

ELECTRONIC SUPPLEMENTARY INFORMATION

Sample transformation in online separations: how chemical conversion advances analytical technology

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S-1 Overview of the described applications

Table S1 summarizes the applications described in the manuscript based on the sample type (e.g. nanoparticles, polymers, or small molecules). For each sample type, the property of interest is highlighted along with the sample transformation that is applied, the approach used, the type of coupling, and the analytical technique. All abbreviations used in the table are described on the below the table.

Table S1: Overview of the properties of interest of the different sample types and its corresponding sample transformation and analytical method.

Sample type	Property of interest	Sample transformation	Approach	Coupling	Technique	Ref
Antibodies						
mAb and bsAb	Charge variants, deamidation, oxidation, isomerization, peptide mapping	MW reduction	Enzymatic (Lys-C, trypsin), reduction (TCEP)	Online	mD-LC-MS	1
mAb	Peptide sequencing	MW reduction	Enzymatic (trypsin)	Online	mD-LC-MS	2
mAb	Deamidation, isomerization, succinimide, peptide mapping	MW reduction	Enzymatic (trypsin), reduction (DTT or TCEP)	Online	mD-LC-MS	3
mAb	Charge variants, deamidation, isomerization, glycosylation, peptide mapping	MW reduction	Enzymatic (trypsin), reduction (DTT)	Online	mD-LC-MS	4
mAb	Oxidation, succinimide, deamidation or glycosylation (without peptide mapping)	MW reduction	Enzymatic (trypsin), reduction (TCEP)	Online	mD-LC-MS	5
mAb	Glycosylation	MW reduction	Enzymatic (IdeS), reduction (TCEP)	Online	mD-LC-MS	6
mAb	Deamidation, oxidation, isomerization, glycosylation, peptide mapping	MW reduction	Enzymatic (IdeS, trypsin), reduction (TCEP)	Online	mD-LC-MS	7
mAb	Deamidation, oxidation, glycation, peptide mapping	MW reduction	Enzymatic (trypsin), reduction (DTT)	Online	mD-LC-MS	8
mAb and bsAb	Deamidation, oxidation, glycation, glycosylation, peptide mapping	MW reduction	Enzymatic (trypsin), reduction (DTT)	Online	mD-LC-MS	8
bsAb	Charge variants, size variants, peptide mapping	MW reduction	Enzymatic (PNGase F, trypsin, Lys-C), reduction (gingiskhan, TCEP, DTT)	Online	LC-MS	9
mAb and bsAb	Charge variants, deamidation, oxidation, isomerization, peptide mapping	MW reduction	Enzymatic (trypsin), reduction (TCEP)	Online	mD-LC-MS	10
mAb	Size variants, sequence variants, aggregates, glycosylation, glycation,	MW reduction	Enzymatic (trypsin)	Online	mD-LC-MS	11
bsAb	Charge variants, deamidation, proline amidation, oxidation,	MW reduction	Enzymatic (trypsin), reduction (DTT)	Online	mD-LC-MS	12

mAb	isomerization, succinimide, peptide mapping	MW reduction	Enzymatic (trypsin)	Online	mD-LC-MS	13
mAb	Charge variants, deamidation, N-terminal glutamine cyclization, oxidation, proline amidation, peptide mapping	MW reduction	Enzymatic (trypsin)	Online	CZE-DAD	14
mAb	Peptide mapping	MW reduction	Enzymatic (trypsin)	Online	CZE-DAD	15
mAb	Peptide mapping	MW reduction	Enzymatic (trypsin), offline-reduction (DTT)	Online	CZE-DAD	16
mAb	Fragment/peptide mapping	MW reduction	Enzymatic (IdeS)	Online	CZE-MS	17
mAb	Charge variants, deamidation, oxidation, peptide mapping	MW reduction	Enzymatic (Pepsin), reduction (TCEP)	Online	2D-CZE-MS	18
ADC						
ADC	Size variants, oxidation, deamidation, aggregates	MW reduction	Enzymatic (trypsin), reduction (TCEP)	Online	mD-LC-MS	19
Fc-fusion protein						
mAb and Fc-fusion protein	Deamidation, succinimide formation, oxidation, C-terminal lysine clipping, N-terminal glutamine cyclization, glycosylation, proline amidation	MW reduction	Enzymatic (trypsin, Lys-C)	Online	mD-LC-MS	20
mAb and Fc-fusion protein	Oxidation, succinimide, deamidation, isomerization, glycosylation, peptide mapping	MW reduction	Enzymatic (trypsin), reduction (TCEP)	Online	mD-LC-MS	21
Nucleic acid						
sgRNA	Nucleotide mapping	MW reduction	Enzymatic (RNase T1, A, U2)	Online	mD-LC-MS	22
gRNA	Nucleotide mapping	MW reduction	Enzymatic (RNase T1)	Online	LC-MS	23
Nanoparticles						
Polymeric (acrylic)	Multi-attribute characterization (size, MW)	Decomposition (disassembly)	Solvent (organic)	Online	HDC×SEC	24
Polymeric (acrylic)	Multi-attribute characterization (size, MW)	Decomposition (disassembly)	Solvent (organic)	Online	HDC×SEC	25
Medicinal (AAV)	Multi-attribute characterization (empty/full, NP components)	Decomposition (disassembly)	Chemical (pH)	Online	AEX-RPLC	26
Medicinal (AAV)	Multi-attribute characterization (peptide mapping)	MW reduction	Enzymatic (trypsin, pepsin)	Offline	LC-MS/MS	27
Medicinal/polymeric (PLGA)	Protein adsorption	Decomposition (desorption), MW reduction	Reduction (DTT), enzymatic (trypsin)	Offline	RPLC-MS/MS	28
Medicinal (polymer)	Drug release	Decomposition (dissolution)	Chemical (pH)	Offline	no LC (DLS, TEM, FLR)	29
Environmental	Polymer quantitation	MW reduction	Thermal	Online	PyGC-MS	30
Medicinal/polymeric (ester)	Drug release	Decomposition (dissolution)	Solvent	Online	RPLC-UV	31
Polymeric	Polymer degradation (with microfluidic chip)	MW reduction	Enzymatic (Novozym 51032 cutinase)	Offline	RPLC-MS	
Polymeric (polyester)	Polymer degradation (with IMER)	MW reduction	Enzymatic (lipase)	Online	SEC-ELSD	32
Synthetic polymers						
Copolymers (styrene/acrylate)	MWD, CCD, blockiness	MW reduction	Thermal	Offline	SEC-Py-GC-MS	33

Homopolymers (styrene) and copolymers (styrene/acrylate)	MWD, CCD, blockiness	MW reduction	Thermal	Online	SEC-Py-GC-MS	34
Copolymers (amide)	BLD	MW reduction	CID	Online	LC-CID-MS/MS	35,36
Copolymers (carboxylic acid)	MWD, CCD	Derivatization	Chemical	Offline	SEC-dRI-UV	36
Copolymers (alcohol)	FTD (end-groups)	Derivatization	Chemical	Offline	CE-UV	37
Medicinal NPs/copolymers (ester)	TPs	Destruction	Enzymatic (lipase)	Online	SEC-ELSD	32
Copolymers (ester/amide)	MWD	MW reduction	Enzymatic (α -chymotrypsin, proteinase K)	Offline	SEC-MS	38
Copolymers (ester/amide)	TPs	Destruction	Enzymatic (α -chymotrypsin)	Online	SEC-MS	39
Copolymers(ester/urethane/urea)	MWD, TPs	MW reduction, destruction	Enzymatic (urease), chemical (hydrolysis)	Offline	SEC-RID, RPLC-MS	40
Homopolymer (bisphenol A carbonate)	TPs	Destruction	Chemical (hydrolysis)	Offline	LCCC/SEC-UV/IR/MS, LCCC \times SEC	41
Copolymer (ester)	TPs	Destruction	Chemical (hydrolysis)	Offline	RPLC-UV	42
Homopolymer (propylene)	TPs	Destruction	Chemical, accelerated-aging chamber	Offline	RPLC-UV-MS	43
Homopolymer (ethylene)	TPs	Destruction	Thermal oxidation	Offline	NPLC-UV, GC \times GC-MS	44
Copolymer (ethylene/terephthalate)	photostability	Destruction	Photodegradation	Offline	IR	45
Homopolymer (vinyl chloride)	photostability	Destruction	Photodegradation	Offline	IR, viscometry	46
Homopolymer (propylene)	photostability, weathering	Destruction	Photodegradation	Offline	IR	47
Small molecules						
Cultural heritage (synthetic dyes)	TPs (photodegradation)	Destruction	Photodegradation	Offline	LC-MS	24
Cultural heritage (synthetic dyes)	TPs (photodegradation)	Destruction	Photodegradation	Offline	LC-UV	48
Cultural heritage (synthetic dyes)	TPs (photodegradation)	Destruction	Photodegradation	Online	LC-UV	49
Cultural heritage (synthetic dyes)	TPs (photodegradation)	Destruction	Photodegradation	Both	LC-UV	50
Cultural heritage (synthetic dyes)	TPs (photodegradation)	Destruction	Photodegradation	Online	2D-LC-UV	51
Cultural heritage (synthetic dyes)	TPs (photodegradation)	Destruction	Photodegradation	Online	recycling-LC-UV	52
Pharmaceuticals (R&D drug)	TPs (phase I metabolism)	Destruction	Electrochemistry	Both	EC-LC-UV-MS	53
Pharmaceuticals (cytokinins)	TPs (phase I metabolism)	Destruction	Electrochemistry	Online	LC-EC-MS	54
Pharmaceuticals (cardiovascular drugs)	TPs (phase I and II metabolism)	Destruction	Electrochemistry	Online	EC-LC-MS	55
Pharmaceuticals (cardiovascular drugs)	TPs (phase I metabolism)	Destruction	Electrochemistry	Online	EC-LC-MS	56
Pharmaceuticals (immunosuppressants)	TPs (phase I and II metabolism)	Destruction	Electrochemistry	Online	EC-LC-MS	57
Pharmaceuticals (fluopyram)	TPs (phase I metabolism)	Destruction	Electrochemistry	Online	EC-LC-MS	58
Pharmaceuticals (thyroxine)	TPs (phase I metabolism)	Destruction	Electrochemistry	Online	EC-LC-MS	59
Food (vitamin D)	TPs (phase I and II metabolism)	Destruction	Electrochemistry	Offline	LC-UV-MS	60
Food (citrus flavonoid)	TPs (phase I and II metabolism)	Destruction	Electrochemistry	Offline	LC-MS	61
Food (lasalocid antibiotic)	TPs (phase I metabolism)	Destruction	Electrochemistry, enzymatic	Offline	LC-UV-MS	62
Food (aged liquors)	TPs (aging)	Destruction	Electrochemistry	Offline	LC-MS	63
Environmental (herbicides)	TPs (environmental degradation)	Destruction	Electrochemistry	Offline	LC-MS	64
Environmental (insecticide)	TPs (phase I metabolism)	Destruction	Electrochemistry	Online	EC-LC-MS	65

Environmental (pesticide)	TPs (reductive metabolism)	Destruction	Electrochemistry	Offline	LC-MS	66
Environmental (PAHs)	TPs (metabolism and photooxidation)	Destruction	Electrochemistry, photodegradation	Both	EC-LC-MS	67
Environmental (pollutant)	TPs (phase I and II metabolism)	Destruction	Electrochemistry	Offline	EC-LC-MS	68

Adeno-associated virus (AAV), anion-exchange chromatography (AEX), antibody-drug conjugate (ADC), bispecific antibodies (bsAb), bond length distribution (BLD), capillary zone electrophoresis (CZE), chemical-composition distribution (CCD), collision-induced dissociation (CID), diode array detection (DAD), dithiothreitol (DTT), dynamic light scattering (DLS), electrochemistry (EC), evaporative light scattering detection (ELSD), fluorescence detection (FLR), functionality type distribution (FTD), gas chromatography (GC), guide ribonucleic acid (gRNA), hydrodynamic chromatography (HDC), immobilized-enzyme reactor (IMER), infrared (IR), liquid chromatography (LC), liquid chromatography at critical conditions (LCCC), mass spectrometry (MS), molecular weight (MW), molecular-weight distribution (MWD), monoclonal antibodies (mAb), multi-dimensional (mD), normal-phase liquid chromatography (NPLC), polyaromatic hydrocarbons (PAHs), poly(lactic-co-glycolic acid) (PLGA), pyrolysis (Py), refractive index detection (RID), research and development (R&D), reversed-phase liquid chromatography (RPLC), ribonuclease (RNase), ribonucleic acid (RNA), signal guide ribonucleic acid (sgRNA), size-exclusion chromatography (SEC), transformation product (TP), transmission electron microscopy (TEM), tris(2-carboxyethyl)phosphine (TCEP), two-dimensional (2D), ultraviolet detection (UV).

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