

**Pharmaceutical aspects of subvisible particles in protein formulations** Weinbuch, D.

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## Abbreviations

%RHPercent relative humidity*CDegree CelsiusµgMicrogramµLMicroliterµmMicrometerABDArea based diameterACSAmerican Chemical SocietyADAAnti-drug antibodyAF4Asymmetric flow field flow fractionationAIAluminumANNArtificial neuronal networksAPCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCaCalciumCD4+Cluster of differentiation 4 positiveCFRCode of federal regulationscIEFCapillary isoelectric focusingcPCentipoisecStCentistokesCTAClinical trial authorizationDLSDynamic light scatteringDNADeoxyribonuclei acidDPDrug substanceDSCDifferential scanning calorimetryEDSEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopyELISAEnzyme-linked immunosorbent assay	%	percent
μgMicrogramμLMicrogramμLMicroliterμmMicrometerABDArea based diameterACSAmerican Chemical SocietyADAAnti-drug antibodyAF4Asymmetric flow field flow fractionationAIAluminumANNArtificial neuronal networksAPCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCaCalciumCD4+Cluster of differentiation 4 positiveCFRCode of federal regulationscIEFCapillary isoelectric focusingcPCentipoisecStCentipoiseCSDynamic light scatteringDNADeoxyribonucleic acidDPDrug productDSDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	%RH	Percent relative humidity
JLMicroliterµmMicrometerABDArea based diameterACSAmerican Chemical SocietyADAAnti-drug antibodyAF4Asymmetric flow field flow fractionationAlAluminumANNArtificial neuronal networksAPCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCaCalciumCD4+Cluster of differentiation 4 positiveCFRCode of federal regulationscIEFCapillary isoelectric focusingcPCentipoisecStCentipoisecStDynamic light scatteringDNADeoxyribonucleic acidDPDrug productDSDynamic light scanteringDSCDifferential scanning calorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	°C	Degree Celsius
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ACSAmerican Chemical SocietyADAAnti-drug antibodyAF4Asymmetric flow field flow fractionationAIAluminumANNArtificial neuronal networksAPCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCalciumCode of federal regulationsCIEFCapillary isoelectric focusingCPCentipoiseCStCentipoiseCTAClinical trial authorizationDLSDynamic light scatteringDNADeoxyribonucleic acidDPDrug productDSDrug substanceDSCDifferential scanning calorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	μm	Micrometer
ADAAnti-drug antibodyAF4Asymmetric flow field flow fractionationAIAluminumANNArtificial neuronal networksAPCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCaCalciumCD4+Cluster of differentiation 4 positiveCFRCode of federal regulationscIEFCapillary isoelectric focusingcPCentipoisecStCentistokesCTAClinical trial authorizationDLSDynamic light scatteringDNADeoxyribonucleic acidDPDrug productDSDrug substanceDSFDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	ABD	Area based diameter
AF4Asymmetric flow field flow fractionationAIAluminumANNArtificial neuronal networksAPCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCaCalciumCD4+Cluster of differentiation 4 positiveCFRCode of federal regulationscIEFCapillary isoelectric focusingcPCentipoiseCStCentistokesCTAClinical trial authorizationDLSDynamic light scatteringDNADeoxyribonucleic acidDPDrug groductDSDrug substanceDSFDynamic scanning calorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	ACS	American Chemical Society
AlAluminumANNArtificial neuronal networksAPCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCaCalciumCD4+Cluster of differentiation 4 positiveCFRCode of federal regulationscIEFCapillary isoelectric focusingcPCentipoiseCStCentistokesCTAClinical trial authorizationDLSDynamic light scatteringDNADeoxyribonucleic acidDPDrug groductDSDifferential scanning calorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	ADA	Anti-drug antibody
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APCAntigen-presenting cellAPIActive pharmaceutical ingredientAspAsparagineAUAbsorption unitAUCAnalytical ultracentrifugationCCarbonCaCalciumCD4+Cluster of differentiation 4 positiveCFRCode of federal regulationscIEFCapillary isoelectric focusingcPCentipoiseCStCentistokesCTAClinical trial authorizationDLSDynamic light scatteringDNADeoxyribonucleic acidDPDrug productDSDrug substanceDSCDifferential scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	Al	Aluminum
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cStCentistokesCTAClinical trial authorizationDLSDynamic light scatteringDNADeoxyribonucleic acidDPDrug productDSDrug substanceDSCDifferential scanning calorimetryDSFDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	CIEF	Capillary isoelectric focusing
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DNADeoxyribonucleic acidDPDrug productDSDrug substanceDSCDifferential scanning calorimetryDSFDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	СТА	Clinical trial authorization
DPDrug productDSDrug substanceDSCDifferential scanning calorimetryDSFDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	DLS	Dynamic light scattering
DSDrug substanceDSCDifferential scanning calorimetryDSFDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	DNA	Deoxyribonucleic acid
DSCDifferential scanning calorimetryDSFDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	DP	Drug product
DSFDynamic scanning fluorimetryECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	DS	Drug substance
ECDEquivalent circular diameterEDXEnergy dispersive X-ray spectroscopy	DSC	Differential scanning calorimetry
EDX Energy dispersive X-ray spectroscopy	DSF	Dynamic scanning fluorimetry
	ECD	Equivalent circular diameter
ELISA Enzyme-linked immunosorbent assay	EDX	Energy dispersive X-ray spectroscopy
	ELISA	Enzyme-linked immunosorbent assay

FDAFood and Drug AdministrationFeIronFTIRFourier transform infrared spectroscopygGramGluGlutaminehHour(s)HHydrogen peroxideHCIHydrogen peroxideHLAHuman leukocyte antigenHLAHuman leukocyte antigenHTFHigh molecular weightHPLCHigh throughput formulationICHInternational Council for HarmonizationIgGImmunoglobulin GIgG1Immunoglobulin MILInterferonKPotassiumkDaKilo DaltonLALicense applicationLDELaser Doppler electrophoresisLMWLow molecular weightLOLight obscurationMKMonoclonal antibodyMDaMega DaltonMABMonoclonal antibodyMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)mLMilliliter	Exp.	Expiration date
FeIronFTIRFourier transform infrared spectroscopygGramGluGlutaminehHour(s)HHydrogenH2Q2Hydrogen peroxideHCIHydrogen chlorideHISHistidineHLAHuman leukocyte antigenHMWHigh performance liquid chromatographyHTFHigh throughput formulationICHInternational Council for HarmonizationIgGImmunoglobulin GIgG1Immunoglobulin MILInterleronKPotassiumkDaKilo DaltonLALicense applicationIDELaser Doppler electrophoresisIMWLow molecular weightLOLight obscurationIDDUmit of detectionmAbMonoclonal antibodyMFIMicro-Flow ImagingmgMilligramMHCMajor histocompatibility complexminMinute(s)	FDA	Food and Drug Administration
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HLAHuman leukocyte antigenHMWHigh molecular weightHPLCHigh performance liquid chromatographyHTFHigh throughput formulationICHInternational Council for HarmonizationIgGImmunoglobulin GIgG1Immunoglobulin G1IgMImmunoglobulin MILInterleukinINFInterferonKPotassiumkDaKilo DaltonLALicense applicationLDELaser Doppler electrophoresisLMWLow molecular weightLOLight obscurationMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	HCI	Hydrogen chloride
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HTFHigh throughput formulationICHInternational Council for HarmonizationIgGImmunoglobulin GIgG1Immunoglobulin G1IgMImmunoglobulin MILInterleukinINFInterferonKPotassiumkDaKilo DaltonLALicense applicationLDELaser Doppler electrophoresisLMWLow molecular weightLOLight obscurationLODLimit of detectionmAbMonoclonal antibodyMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	HMW	High molecular weight
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IgMImmunoglobulin MILInterleukinINFInterferonKPotassiumkDaKilo DaltonLALicense applicationLDELaser Doppler electrophoresisLMWLow molecular weightLOLight obscurationLODLimit of detectionmAbMonoclonal antibodyMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	IgG	Immunoglobulin G
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LMWLow molecular weightLOLight obscurationLODLimit of detectionmAbMonoclonal antibodyMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	LA	License application
LOLight obscurationLODLimit of detectionmAbMonoclonal antibodyMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	LDE	Laser Doppler electrophoresis
LODLimit of detectionmAbMonoclonal antibodyMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	LMW	Low molecular weight
mAbMonoclonal antibodyMDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	LO	Light obscuration
MDaMega DaltonMFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	LOD	Limit of detection
MFIMicro-Flow ImagingmgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	mAb	Monoclonal antibody
mgMilligramMgMagnesiumMHCMajor histocompatibility complexminMinute(s)	MDa	Mega Dalton
MgMagnesiumMHCMajor histocompatibility complexminMinute(s)	MFI	Micro-Flow Imaging
MHC Major histocompatibility complex   min Minute(s)	mg	Milligram
min Minute(s)	Mg	Magnesium
	МНС	Major histocompatibility complex
mL Milliliter	min	
	mL	Milliliter

mM	Millimolar
mm	Millimeter
MS	Mass spectrometry
NaCl	Sodium chloride
nDSF	Intrinsic dynamic scanning fluorimetry
ng	Nanogram
NIST	National Institute of Standards and Technology
NK	Natural killer cells
nm	Nanometer
NPI	Nanoparticulate impurities
NTA	Nanoparticle tracking analysis
0	Oxygen
Р	Phosphorus
Part./mL	Particles per milliliter
PBMC	Peripheral blood mononuclear cells
PDI	Polydispersity index
Ph.Eur.	European Pharmacopeia
PK/PD	Pharmacokinetics / pharmacodynamics
рКа	Acid dissociation constant
PVDF	Polyvinylidene fluoride
QC	Quality control
R <sup>2</sup>	Coefficient of determination
RI	Refractive index
RMM	Resonant mass measurement
RNA	Ribonucleic acid
rpm	Rounds per minute
S	Second(s)
S	Sulfur
SEC	Size-exclusion chromatography
SEM	Scanning electron microscopy
Si	Silicon
SLS	Static light scattering
SMR	Suspended microchannel resonator
TCR	T cell receptor
TFF	Tangential flow filtration

Tm	Melting temperature
TNF	Tumor necrosis factor
UPLC	Ultra performance liquid chromatography
US	United States
USP	United States Pharmacopeia
UV	Ultra-violet
v/v	Volume per volume
w/v	Weight per volume
w/w	Weight per weight
λ	Wavelength

#### List of publications

**Weinbuch D**\*, Zölls S\*, Wiggenhorn M, Friess W, Winter G, Jiskoot W, Hawe A. Micro-flow imaging and resonant mass measurement (Archimedes) - complementary methods to quantitatively differentiate protein particles and silicone oil droplets. *Journal of Pharmaceutical Sciences* 2013 Jul;102(7):2152-65.

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**Weinbuch D**, Cheung JK, Ketelaars J, Filipe V, Hawe A, den Engelsman J, Jiskoot W. Nanoparticulate impurities in pharmaceutical-grade sugars and their interference with light scattering-based analysis of protein formulations. *Pharmaceutical Research* 2015 Jul;32(7):2419-27

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**Weinbuch D**, Fogg M, Ruigrok M, Jiskoot J, Hawe A. Nanoparticulate impurities in pharmaceutical-grade sucrose are a potential threat to protein stability. Manuscript submitted for publication.

\*shared first authors

#### Curriculum vitae



Daniel Weinbuch was born on May 1<sup>st</sup> 1985 in Illertissen, Germany. In September 2004, he started his career by earning an associate degree as a pharmaceutical production technician at Merckle in Ulm, Germany and further gained experience in fill-finishing processes by working at the validation/qualification department for sterile dosage forms at ratiopharm in Blaubeuren, Germany, until August 2015. He subsequently pursued an academic study in Pharmaceutical Biotechnology at the Biberach University of Applied Sciences in

Germany from which he graduated in January 2010. During this study, he wrote his Bachelor thesis on the development of human monoclonal antibodies by phage display at Boehringer Ingelheim in Ridgefield, CT, USA. He further worked as a scientist at the Kobe Pharma Research Institute in Japan in 2010 before earning his Master's degree in Biopharmaceutical Sciences from the Leiden University in the Netherlands in September 2012, where he focused on protein aggregation and unwanted immunogenicity. In February 2013, Daniel Weinbuch started his PhD project under the supervision of Prof. Dr. Wim Jiskoot at the Leiden Academic Centre for Drug Research (LACDR) in the Netherlands in collaboration with Dr. Andrea Hawe at Coriolis Pharma in Munich, Germany. While focusing on the topic "pharmaceutical aspects of subvisible particles in protein formulations", he (co-)authored seven peer-reviewed publications and gave podiums presentations at international conferences on several occasions. During the PhD projectcollaboration, Daniel Weinbuch worked part-time as a formulation scientist at Coriolis Pharma. Since March 2016, he is employed as the Manager GRP (Good Research Practice) at Coriolis Pharma.