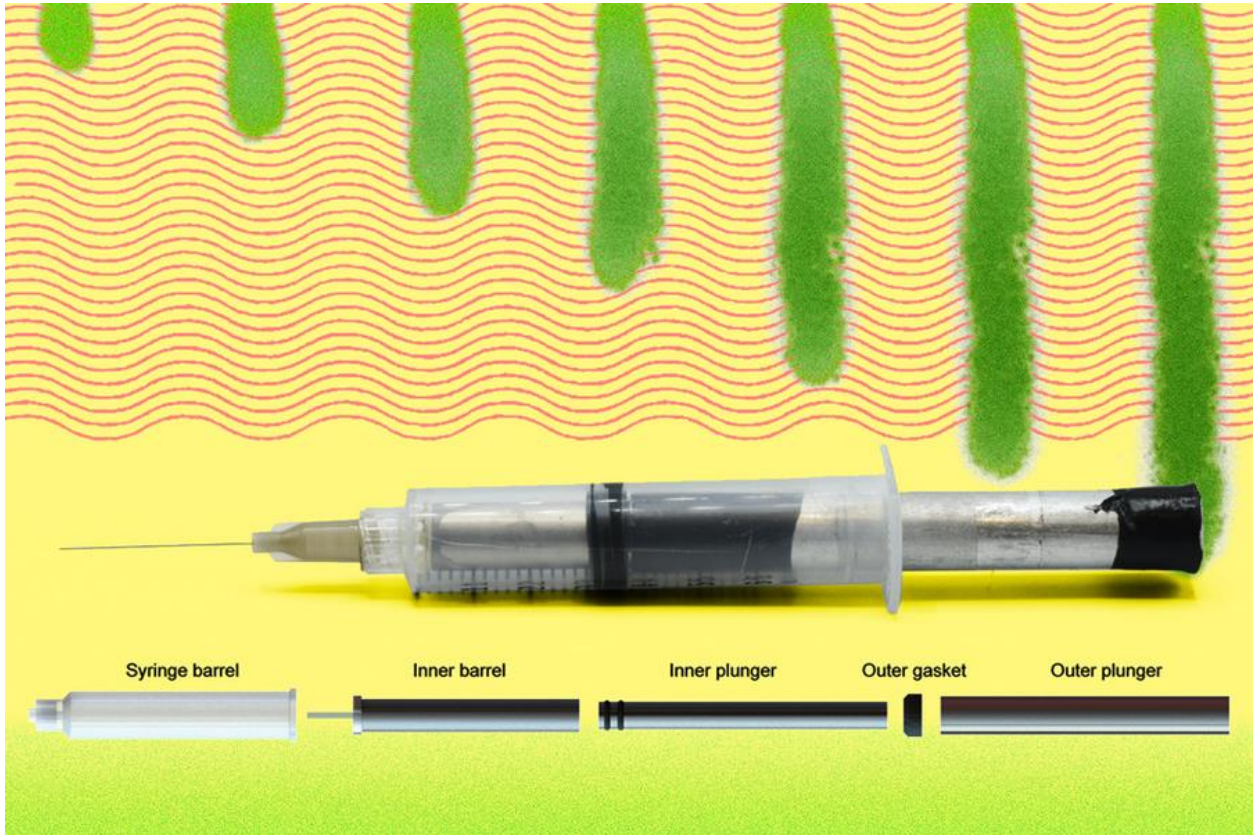
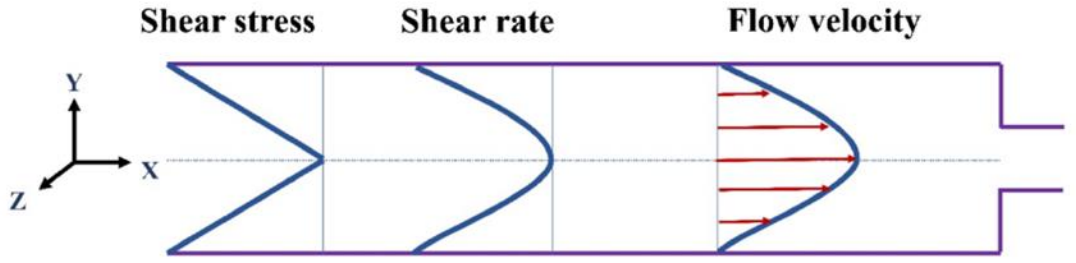


Fig. 2 Relative diameter of needles according to the gauge system (G). Values in the upper part indicate the external diameter in millimeters

$$\eta = \frac{\text{SHEAR STRESS}}{\text{SHEAR RATE}} = \frac{F/A}{V/h} = \frac{\tau}{\dot{\gamma}}$$

The Greek letters τ (tau) and $\dot{\gamma}$ (gamma dot) are conventionally used to designate the shear stress and shear rate, respectively.





The velocity profile is quasi-parabolic

Adv Ther (2019) 36:2986–2996

Viscosity is always influenced by formulation composition

Einstein recognized that in the dispersed systems, single particles enhanced the viscosity of a liquid as a simple function of their phase volume, according to this equation:

where η is the viscosity of the suspension, η_{medium} is the viscosity of the medium, and Φ is the volume fraction of solids in the suspension.

$$\eta = \eta_{\text{medium}} (1 + 2.5\phi) \ldots\ldots$$

However, in many biologics and biopharmaceutical formulations, particle loadings are high with greater proximity to each other and thus higher viscosity due to the crowding effect.
Krieger and Doughetry developed a semi-empirical model to account for this crowding effect:

Where Φm is the maximum volume fraction of solids in the system, [η] is the intrinsic viscosity with value of 2.5 for spheres. Addition of Φm parameter shows that there is a maximum volume of particles that can be added before the system becomes too viscous.

$$\frac{\eta}{\eta_{\text{medium}}} = \left(1 - \frac{\eta}{\eta_{\text{medium}}}\right)^{-[\eta]\phi_m} \ldots\ldots$$

Using the Hagen Poiseuille equation, which is used to assess required force across a pipe or syringe to cause flow can be measured:

$$F = \frac{128QL\mu A}{\pi D^4} \ldots\ldots$$

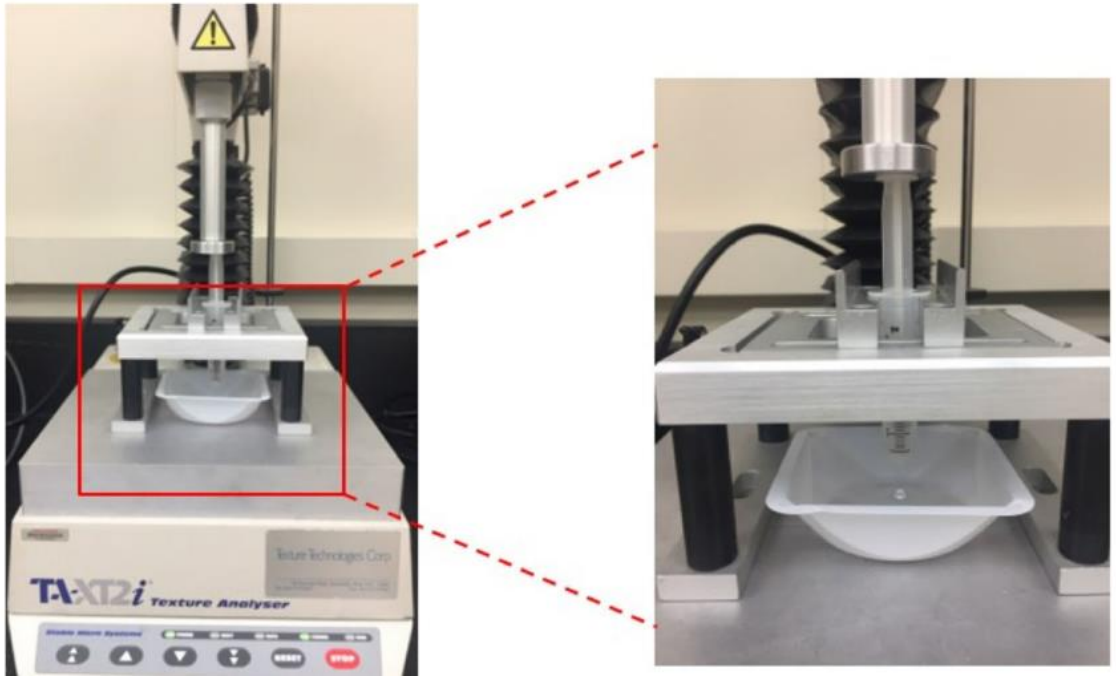
where F is the force, Q is the volumetric flow rate, μ is the viscosity of the fluid , L is the length, D is the diameter of the pipe/needle bore diameter, and A is the area (i.e., syringe plunger area).

We used AUC of the force-distance (F-D) profiles representing total work done (WT) to completely extrude the syringe content. Using the equation:

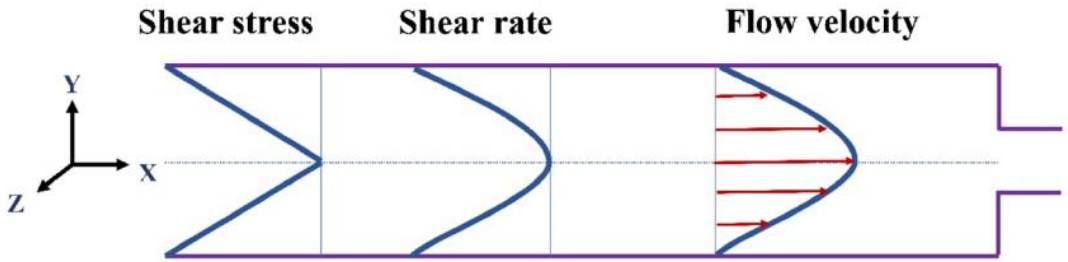
$$W_T = \int_{D_{F=0}}^{D_{\max}} F.dD \ldots\ldots$$

Q Zhang, Mona A. Fassihi, and Reza Fassihi ; AAPS PharmSciTech, Vol. 19, No. 4, May 2018

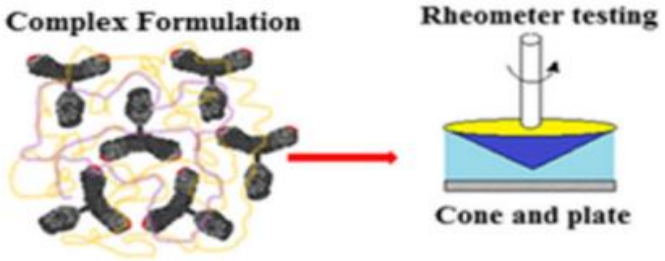
Measurement of the Injectability

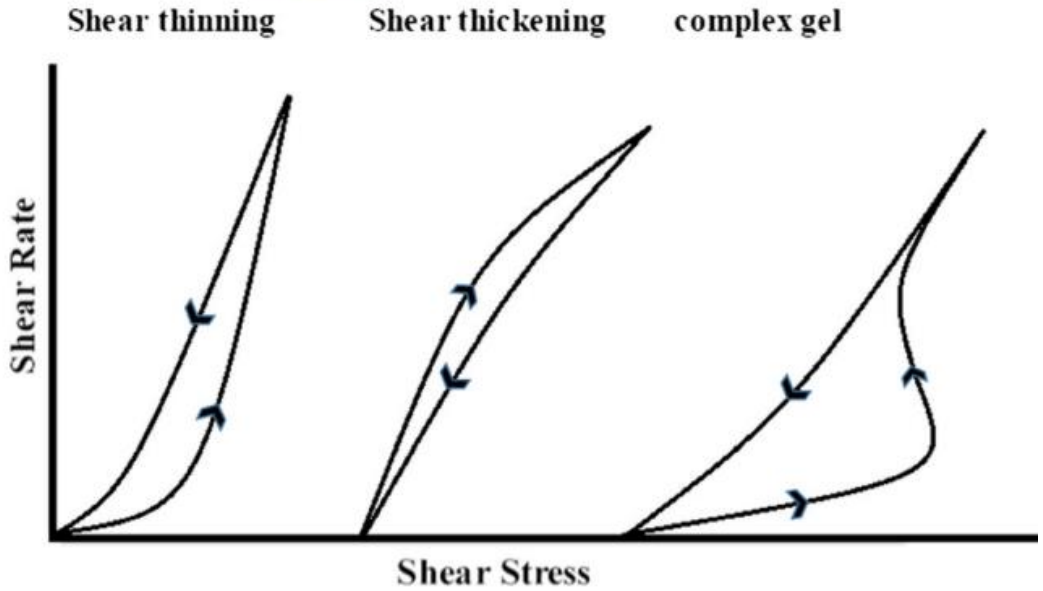


Analog system of injection carried out by a software-controlled texture analyzer in compression mode.



Representation of dynamics of flow through the syringe barrel, showing the wall and center velocity



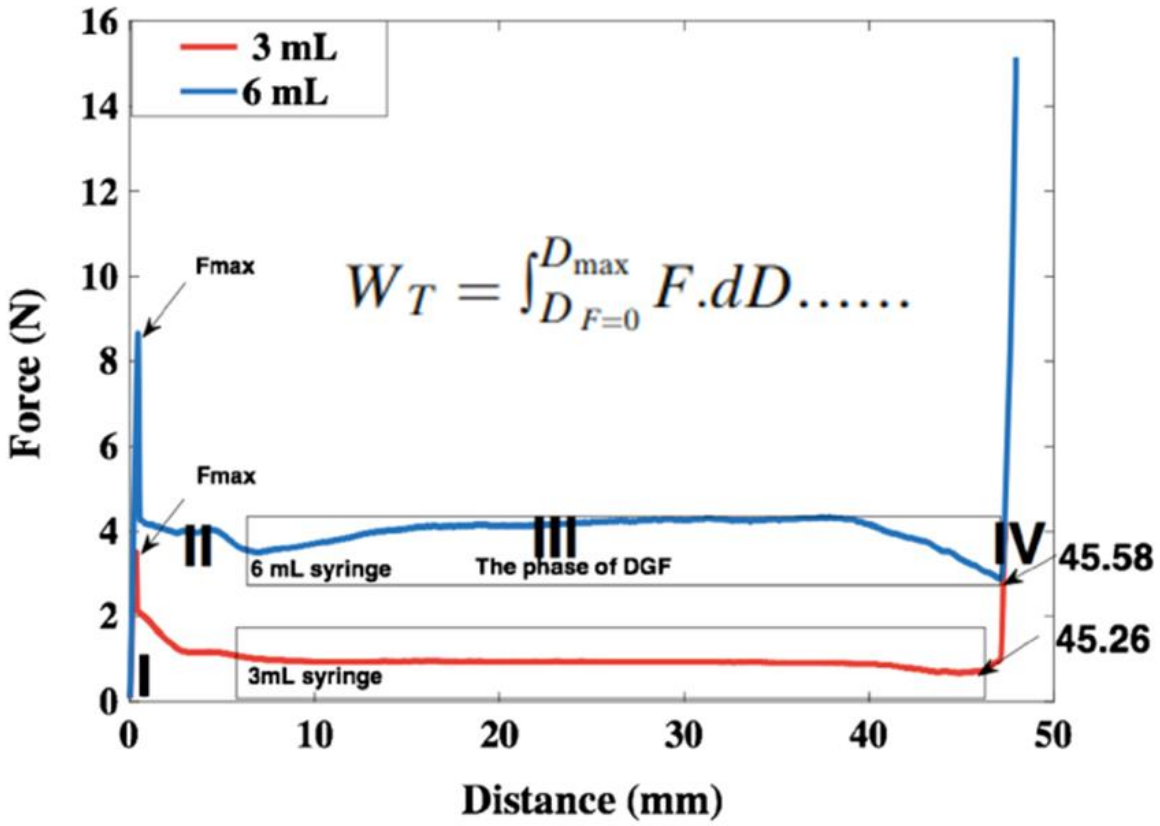


$$F^N = \acute{\eta} G \ldots\ldots$$

where "F^N" is shearing stress required to produce a definite shearing rate "G"; the term "$\acute{\eta}$" is a viscosity coefficient. The exponent "N" rises as the flow tends toward a non-Newtonian and when $N = 1$, the flow is Newtonian. ή eta

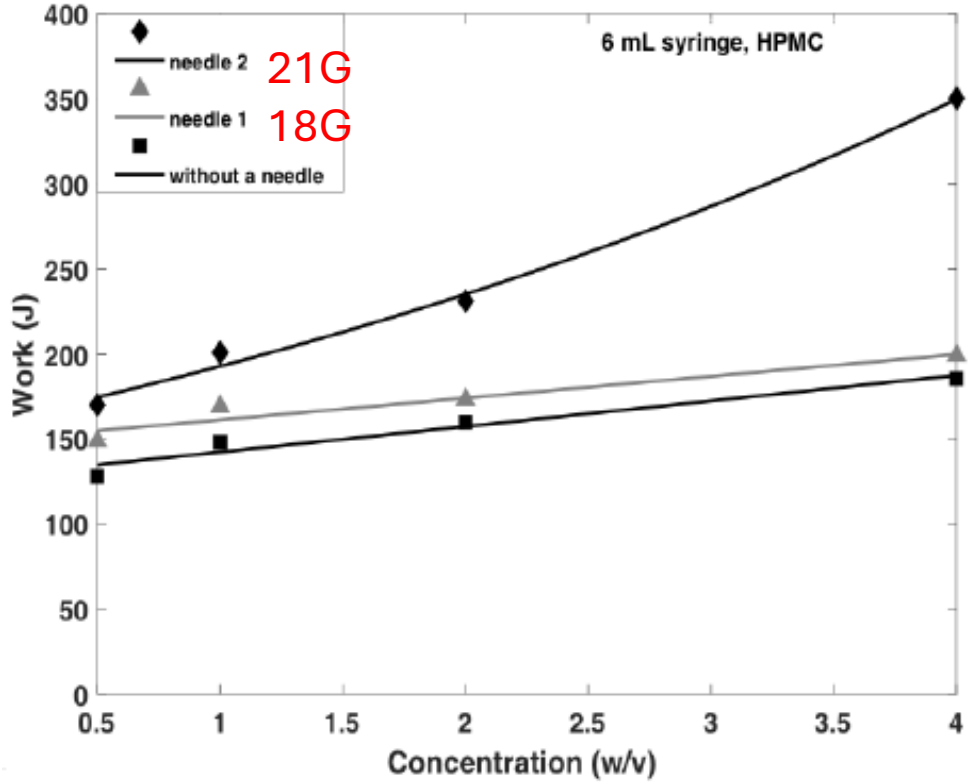
Zhang and Fassihi; AAPS PharmSciTech, Vol. 19, No. 4, May 2018 (# 2018), DOI: 10.1208/s12249-018-0963-x

An investigation into Syringeability and injectability of biopharmaceuticals: A trio of needle-syringe-formulation



Force-distance profile for a 4% (W/V) HPMC in 3- and 6-mL syringes with no needle attached.

DGF=The dynamic glide force (DGF)



- **The work of the injection is positively related to the volume of syringe and the concentration of the solution**
- **The dilatant flow type of polymeric solution (typical of formulation) requires examination.**

Zhang and Fassihi; AAPS PharmSciTech, Vol. 19, No. 4, May 2018 (# 2018), DOI: 10.1208/s12249-018-0963-x

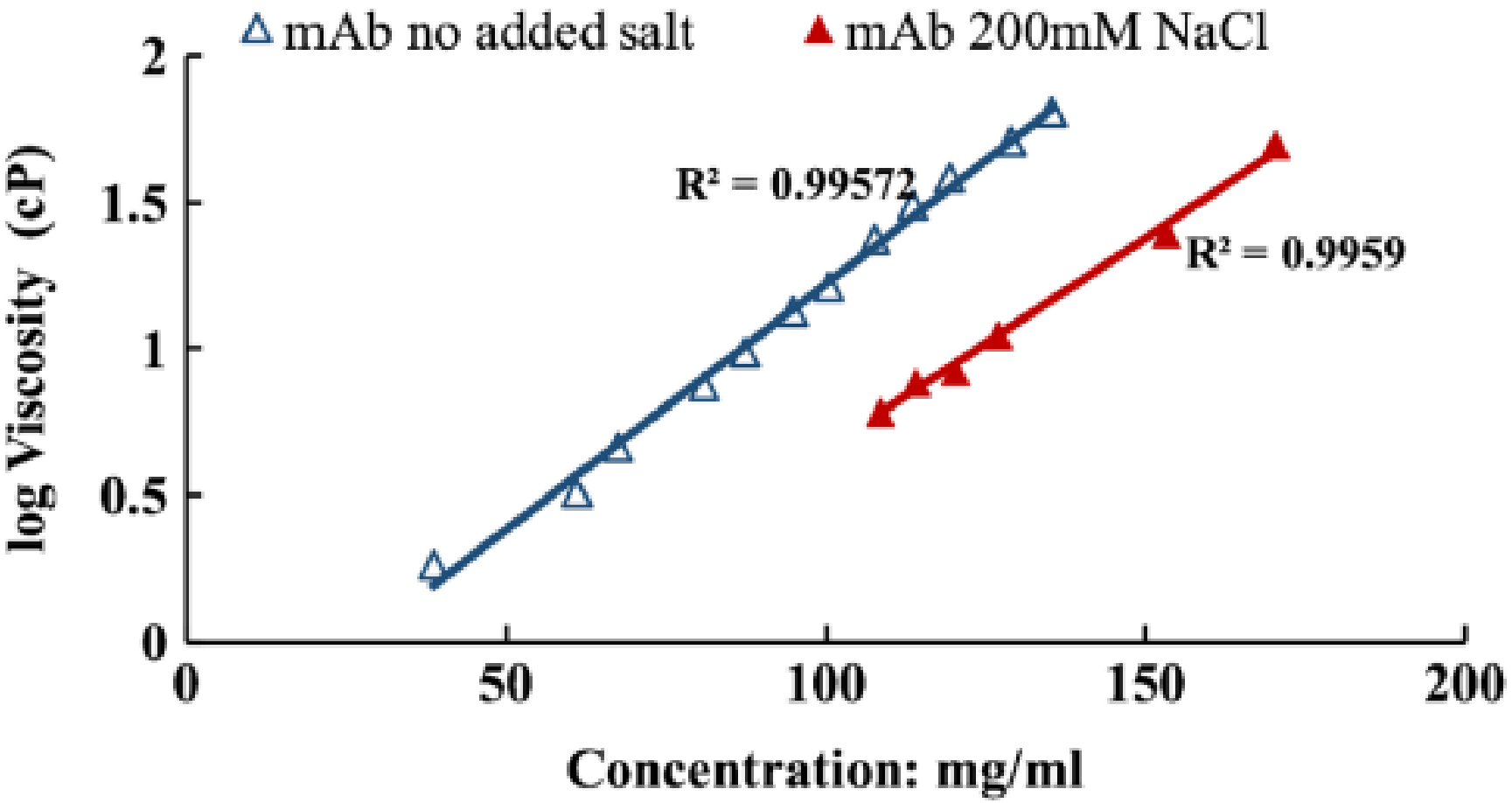


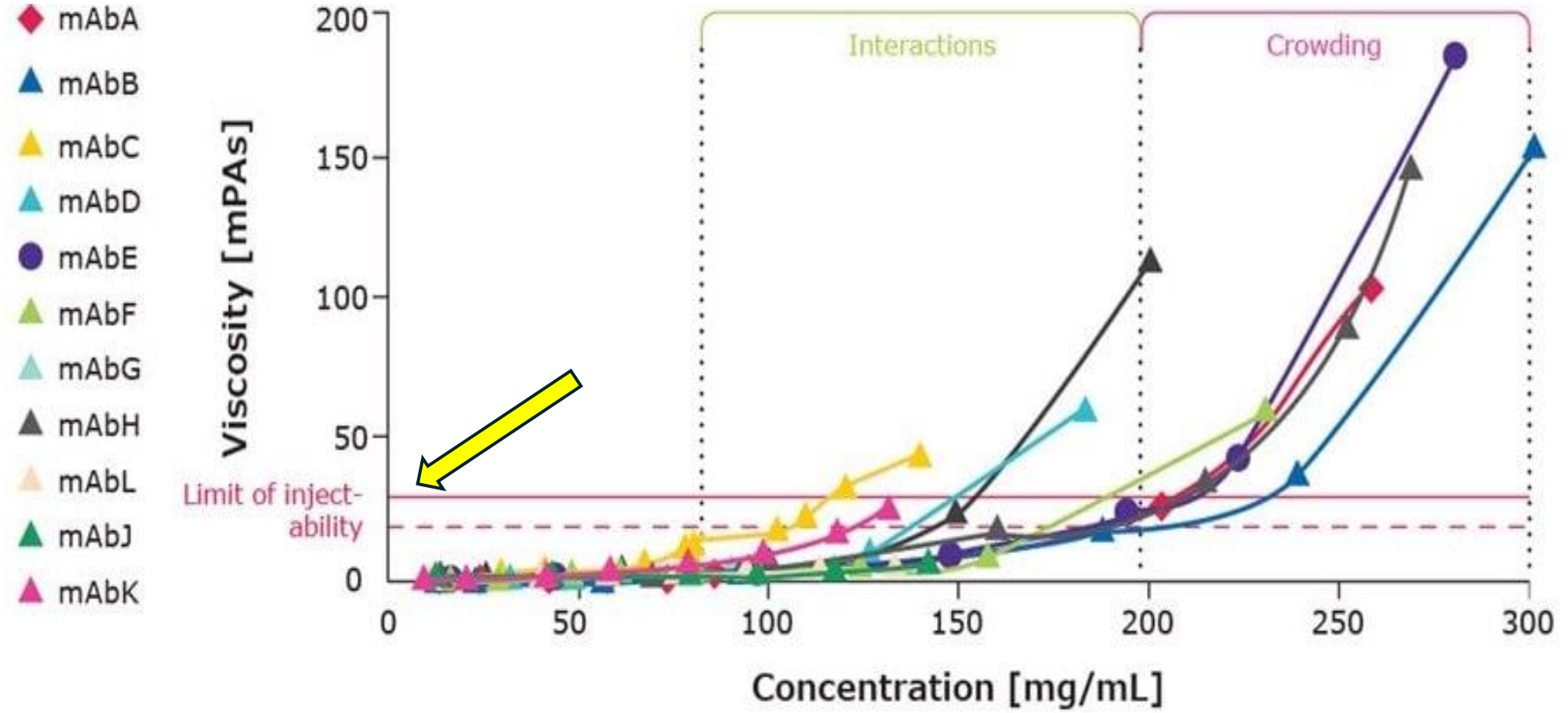
Fig. 2. Changes in solution viscosity of mAbs in 30 mM histidine buffer at pH 6.0, with and without added salt in the formulations

Q Zhang, Mona A. Fassihi, and Reza Fassihi ; AAPS PharmSciTech, Vol. 19, No. 4, May 2018

Biopharmaceutics of SC Formulations

- As doses of mAb drugs increases a highly concentrated antibody solution with high viscosity is created.
- Many kinds of methods for high-concentration antibody solutions have been reported, such as lyophilization, ultrafiltration, spray drying, gelation, crystallization, nanoparticle formation, and liquid-liquid phase separation.
- In a highly concentrated antibody solution, there is interactions between antibodies resulting in high viscosity.
- Considerable effort has been directed toward lowering the viscosity of concentrated antibody solutions below 50 cP through the applications of small molecule additives, such as salts, sugars, arginine, and hydantoin.

Concentration dependency of viscosity in drug formulations



Typically, a solution is no longer administrable when the viscosity increases above 20 or 25 millipascal seconds

Selection of excipient combinations affords the flexibility needed to effectively balance viscosity reduction and protein stability for subcutaneous formulations.

From : MilliporeSigma; Research & Development. Oct 09, 2024

High-Concentration Solution (HCS) Formulation

Some excipients used to reduce the viscosity of protein HCS.

Protein (s)	Protein Conc. (mg/mL)	Viscosity-Lowering Excipients/Solvents
A mAb provided by Janssen	~ 230	Arginine HCl[154]
A mAb provided by Pfizer	~ 200	Arginine HCl, Histidine HCl, Guanidinium HCl, Imidazole HCl[155]
An IgG mAb provided by Equitech-Bio	~ 260	Arginine HCl[63]
An IgG1 mAb & an IgG4 mAb provided by Janssen	> 150	56 additives and excipients were screened, and Arginine, Histidine, and Lysine were identified to have the most pronounced effect on viscosity reduction[156]
An IgG1 mAb provided by Abbvie	~ 250	Arginine HCl, Arginine Glutamate[157]
An IgG1 mAb provided by Abbvie	~ 220	Arginine HCl, Histidine HCl, Imidazole, Camphorsulfonic acid[158]
An IgG1 mAb provided by Abbvie	~ 225	Proline[159]
An IgG1 mAb provided by Genentech	~ 150	Polar co-solvents such as DMSO, DMA[160]
Bovine gamma globulin (BGG)	~ 250	Arginine HCl[63]
Cetuximab	~ 200	1- (3-aminopropyl)-2-methyl-1H-imidazole, Thiamine, Scopolamine (161)
Human gamma globulin (HGG)	~ 292	Arginine HCl[63]
Infliximab	~ 150	Caffeine[65]
Ipilimumab	~ 200	Caffeine[65]
Rituximab	~ 180	Procaine, 4-Aminopyridine[161]
Three mAbs provided by industry	~ 200	Arginine HCl, Imidazole HCl[59]
Trastuzumab	~ 230	1-butyl-3-methylimidazolium, 4-Aminopyridine[161]
Two IgG1 mAbs provided by Janssen	~ 195 ~ 165	Arginine HCl, Histidine HCl, Guanidinium HCl, Lysine HCl, Glutamic Na, NaCl, NaAc, Na_2SO_4, NH_4Cl[162]

H. Lou et al. / Journal of Pharmaceutical Sciences 111 (2022) 2968–2982

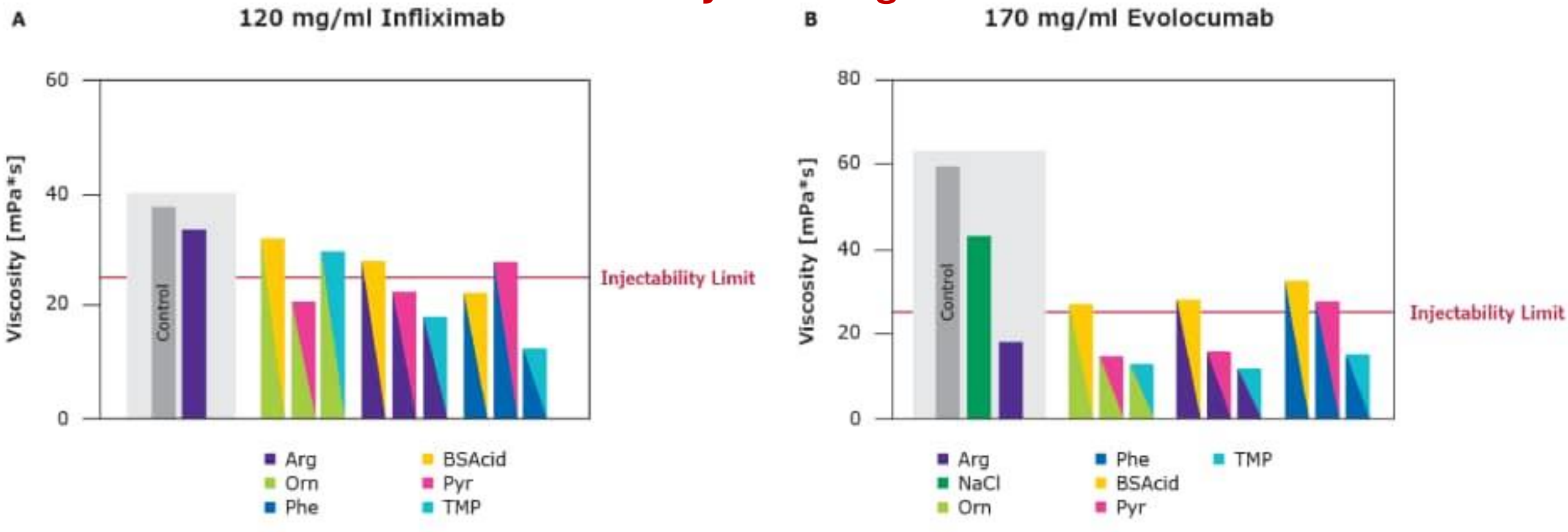
Formulation additives & Viscosity Reduction

- **Excipient Combinations in synergy may reduce viscosity and improve stability**
  Examples include:
- **Buffers/solvents, salts, bulk polar additives, surfactants, reducing agents, cyclodextrin, polyols, carboxylic acids, amino acids, etc.**

- **Arginine is commonly used as an effective viscosity-lowering excipient, especially for mAb HCS formulations, mechanism of arginine in viscosity reduction is complex and still not fully understood. Previous studies suggested that:**
  - **at low arginine concentration (e.g., below 200mM), arginine suppresses electrostatic interactions;**
  - **at high arginine concentration (e.g., 500-1000mM), apart from electrostatic interactions, arginine further suppresses other interactions such as Cation–π interaction.**
  - **Arginine is not a "panacea" for every formulation; instead of acting as a viscosity-reduction agent and protein aggregation suppressor, arginine could accelerate the aggregation for some proteins (e.g., a-lactalbumin) under certain solvent conditions.**
  - **A recent study suggests that caffeine can act as a viscosity-reducing agent for highly-concentrated mAb solutions.**

H. Lou et al. / Journal of Pharmaceutical Sciences 111 (2022) 2968–2982

Excipient Combinations from Different Functional Groups Address Viscosity Challenges



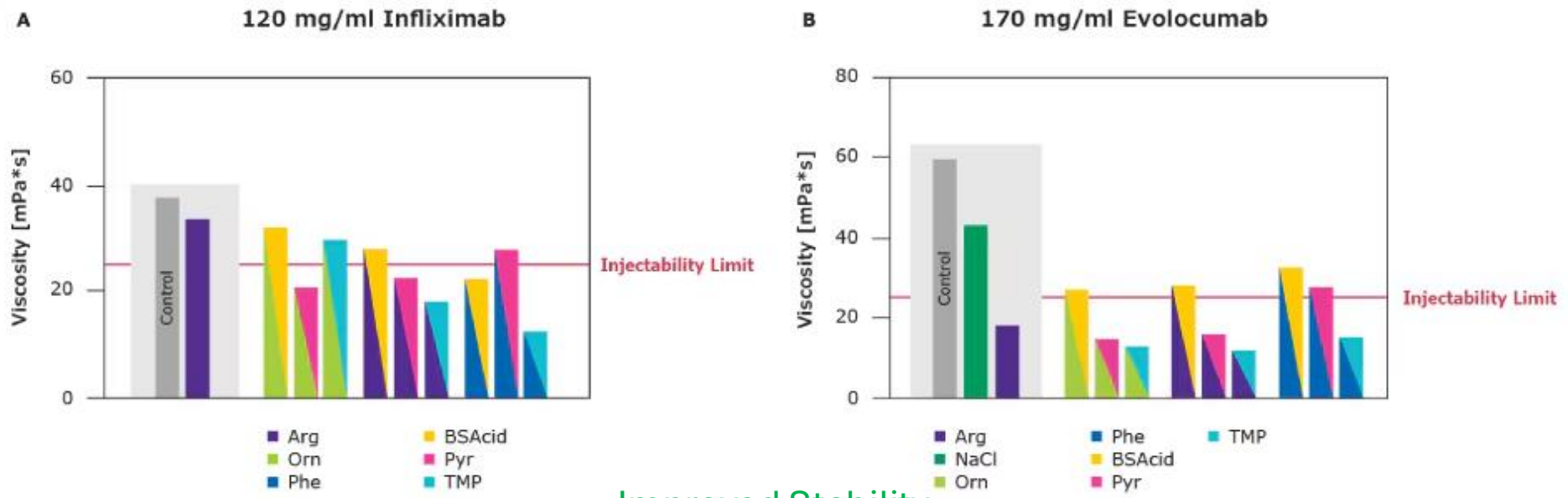
The ability of a combination of an amino acid (ornithine, phenylalanine, arginine) with an anionic excipient (benzenesulfonic acid, pyridoxine, thiamine phosphoric acid ester) can reduce viscosity and stabilize an antibody drug. (based on the data using two marketed drugs Infliximab and Evolocumab.

From : MilliporeSigma; Research & Development. Oct 09, 2024

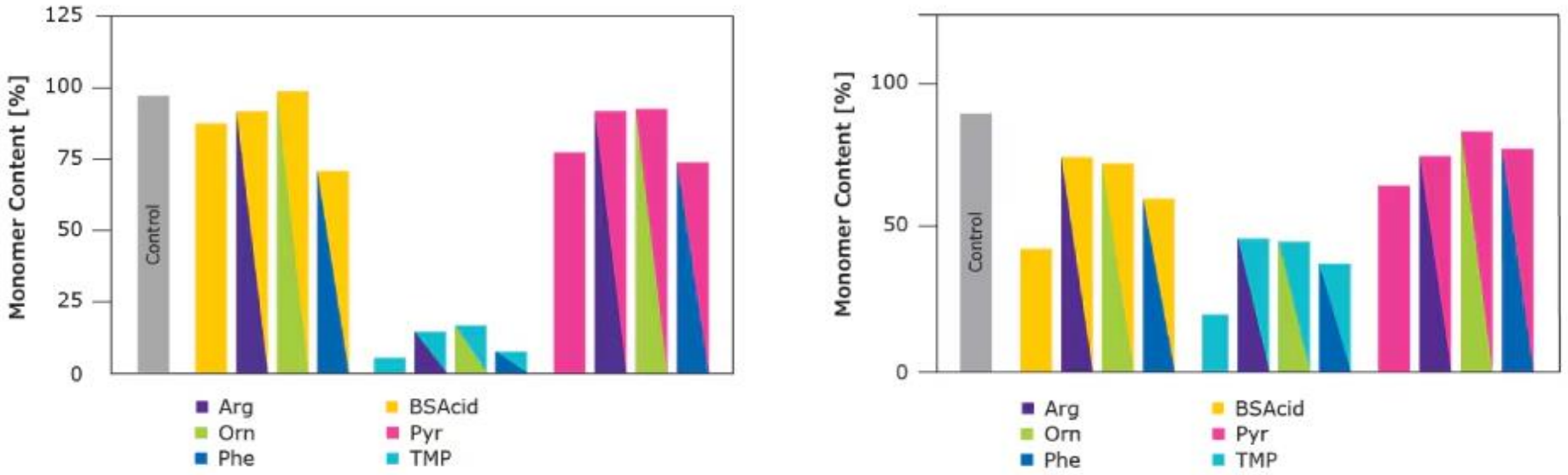
Excipient Combinations from Different Functional Groups Address Viscosity Challenges

Through synergistic effects, these combinations offered superior viscosity reduction, improved protein stability, storage stability, and better syringability in comparison to the industry benchmark arginine and single excipients alone.

Superior Viscosity Reduction



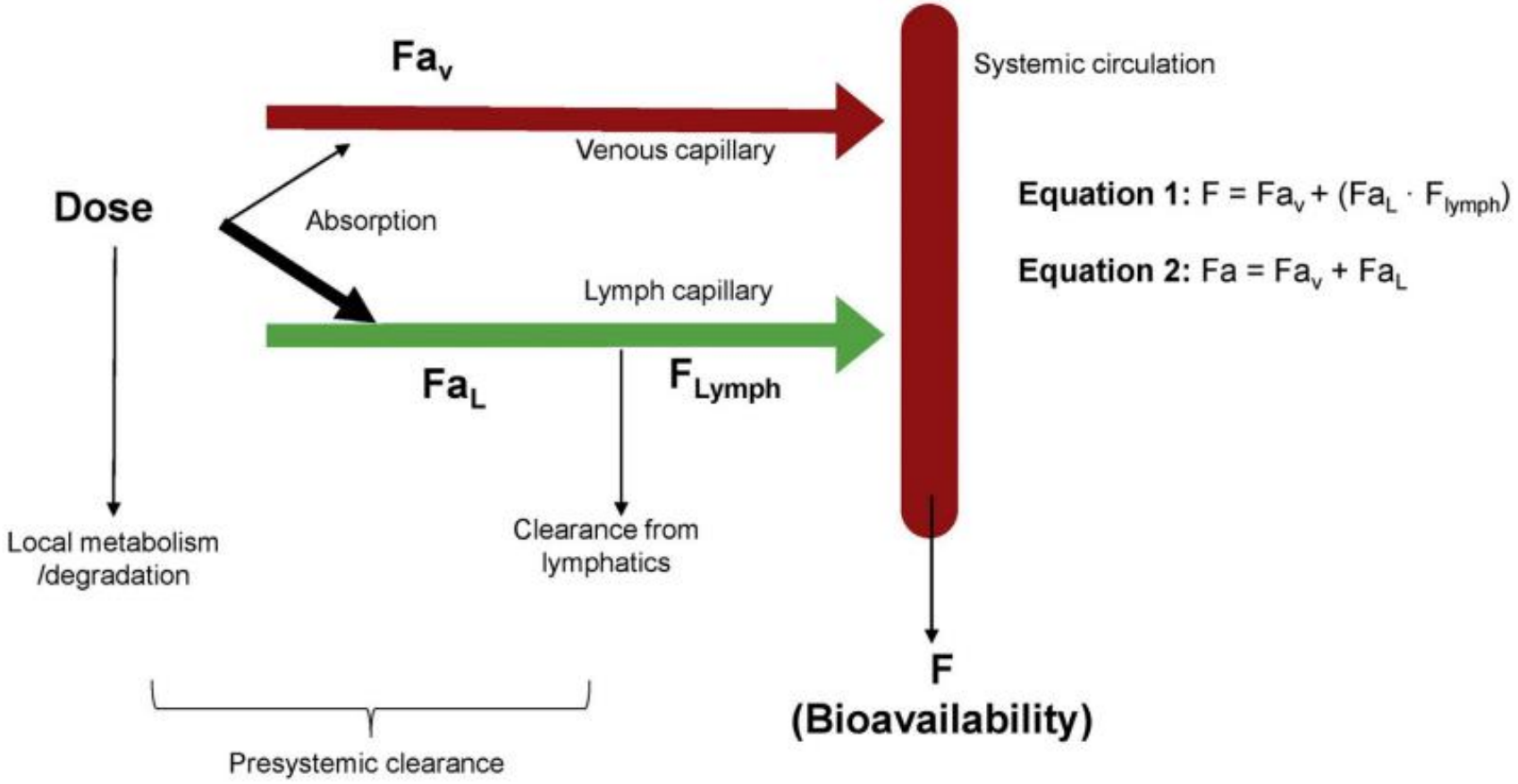
Improved Stability



From : MilliporeSigma; Research & Development. Oct 09, 2024

SC bioavailability

Pre-systemic catabolism either locally or in the lymphatics may limit the amount of mAb ultimately reaching the central compartment.



Equation 1: $F = Fa_v + (Fa_L \cdot F_{lymph})$

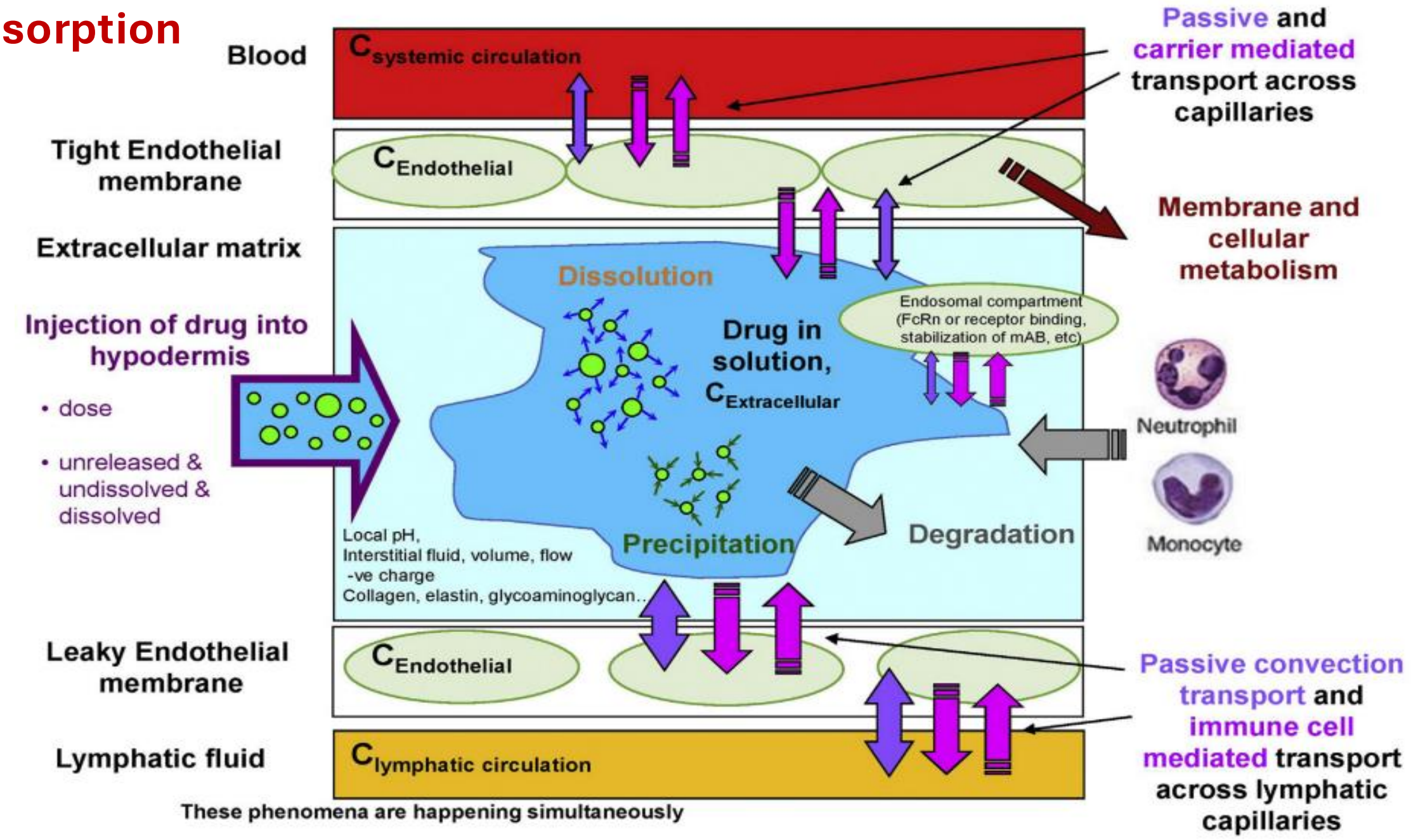
Equation 2: $Fa = Fa_v + Fa_L$

F, bioavailability;
Fa, fraction absorbed;
FaL, fraction absorbed via lymph;

Fav, fraction absorbed via venous capillary;
F_{lymph} , fraction escaping lymphatic clearance

M. Sánchez-Félix et al. / Advanced Drug Delivery Reviews 167 (2020) 66–77

SC absorption



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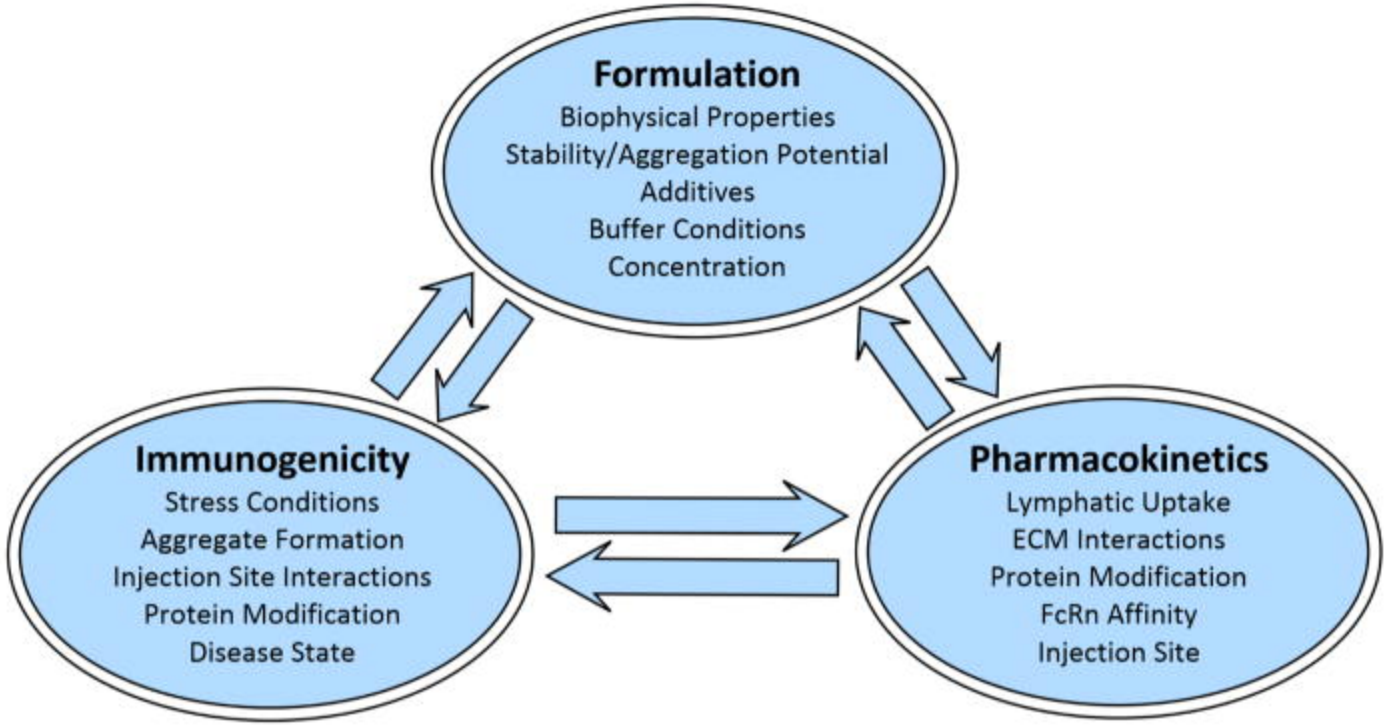
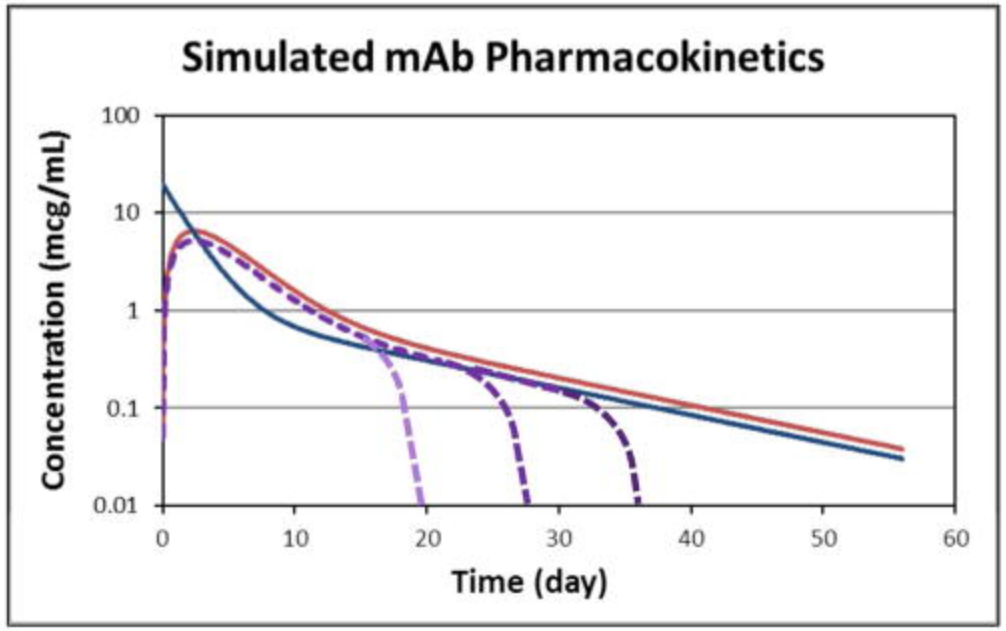
Many of the obstacles associated with SC delivery can be categorized based on three general concerns: formulation issues, immunogenicity, and PK





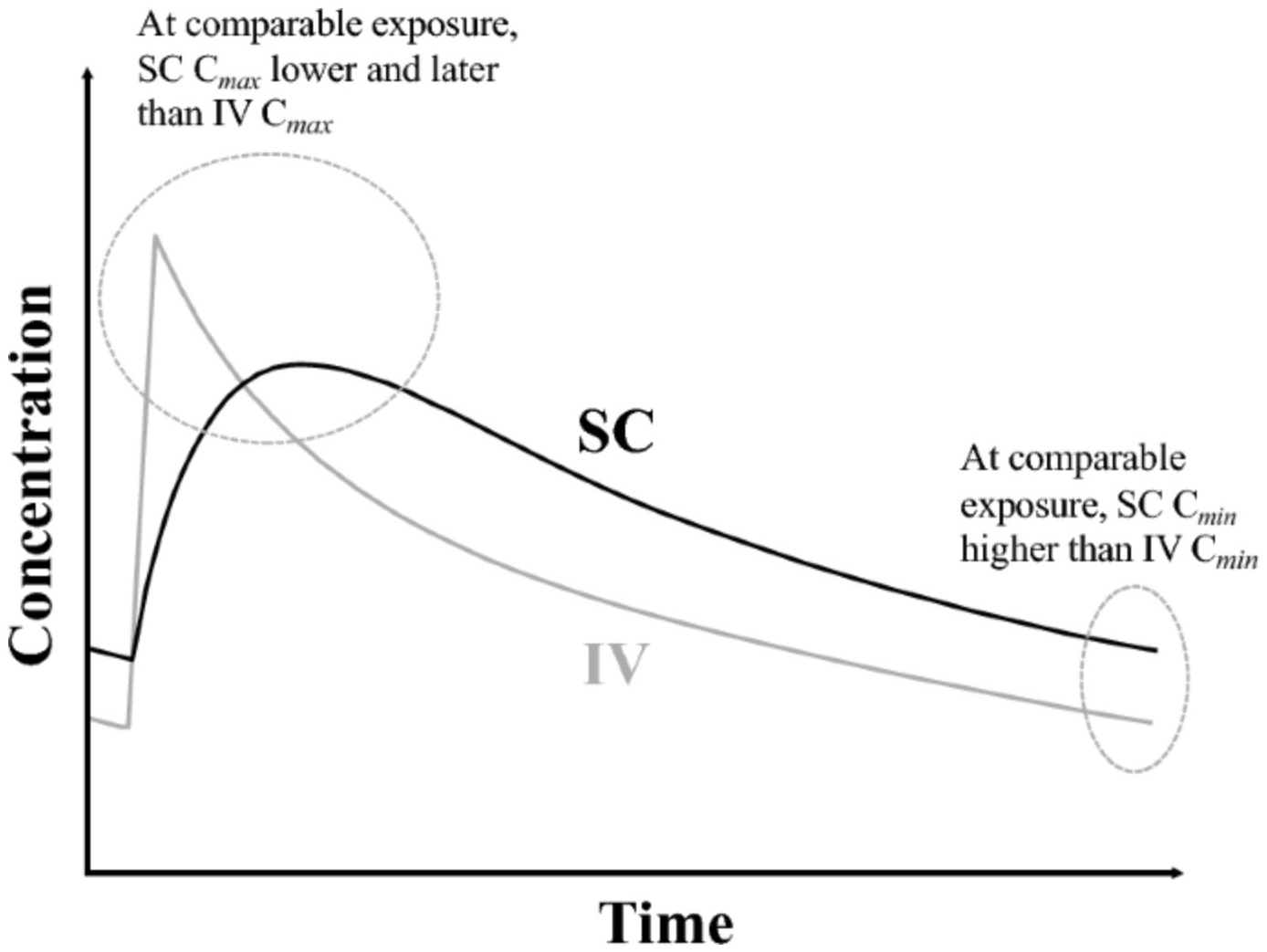
J Pharm Sci. 2018 May; 107(5): 1247–1260.

pK Bridging between IV and SC delivery

- The pharmacokinetic-based bridging approach has become the standard method for developing SC dosing alternatives for mAbs with IV infusion regimens.
- Initially, both pharmacokinetic and efficacy measures were used as co-primary endpoints, but recent development programs have focused on pharmacokinetic parameters as the only primary endpoint.
- This shift is supported by the available clinical evidence showing that despite lower C_{max} levels, SC versions of a given mAb exhibit non-inferior efficacy to the IV formulation when overall mAb exposure (AUC) and C_{trough} are comparable.

Bridging Approach from IV to SC Dosing

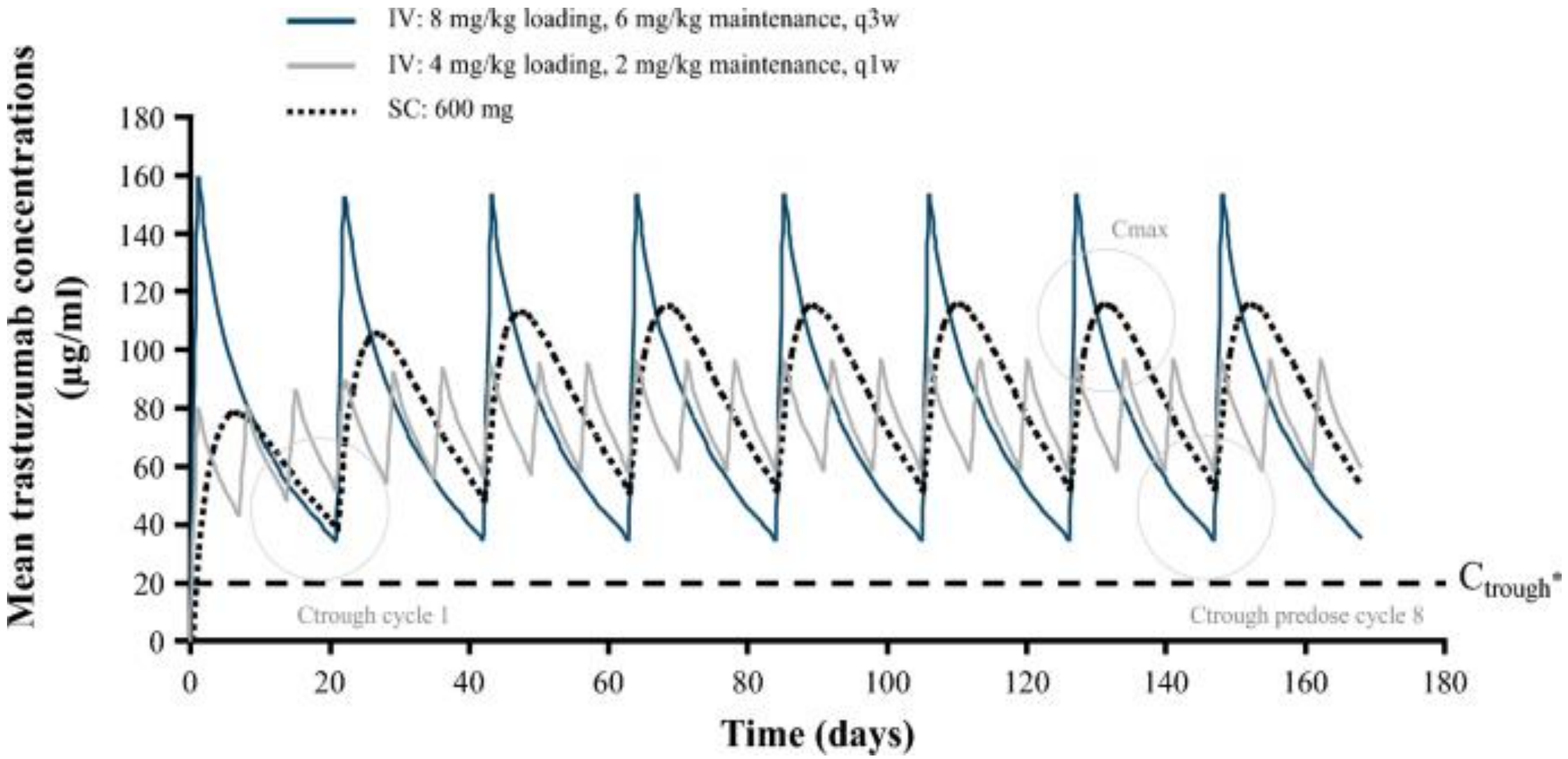
The established bridging approach for transitioning from an IV to an SC regimen for the same mAb relies on utilizing the same antibody in different formulations. It is anticipated that with comparable exposure (measured as area under the serum concentration–time curve [AUC]), the systemic safety profile of the mAb remains unchanged regardless of the administration route.



Impact of SC versus IV delivery on the pharmacokinetic profile of a mAb.

BioDrugs (2024) 38:23–46. https://doi.org/10.1007/s40259-023-00626-1

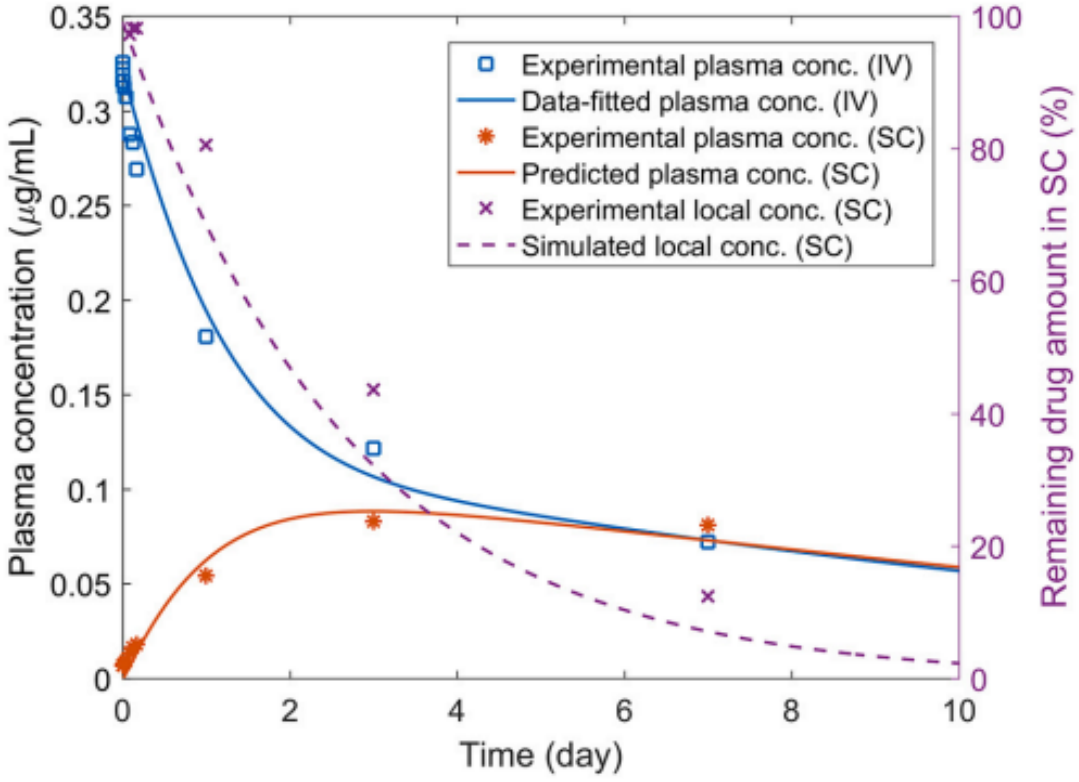
Evidence generation with pharmacokinetic-based clinical bridging approach



Subcutaneous dose selection concept: C_{trough} at least as high as with IV regimen; C_{max} bracketed by C_{max} of q1w and q3w IV regimens; comparable AUC with IV and SC regimens.

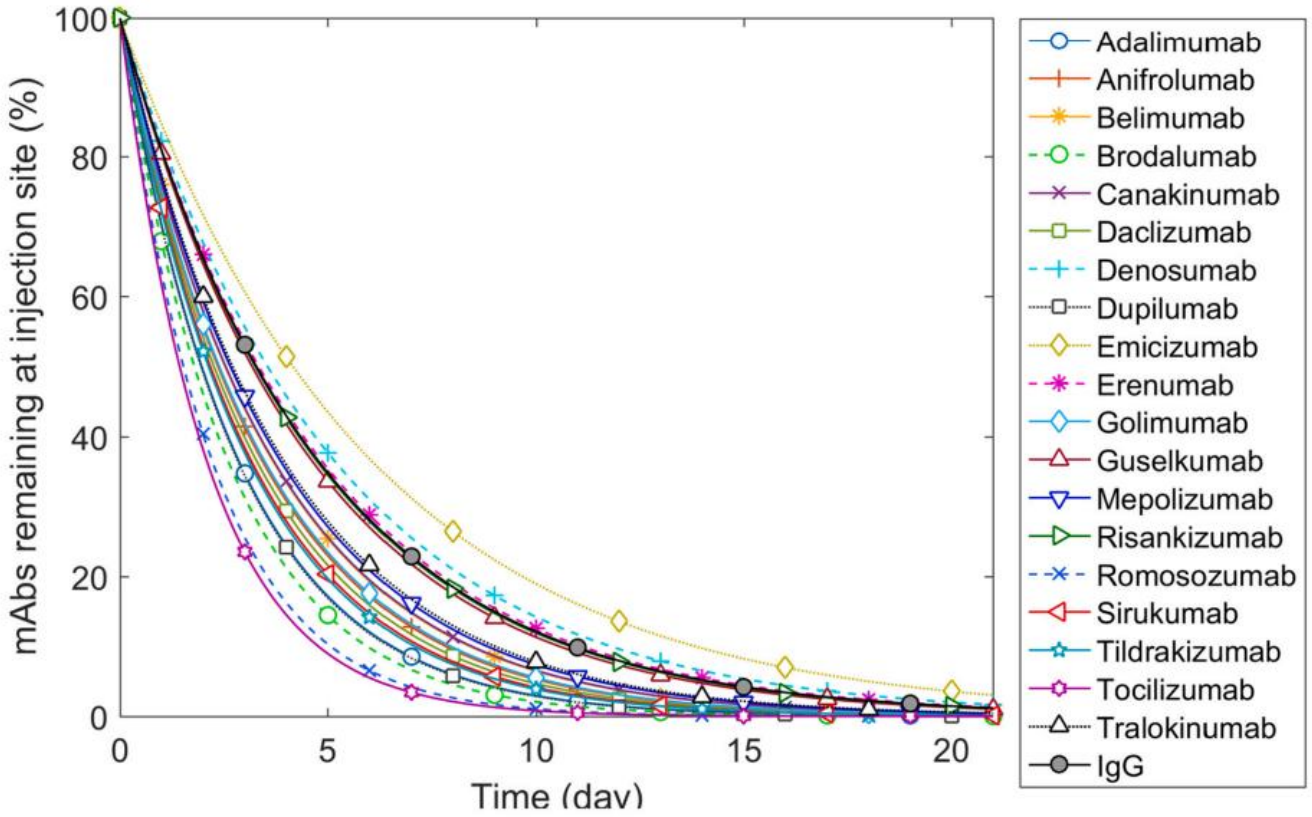
BioDrugs (2024) 38:23–46

Multiscale pharmacokinetic modeling of systemic exposure of subcutaneously injected biotherapeutics



Simulated and observed PK profiles of IV and SC administration for albumin.

SC bioavailability of albumin based on the calculated AUC∞ was estimated to be 82% (while that based on AUCt was 60%).



Overlay of derived local absorption profiles of mAbs at 50 mg dose.

Journal of Controlled Release 337 (2021) 407–416

SC bioavailability in human and corresponding preclinical species data for a range of marketed mAb and Fc-fusion proteins

Molecule	Tradename	MW (kDa)	SC bioavailability	Other information
Adalimumab	Humira®	148	Human: 52–82% (64%) Monkey: 94–100% (96%)	Human PK study: [68,69]
Alirocumab	Praluent®	146	Human: 85% Monkey: 73–77% Rat: 44–97%	T_{max}: Human: 3–7 days Monkey: 3–4 days Rat: 2–3 days
Canakinumab	Ilaris®	145	Human: 63–67% Monkey: 60%	IV bolus mice, rat, and cynomolgus monkey PK data: [71] Human PK data: [72]
Certolizumab pegol	Cimzia®	91	Human: 76–88% Rat: 24–34%	Fab conjugated to 40 kDa PEG [73]
Etanercept	Enbrel®	150	Human: 76% Monkey: 73% Mice: 58%	Fusion protein with IgG1 Fc
Golimumab	Simponi®	150	Human: 53% Monkey: 77%	Study in humans evaluating impact of SC injection site on bioavailability (includes IV data): [74]
Omalizumab	Xolair®	149	Human: 53–71% (62%) Monkey: 64–104% (84%) Mice: 90%	
Bevacizumab	Avastin®	149	Monkey: 98% Rat: 69% Mice: >100%	
Rilonacept	Arcalyst®	251	Human: 43% Monkey: 70% Rat: 60% Mice: 78%	Fusion protein with IgG1 Fc [78]
Rituximab	Mabthera®	145	Human: 71% Minipig: 71% Mice: 63%	T_{max}: Human: 3 days Minipig: 1 day Mice: 2 h
Sarilumab	Kevzara®	150	Human: 80% Monkey: 78%	T_{max}: Human: 2–4 days Monkey: 2–5 days
Trastuzumab	Herceptin®	148	Human: 82% Minipig: 82% Mice: 83%	T_{max}: Human: 4 days Minipig: 1 day Mice: 7 h

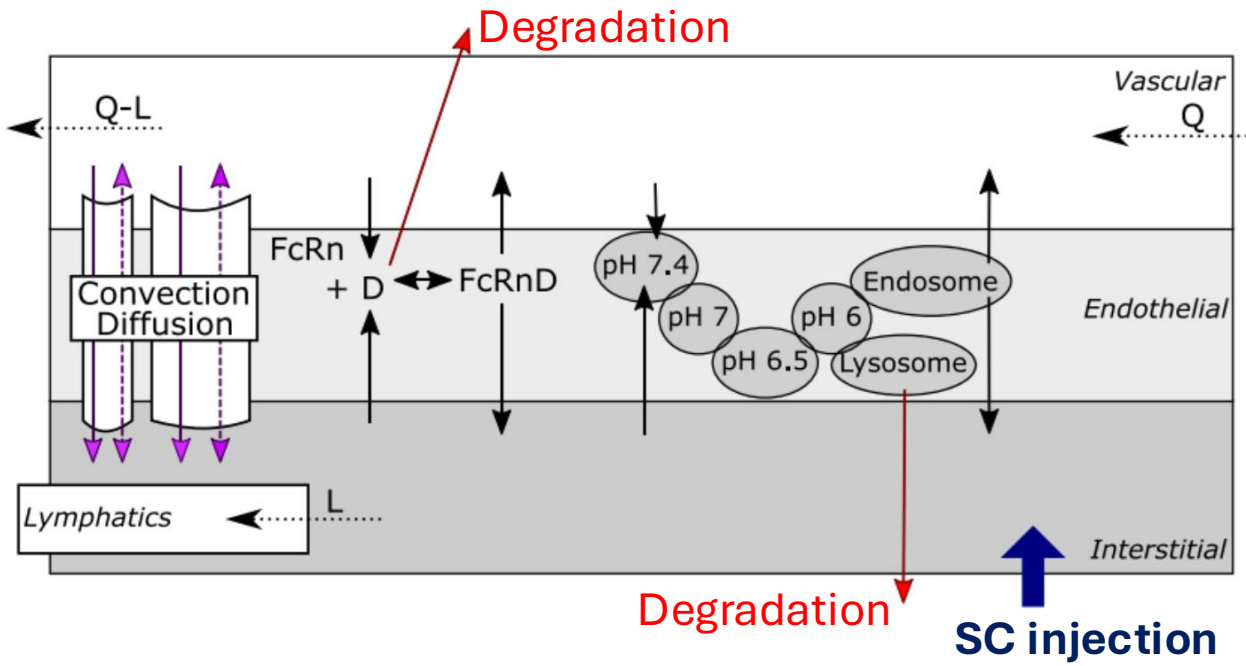
A survey of bioavailability data from marketed immunoglobulin (Ig)G, (-150 kDa), IgG fusion proteins (100-250 kDa), and smaller biotherapeutics ranging in molecular weight from 4 to 60 kDa. Marked interspecies variation in SC bioavailability of mAbs is evident.

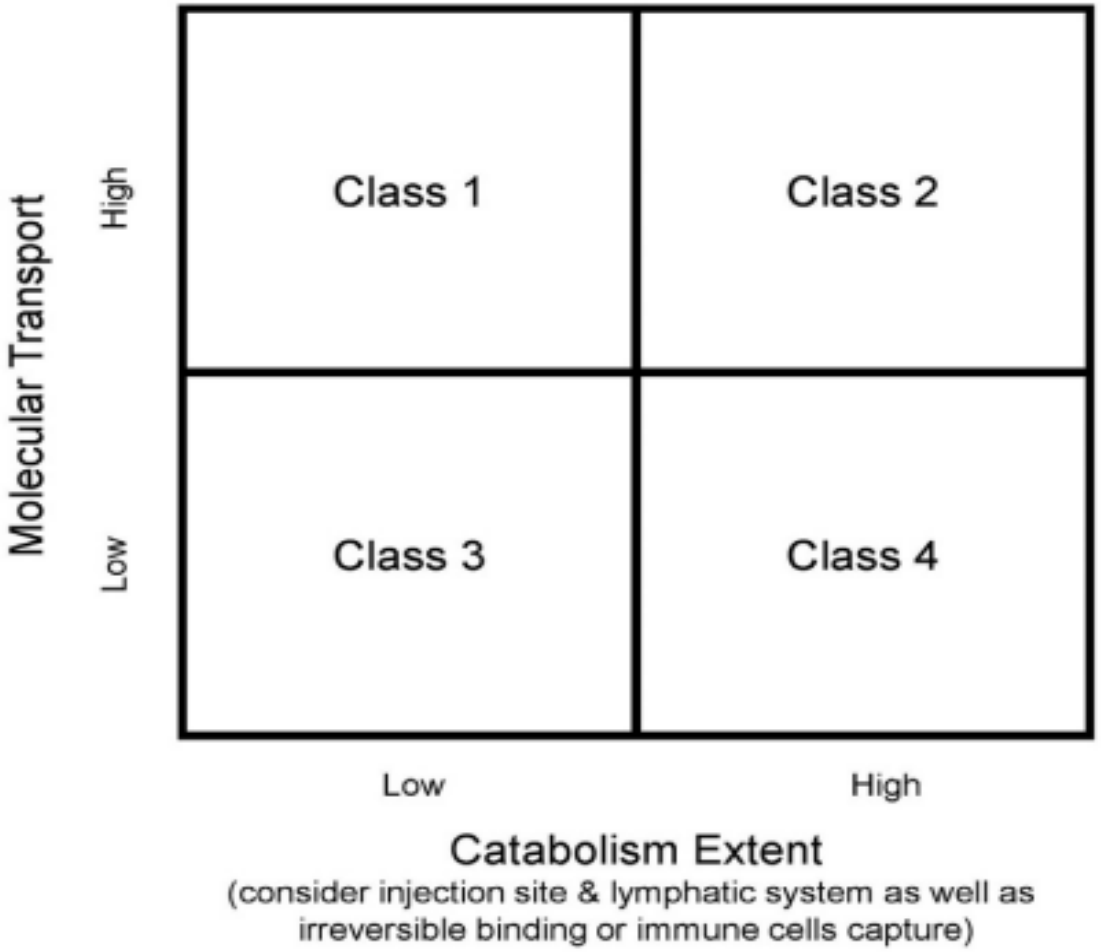
IV, intravenous; Fab, fragment antigen-binding; Fc, fragment crystallizable; MW, molecular weight; PEG, polyethylene glycol; PK, pharmacokinetic; SC, subcutaneous; Tmax, time to reach maximum concentration.

Advanced Drug Delivery Reviews 167 (2020) 66–77

Classification system concept for mAbs: molecular transport versus catabolism extent.

While the true rate-limiting factors are yet to be determined; one can use the broad categories of molecular transport and catabolism extent to create a simple classification system as shown.





The neonatal Fc receptor (FcRn) plays an important and well-known role in immunoglobulin G (IgG) catabolism.

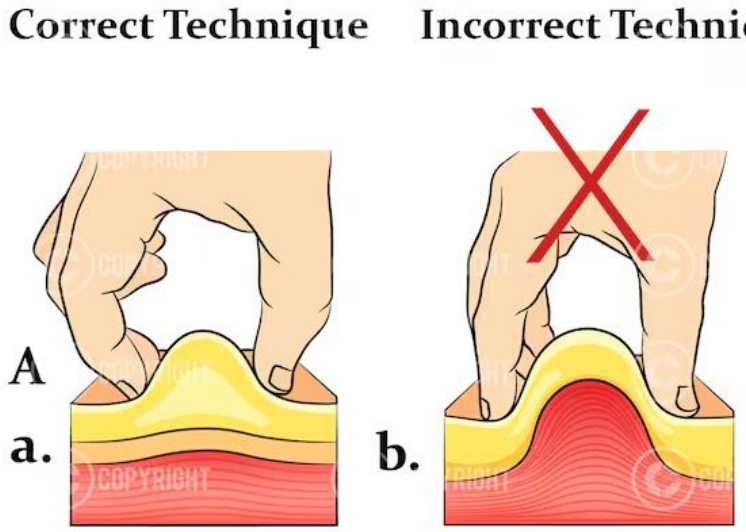
By means of the classification system concept presented in the Figure, one may be able to develop a unique model for each class of mAbs, with more predictive power.

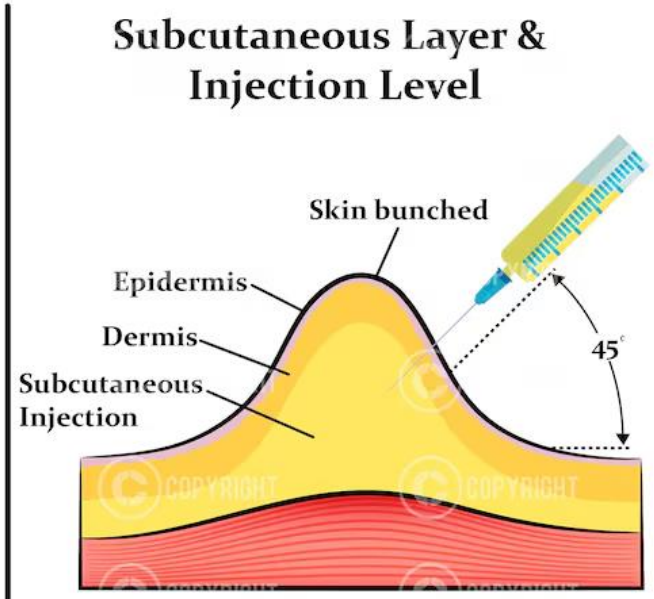
M. Sánchez-Félix et al. / Advanced Drug Delivery Reviews 167 (2020) 66–77

Conclusions and Future Outlooks

- The SC route is becoming more popular as product development has continued to shift towards patient centricity by enabling self-administration and ease of use for patients, improving compliance and reducing the burden on healthcare systems.
- There is an enormous potential for design of advanced SC delivery systems and improving drug efficacy, safety, and quality.
- For lymphatics targeting and/or being an adjuvant, SC delivery and use of nanoparticles are promising especially for large molecular weight biotherapeutics.
- Challenges in SC delivery include how to increase dose strength, patient compliance, high concentration and large volume formulation with reduced viscosity via coformulation, cluster/complex formulation, suspension etc.
- Development of sustained release SC system using suspension, micro and nano particles, delivered in a solution resulting in “in-situ formation of hydrogel depot” is of value.
- Given difficulties in correlating the in vitro release kinetics and in vivo outcomes, (i.e., difficult to establish IVIVC), we can ask whether the current dissolution methods of studying “In-vitro” release kinetics has any practical value. Most of the current methods reported do not reveal, even remotely, the physiological complexity of injection site, and hence, the results may have little value in predicting in vivo performance of immunoglobulin upon administration, although SC administration shows meaningful bioavailability and therapeutic efficacy.

THANK YOU.





QUESTIONS?