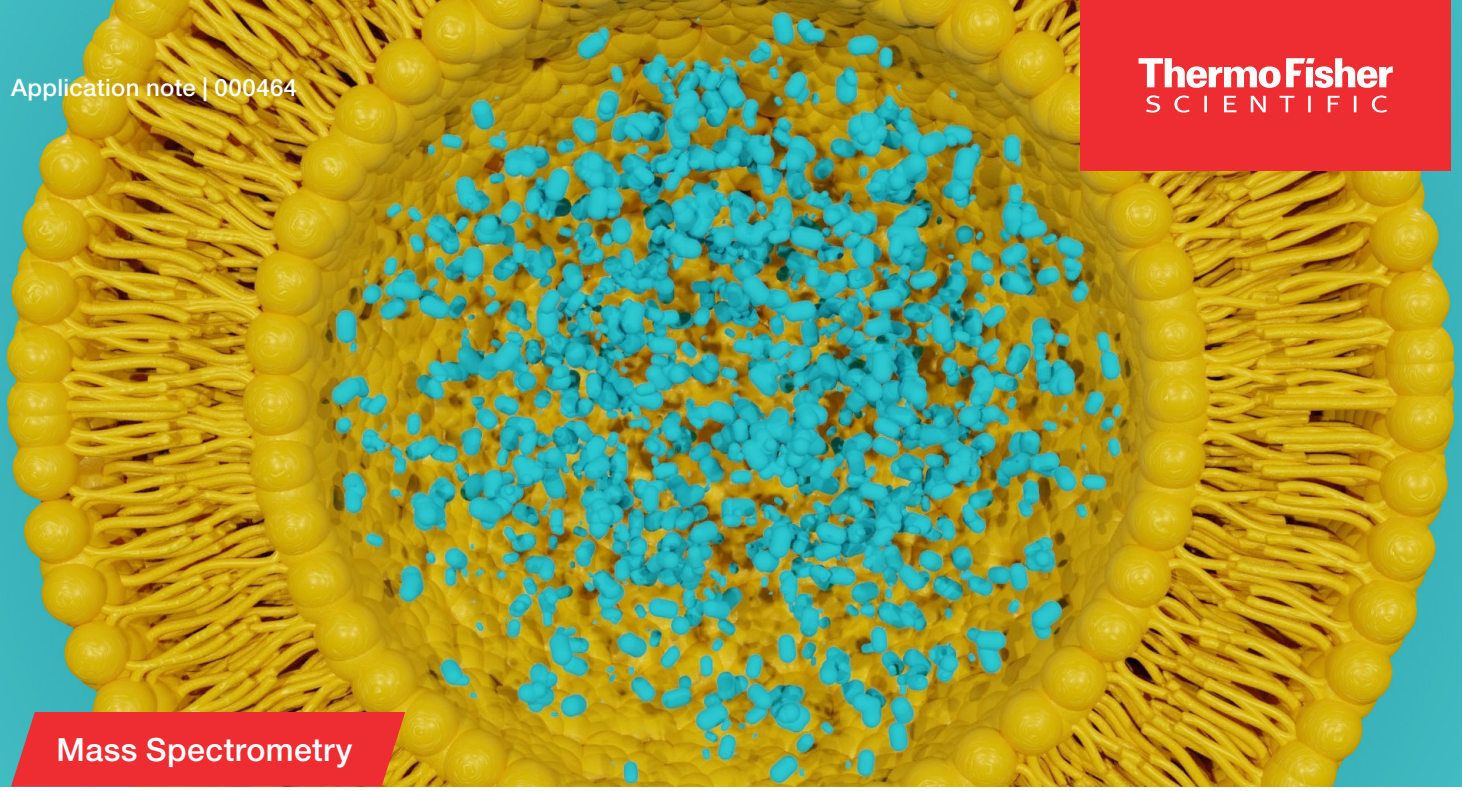
Application note | 000464



Mass Spectrometry

Characterization and quantification of lipid nanoparticle components and their impurities/degradants using an LC-HRAM MS platform

Authors

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Keywords

Lipid nanoparticle (LNP), ionizable lipids, PEG-lipids, high resolution accurate mass (HRAM), Orbitrap mass spectrometer, data-dependent MS/MS, targeted MS/MS, simultaneous untargeted lipid characterization and targeted lipid quantification

Application benefits

- Confident lipid nanoparticle (LNP) component confirmation through high-resolution, accurate mass MS and MS/MS data
- Confident characterization and quantification of impurities and degradants in LNP products
- Untargeted metabolite profiling and targeted LNP lipid component quantification with excellent sensitivity and confidence for the biological matrix samples in a single LC MS-MS/MS analysis
- A platform method for both early LNP formulation development and late LNP formulation quality control and quality assurance

Goal

- Develop an optimized LC-MS/MS method for separating and identifying LNP lipid components and their degradants.
- Develop a highly sensitive and selective LC-MS/MS method to simultaneously characterize the metabolites of the LNP lipid components and quantify the LNP components in the biological matrix samples.

Introduction

Lipid nanoparticles (LNPs) have emerged across the pharmaceutical industry as promising vehicles to deliver a variety of therapeutic agents. Currently in the spotlight as a vital component of the COVID-19 mRNA vaccines, LNPs play a key role in effectively protecting and transporting mRNA to cells.[1] LNP formulations are typically composed of (1) an ionizable or cationic lipid or polymeric material, bearing tertiary or quaternary amines to encapsulate the polyanionic mRNA; (2) a zwitterionic lipid (e.g., 1,2-dioleoyl-snglycero-3-phosphoethanolamine [DOPE]) that resembles the lipids in the cell membrane; (3) cholesterol to stabilize the lipid bilayer of the LNP; and (4) a polyethylene glycol (PEG)-lipid to lend the nanoparticle a hydrating layer, improve colloidal stability, and reduce protein absorption.[2] It is desirable to develop LNPs with high biodegradability properties of ionizable lipids to avoid toxicity mediated by lipids.[3] Controlling the circulation time of a LNP form is also important to avoid toxicity. A key aspect to design and optimize a LNP formulation is the development of biodegradable ionizable lipids, which improve LNPs clearance and reduce toxicity in vivo while maintaining the structural features required for lipid potency.[4,5] In addition, it is known that a longer circulation time of the bound PEG–lipid may promote immunogenicity and antibody response (against the surface PEG) of the LNPs enclosing nucleic acids.[3] Consequently, in order to understand the distribution/exposure, clearance rate and biodegradation pathway of the LNP lipid components in vivo, the quantitative changes of synthetic lipids (ionizable lipids and PEG-lipids) need to be measured in the biological matrix samples. Plus, the metabolites generated from the LNP lipid components need to be identified and monitored from the same biological matrix samples.

An HPLC MS-MS/MS approach provides excellent analytical solutions for addressing the critical quality attributes[6] of raw materials and LNP formulations by enabling confident identification of lipid components and direct measurement of impurities and degradants of lipid components.[7] It enables high sensitivity and selectivity for unknown lipid characterization and targeted lipid quantification, and it has been used successfully to study chemical structure and pharmacokinetics of lead lipids in the LNP development of Moderna's Covid-19 vaccine.[8]

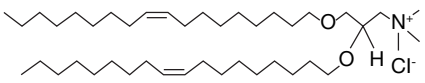
In this work, we applied HPLC MS-MS/MS approaches to the analysis of LNP lipid components for both pure lipid standard mixture samples and biological matrix samples. A Thermo Scientific™ Orbitrap Exploris™ 120 mass spectrometer coupled with a Thermo Scientific™ Vanquish™ Horizon UHPLC system was used for all experiments. Great chromatography separation efficiency was achieved for both the pure lipid standard mixture and the biological matrix samples. The high resolving power and accurate mass measurement offered by the Orbitrap Exploris 120 mass spectrometer enabled confident confirmation of lipid components including structure confirmation, while the high sensitivity allowed low abundant lipid degradant detection at 0.001%. The instrument acquisition versatility allowed simultaneous targeted quantification of ionizable lipid/PEG-lipid and unknown lipid metabolite characterization within a single HPLC MS run. The analytical results are reported here.

Experimental

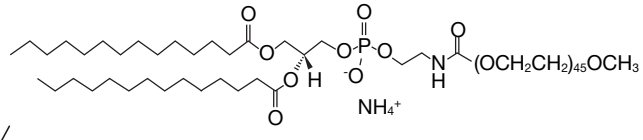
Sample

Five commonly used LNP lipid components and a bovine liver total lipid extract were purchased from Avanti™ Polar Lipids. The detail description and the structure of the five lipid components are shown in Figure 1.

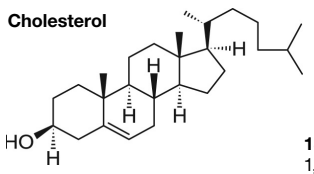
DOTMA
1,2-di-O-octadecenyl-3-trimethylammonium propane (chloride salt)



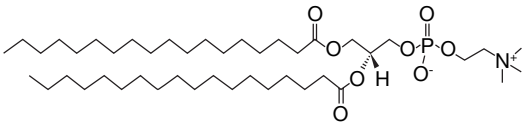
DMG PEG 2000
1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (ammonium salt)



Cholesterol



18:0 PC (DSPC)
1,2-distearoyl-sn-glycero-3-phosphocholine



18:0 PE (DSPE)
1,2-distearoyl-sn-glycero-3-phosphoethanolamine

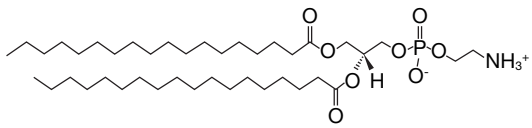


Figure 1. The description and structure of five analyzed lipid components

Sample preparation

1 mg/mL stock concentration of each lipid standard solution was prepared using chloroform/methanol (1/1).

Sample 1: The prepared stock lipid standard solutions were diluted using methanol and a mixture of 5 lipid standards was prepared at the 1 µg/mL concentration.

Sample 2: A 10 µg/mL concentration of DOTMA solution was prepared by diluting the DOTMA stock solution with methanol.

Sample 3: A mimic biological matrix sample series.
Five lipid standards were spiked in the 0.1 mg/mL concentration of bovine liver total lipid extract as a dilution series at nine concentrations: 0.1 ng/mL, 0.25 ng/mL, 0.5 ng/mL, 1 ng/mL, 5 ng/mL, 10 ng/mL, 50 ng/mL, 100 ng/mL, 1 µg/mL.

Chromatography

For all experiments, chromatographic separations were carried out using a Thermo Scientific™ Accucore™ C30 column (2.1 × 150 mm, 2.6 µm, P/N 27826-152130) on the Vanquish Horizon UHPLC system, consisting of the following modules:

Thermo Scientific™ System Base Vanquish™ Horizon/Flex	(P/N VF-S01-A-02)
Thermo Scientific™ Vanquish™ Binary Pump H	(P/N VH-P10-A)
Thermo Scientific™ Vanquish™ Split Sampler HT	(P/N VH-A10-A)
Thermo Scientific™ Vanquish™ Column Compartment H	(P/N VH-C10-A)

Solvent A: 60% ACN/40% H_2O containing 10 mM ammonium formate and 0.1% difluoroacetic acid

Solvent B: 90% IPA/10% ACN containing 10 mM ammonium formate and 0.1% difluoroacetic acid

Chromatographic separation details are shown in Table 1. The column temperature was set to 50 °C. 2 µL of sample were injected on column. For the analysis of the dilution series of lipid standards spiked in the bovine liver total lipid extract (mimic biological matrix samples), each sample was injected in triplicate.

Table 1. HPLC gradient condition

Time	Flow (mL/min)	%B
0	0.35	30
2	0.35	43
2.1	0.35	55
10	0.35	65
13	0.35	85
14	0.35	100
16.5	0.35	100
16.6	0.35	30
22	0.35	30

Mass spectrometry

The Orbitrap Exploris 120 mass spectrometer was used for MS data collection. The instrument was operated with Thermo Scientific™ Chromeleon™ 7.2 Chromatography Data System (CDS) software and controlled by Orbitrap Exploris Series 3.1 instrument control software. For lipid identification and impurities/degradants analysis of the lipid components in the pure standard mixture samples, a data-dependent MS/MS experiment was carried out (Table 2). For unknown lipid metabolite characterization and targeted lipid quantification in the mimic biological matrix samples, a data-dependent MS/MS experiment, followed by a targeted MS/MS experiment, was carried out. Table 3 shows the detail settings for the two alternate experiments.

Table 2. MS parameter settings for analysis of pure lipid standard mixtures

MS source setting	Value
Sheath gas	40
Aux gas	8
Sweep gas	1
Spray voltage (+V)	3,400
Capillary temperature (°C)	300
Vaporizer temperature (°C)	350
MS full MS/dd MS/MS setting (top 3)	**Value**
General	
Application mode	Small molecule
Pressure mode	Standard
RF lens (%)	50
Full MS	
Scan range (*m/z*)	300–1,400
Resolution	120,000 at *m/z* 200
AGC target value (%)	300
Max inject time (ms)	100
dd-MS/MS	
Resolution	30,000 at *m/z* 200
Isolation window (*m/z*)	1.5
AGC target value (%)	100
Max inject time (ms)	100
Fixed first mass (*m/z*)	60
Collision energy mode	Stepped
HCD collision energy (%)	15, 30, 50

Table 3. MS parameter settings for analysis of biological matrix samples

MS source setting	Value
Sheath gas	40
Aux gas	8
Sweep gas	1
Spray voltage (+V)	3,400
Capillary temperature (°C)	300
Vaporizer temperature (°C)	350
Experiment #1: MS full MS/dd MS/MS setting (top 3)	**Value**
General	
Application mode	Small molecule
Pressure mode	Standard
RF lens (%)	50
Full MS	
Scan range (*m/z*)	300–1,400
Resolution	120,000 at *m/z* 200
AGC target value (%)	300
Max inject time (ms)	100
dd-MS/MS	
Resolution	30,000 at *m/z* 200
Isolation window (*m/z*)	1.5
AGC target value (%)	100
Max inject time (ms)	100
Fixed first mass (*m/z*)	60
Targeted mass exclusion	On
Collision energy mode	Stepped
HCD collision energy (%)	15, 30, 50
Experiment #2: Targeted MS/MS setting	**Value**
tMS/MS	
Resolution	30,000 at *m/z* 200
Isolation window (*m/z*)	2
AGC target value (%)	100
Max inject time (ms)	200
Fixed first mass (*m/z*)	60
Collision energy mode	Stepped
HCD collision energy (%)	15, 45
Targeted precursor mass list	
m/z 836.5353, +3	RT window: 4–5.5 min
m/z 634.6508, +1	RT window: 9–10.5 min

Data processing

The lipid identification, impurity/degradant characterization, and relative quantification were carried out using Thermo Scientific™ Compound Discoverer™ 3.3 software and Thermo Scientific™ LipidSearch™ 5.0 software. The calibration curve generation was carried out using Chromeleon 7.2.10 Chromatography Data System (CDS) software.

Results and discussion

Lipid components confirmation using high-resolution, accurate mass MS and MS/MS data

The full MS and MS/MS data of sample 1 (mixture of five lipid standards at the 1 µg/mL concentration) were collected using the data-dependent MS/MS method described in Table 2. The five lipid components were efficiently separated using the C30 column. DMG PEG-2000 exists as a non-uniform polydisperse polymer and contains uneven PEG chain lengths. In this study, the identified PEG chain length was from 34 to 54 (CH_2CH_2O) units. The extracted ion chromatogram of the precursor ion observed from DMG PEG-2000 with 45 (CH_2CH_2O) units is shown in Figure 2 along with the other four lipid components. Less than 3 ppm mass accuracy for the precursor ions was observed across all lipid peaks, enabling confident identification of all lipid components. In addition to the accurate MS data, the MS/MS data provides more structure-related information of the lipid components. Figure 3 shows the 18:0 fatty side chains of the DSPE were unambiguously confirmed using the MS/MS fragment ions information.

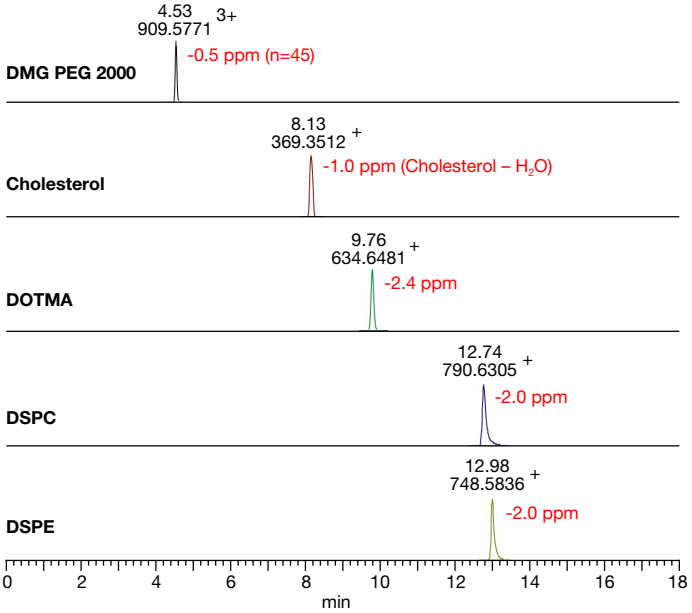


Figure 2. Extracted precursor ion chromatograms of the five lipid components. Excellent chromatography separation efficiency and less than 3 ppm mass accuracy were achieved using the developed platform HPLC MS-MS/MS method.

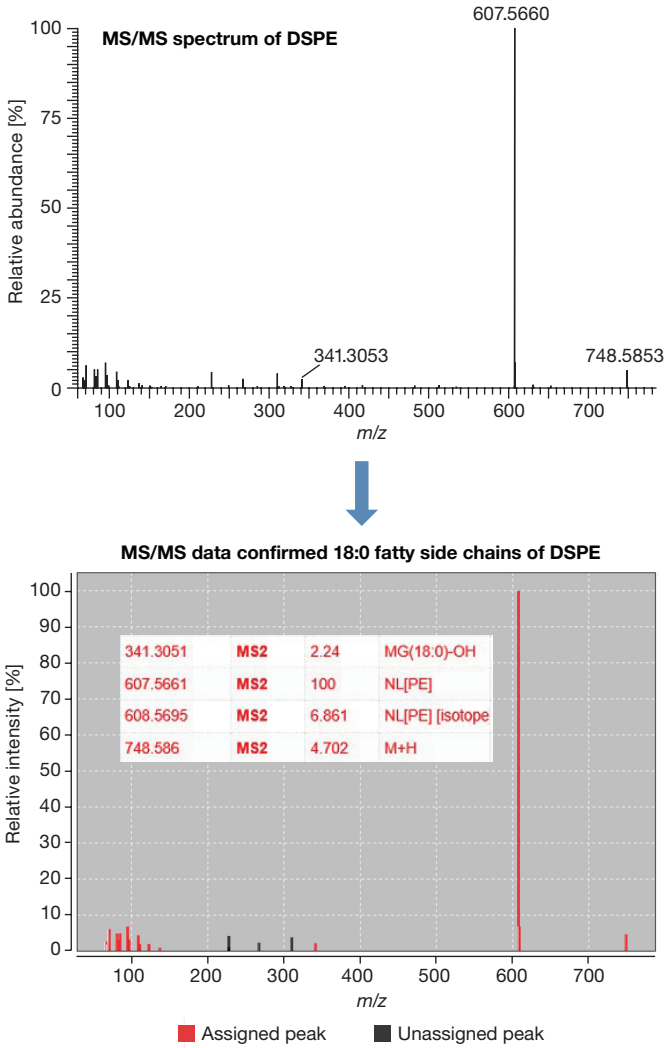


Figure 3. Structure confirmation of the DSPE by fragment ion matches using LipidSearch 5.0 software

Simultaneous lipid components and their degradants identification and relative quantification using high-resolution, accurate mass MS and MS/MS

The high sensitivity offered by the Orbitrap Exploris 120 MS allows detection and characterization of low abundant lipid component degradants with the developed HPLC MS-MS/MS method. Figure 4 shows multiple low degradant peaks of DOTMA with +16 Dalton were clearly detected from sample 2 (DOTMA standard sample at 10 µg/mL concentration). The ratios of oxidized degradants were determined to be less than 0.1% compared to the DOTMA by comparing the integrated peak areas. Despite their low abundance, high quality MS/MS spectra were collected, showed a similar fragmentation pattern with that of DOTMA, and confirmed the identities of the oxidized DOTMA degradants.

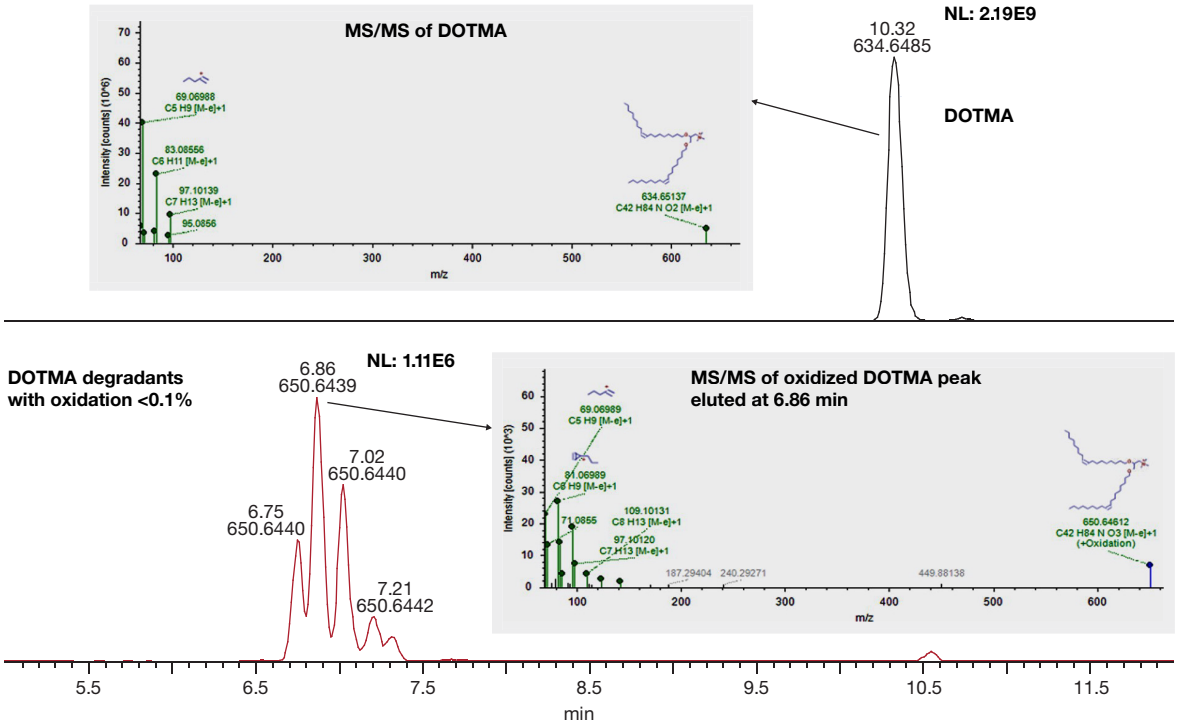


Figure 4. The upper section shows the extracted ion chromatogram of DOTMA and its MS/MS spectrum. The lower section shows the extracted ion chromatograms of DOTMA with oxidization (+16 Da) and a representative MS/MS spectrum of the oxidized DOTMA degradant eluted at 6.86 min. The very low abundant oxidized DOTMA peaks were confidently identified using both MS and MS/MS data.

Simultaneous targeted lipid quantification and unknown lipid metabolite analysis in biological matrix using high-resolution, accurate mass MS and MS/MS data

It is challenging to rapidly monitor the clearance rate and biodegradation pathway of the LNP lipid components in vivo with limited volume of biological matrix (such as tissues, serum, plasma) samples. We were able to develop a single LC-MS method for both metabolite profiling and targeted lipid quantification. After a full MS scan, MS/MS spectra on the three most intense precursor ions are collected for unknown metabolite identification. In the same cycle, MS/MS spectra on targeted precursor ions (DOTMA and PEG-lipid) are collected only when they are eluted, maximizing the duty cycle. The specific fragment ions from the collected targeted MS/MS data were used for quantification. This hybrid approach enables rapid analysis of clearance rate and biodegradation pathway in vivo using minimum amount of samples.

For proof of concept, we applied the method to analyze a series of liver total lipid extract samples that have spiked-in lipid standards at different concentrations to mimic the biological matrix samples across different time points after a LNP administration. Unlike the quantification approach using full scan MS data that uses extracted precursor ions for peak area integration and quantification, the targeted MS/MS (tMS/MS) quantification approach uses integrated peak areas of extracted unique fragment ion(s) for quantification. tMS/MS increases ion trapping efficiency and selectivity, significantly improving the LOD/LOQ of targeted components. Figure 5 shows that the peak of DMG PEG 2000 spiked in the bovine liver extract at 0.25 pg/µL (0.25 ng/mL; 0.5 pg on column) was not detected using full MS scan, but clearly detected using tMS/MS.

Great sensitivity and wide dynamic range were achieved for DOTMA using the tMS/MS approach. Figure 6 shows the calibration curve of DOTMA generated from the dilution series (0.1 ng/mL, 0.25 ng/mL, 0.5 ng/mL, 1 ng/mL, 5 ng/mL, 10 ng/mL, 50 ng/mL, 100 ng/mL, 1 µg/mL). Excellent linearity was observed with R^2 = 0.9995 over four orders of dynamic range.

The data collected from data-dependent MS/MS were used for unknown metabolites characterization using either Compound Discoverer 3.0 software or LipidSearch 5.0 software. Figure 7 shows a representative base peak chromatogram of MS and MS/MS from the liver total lipid extract with spiked-in lipid standards at 50 ng/mL concentration. Multiple classes of lipid species were identified using both full MS and MS/MS data using the default search parameters included in the ProductSearch QEX search template of LipidSearch software.[10]

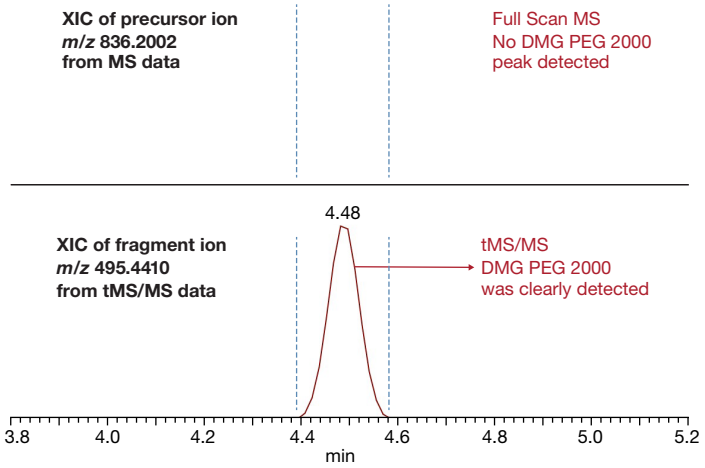


Figure 5. The LOD comparison of DMG PEG 2000 at a concentration of 0.25 ng/mL (50 pg on column) using full MS vs. tMS/MS approaches. The most abundant C13 isotopic mass of DMG PEG 2000 (n=40) (*m/z* 836.5353^{3+}) was the targeted precursor ion for generating tMS/MS data, and the signature fragment ion of DMG PEG-lipids (*m/z* 495.4410) was used for quantification.

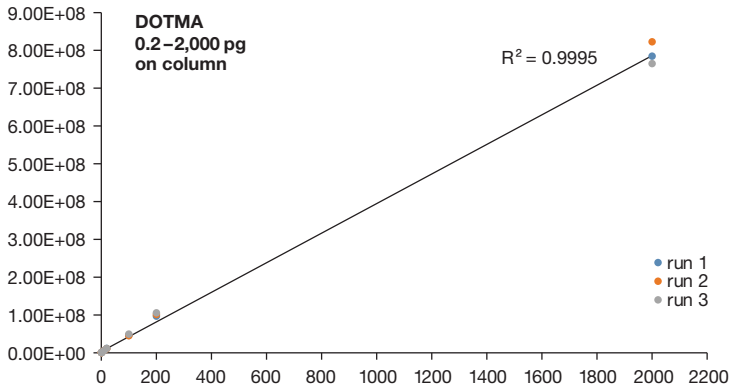


Figure 6. Calibration curve of DOTMA generated using the tMS/MS data

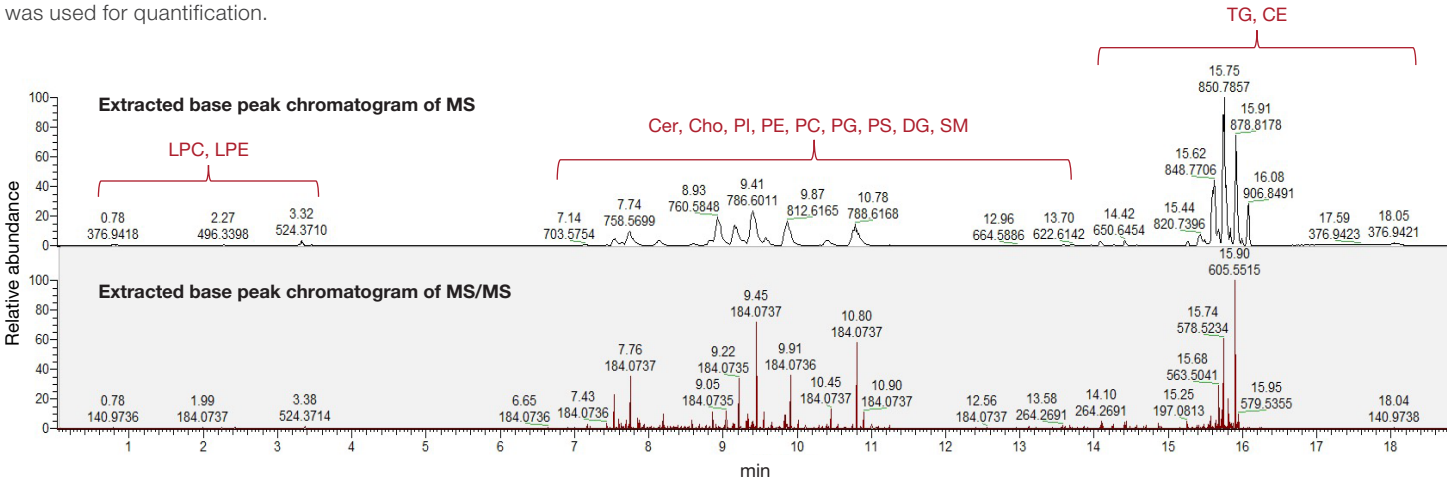


Figure 7. Representative base peak chromatogram of the liver total lipid extract with spiked-in lipid standards at 50 ng/mL concentration. Great separation efficiency was achieved with multiple class of lipid species using the C30 column.

Of the five lipid components studied, cholesterol, 18:0 PC, and 18:0 PE are endogenous lipid components. A previous study has shown that 18:0 Lyso PC could be generated by the hydrolysis of an 18:0 PC molecule.[9] Since 18:0 lyso PC is also an endogenous lipid molecule, our approach should be able to detect it from the bovine liver total lipid matrix sample (0.1 mg/mL). As expected, the endogenous 18:0 Lyso PC was identified confidently by the great quality of MS and MS/MS data using LipidSearch 5.0 software (Figure 8). The measured molecule weight error was 1.3 ppm. The fragment ion information enabled confident confirmation of the 18:0 Lyso PC structure.

To mimic the 18:0 Lyso lipid concentration changes across different time points for a biological sample, the bovine liver total lipid matrix (0.1 mg/mL) sample was injected with 1 µL, 2 µL, and 3 µL, in triplicate. The quantification trend of the endogenous 18:0 Lyso PC across three samples having different injecting volumes is shown in Figure 9.

ID	Formula	ObsMz	CalcMz	TopRT	Height	Area
LPC(18:0)+H	C26 H55 O7 N1 P1	524.3718	524.3711	3.33	1.227E07	4.094E07

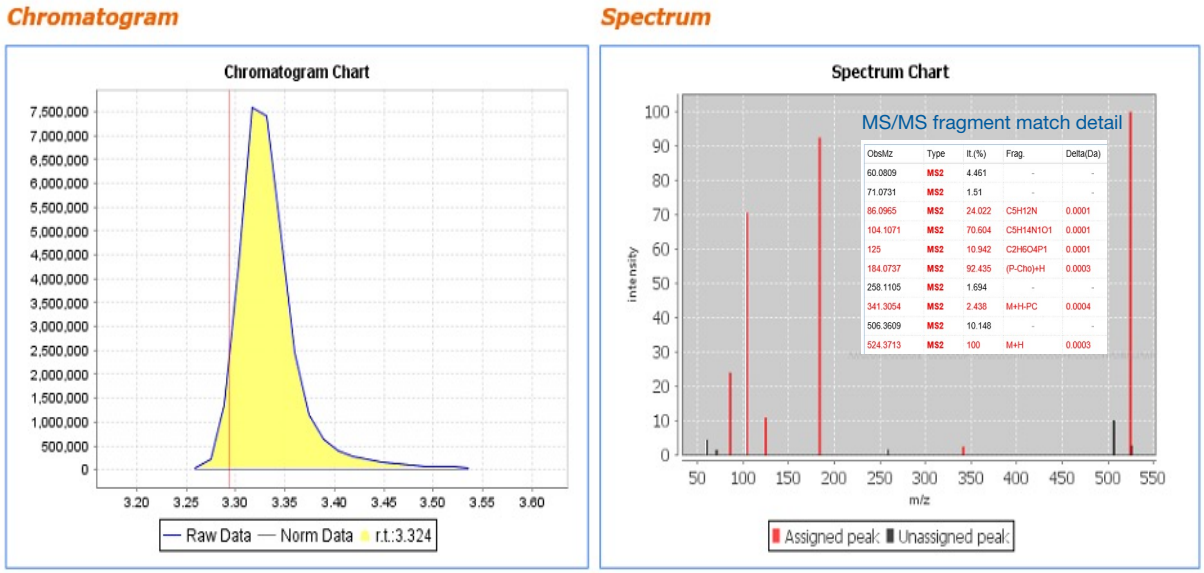


Figure 8. Confident identification of 18:0 Lyso PC using LipidSearch 5.0 software

Chk	Sample Group	Lipid Molec key	BaseRt	Ion key	Scan Type	Polarity	Ion Formula	Obs Mz	Delta(ppm)	Area	Area RSD	Height RSD
☑	s2	LPC(18:0)	3.3275	+H	MS2	P	C26 H55 O7 N1 P1	524.3715	0.7854	3.717E07	12.0027	14.1458
☑	s1	LPC(18:0)	3.3275	+H	MS2	P	C26 H55 O7 N1 P1	524.3715	0.9018	1.628E07	8.9773	22.4102
☑	c	LPC(18:0)	3.3275	+H	MS2	P	C26 H55 O7 N1 P1	524.3715	0.7854	9.552E06	20.1656	18.1053

Figure 9. Endogenous 18:0 Lyso PC quantitation trend observed from the bovine total lipid extract (0.1 mg/mL) with different sample injection volumes (1 µL, 2 µL and 5 µL, in triplicate)

As the data shown in the previous session revealed, the DOTMA standard includes very low abundant (<0.1%) oxidized degradants. These low abundant DOTMA degradants with oxidization in multiple sites were confidently identified using the predefined metabolite workflow template “MetID w Stats Expected w FISh Scoring” (Figure 10) included in the Compound Discoverer 3.3 software. The software detects the metabolites from the expected metabolite list, which was generated based on the common metabolic pathways list. Subsequently, the FISh Scoring node (FISh = fragment ion search) automatically annotates the MS/MS fragments that match and compare with the parent MS/MS and color codes/annotates the fragment ions.[11] Figure 11 shows oxidized DOTMA degradants identification using MS and MS/MS data in the complex bovine liver total lipid extract matrix. The measured molecule weight errors for the oxidized metabolites were less than 1 ppm.

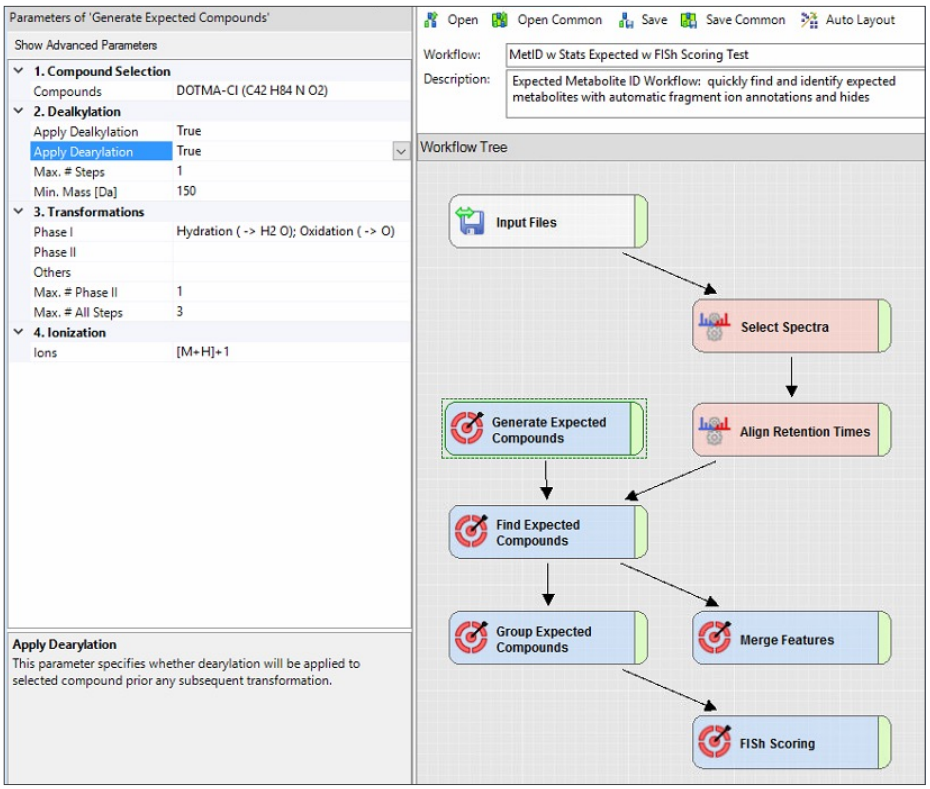


Figure 10. Compound Discoverer software predefined processing workflow: MetID with Stats Expected

Formula	Parent Compound	Dealkylated	Transformations	Composition Change	Annot. ΔMass [ppm]	Calc. MW	RT [min]	FISh Cover.	Area (Max.)	MS2
C42 H84 N O2	DOTMA-Cl				-0.99	634.64958	9.349	87.78	19614503526	
C42 H84 N O3	DOTMA-Cl		Oxidation	+(O)	0.42	650.64539	6.345	80.77	6727246	
C42 H84 N O3	DOTMA-Cl		Oxidation	+(O)	0.54	650.64547	6.240	65.22	2804073	
C42 H84 N O3	DOTMA-Cl		Oxidation	+(O)	0.67	650.64555	6.731	64.71	681842	
C42 H84 N O3	DOTMA-Cl		Oxidation	+(O)	0.49	650.64544	6.630	60.00	1410800	
C42 H84 N O3	DOTMA-Cl		Oxidation	+(O)	0.20	650.64525	6.472	57.89	4139022	
C42 H84 N O4	DOTMA-Cl		Oxidation, Oxidation	+(O2)	0.52	666.64038	5.744	53.12	1345421	
C42 H84 N O4	DOTMA-Cl		Oxidation, Oxidation	+(O2)	0.73	666.64052	5.634	52.24	796830	

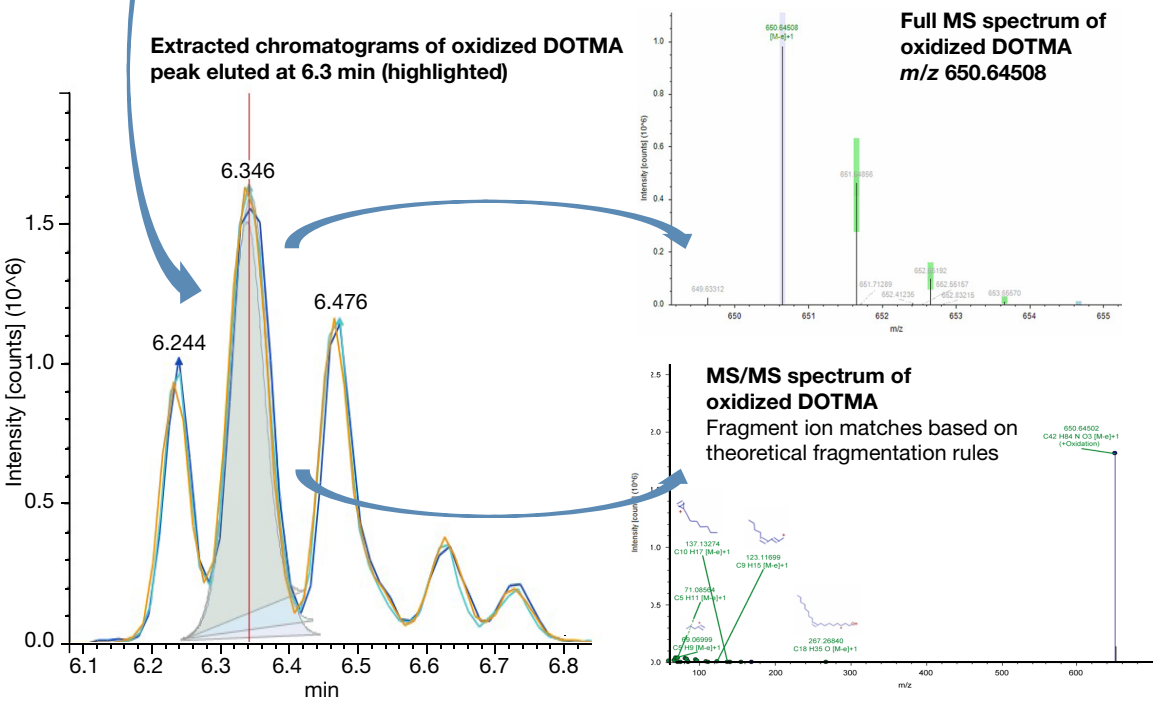


Figure 11. Confident identification of oxidized metabolites of DOTMA in the bovine total lipid extract matrix using Compound Discoverer 3.3 software. The software allows automatic MS/MS fragment ion assignments based on the theoretical fragmentation rules using the pre-defined DOTMA structure.

Conclusion

In summary, the Orbitrap Exploris 120 mass spectrometer coupled with the Vanquish Horizon UHPLC system and Accucore C30 column provides excellent analytical solutions for rapid and confident characterization of LNP lipid components and degradants and can be applied to support LNP product development and manufacturing, including raw material testing, formulation stability study, in process testing, scale-up, and DMPK.

- The developed HPLC MS-MS/MS methods are platform methods and can be applied to different types of LNP formulations, offering excellent analytical solutions for quality control and quality assurance of raw materials and LNP formulations.
- The high resolution, high sensitivity, and the instrument acquisition versatility offered by Orbitrap MS enables rapid lipid quantification and unknown metabolite identification in vivo, helping to speed up the LNP optimization and pre-clinical studies.
- Comprehensive software tools enable rapid and confident characterization and quantification of lipid components and their metabolites/degradants.

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