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Development and Validation of a High-Throughput Method for NDMA Quantitation in Drug Products Using Headspace–SIFT-MS

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ABSTRACT

We have created and validated a high-throughput approach for assessing N-nitrosodimethylamine (NDMA) in medical items utilizing (HS-Channel MS), which is a huge step forward in pharmaceutical analysis. Due to low levels of the carcinogenic N-nitrosodimethylamine (NDMA) contamination, angiotensin receptor blockers were initially evaluated in 2018. A lot of pharmaceutical medicines with various APIs have been tested since then. In order to understand and resolve this massive problem, the industry and authorities are working together. Using methods based on gas chromatography or liquid chromatography, conventional NDMA analysis entails sluggish model analysis and complex model preparation. Selected ion flow tube mass spectrometry (Channel MS) provides a straightforward method for analyzing NDMA in gas phase using soft chemical ionization, with a quantification limit of 2 ng g−1. The novel (MHE) method allowed for the efficient and rapid quantification of NDMA from the drug substance without dissolving it, and at concentrations significantly lower than the 96-ng day−1 regulation OK consumption. A comparable study that evaluated metformin using MHE-Channel MS and a more conventional (LC-MS/MS) method also discovered excellent agreement. The novel MHE-Channel MS method may allow for more thorough testing of pharmaceutical items since it boosts the throughput of standard models by about multiple orders of magnitude.

Keywords: High-Throughput Method, N-nitrosodimethylamine (NDMA), Quantitation, Drug Products, headspace-selected ion flow tube mass spectrometry (Headspace–SIFT-MS), Active Pharmaceutical Ingredients (APIs), Multiple Headspace Extraction (MHE) Technique

1. INTRODUCTION

The pharmacological product N-nitrosodimethylamine (NDMA) has been the focus of extensive research due to its classification as a potential human carcinogen [1]. The substantial public health risk that NDMA contamination in pharmaceuticals poses makes the development of sensitive and reliable analytical procedures for its quantification an essential matter [2]. Despite their success, conventional methods like gas chromatography–mass spectrometry (GC–MS) are ill-suited to high-throughput scenarios due to the considerable model preparation and analysis time required [3]. This is why there is a growing need for innovative methods that can quantify NDMA in pharmaceuticals quickly, accurately, and with high throughput [4].

We have created and supported a (HS-Channel MS) high-throughput analytical technique in answer to this need [5]. The benefits of headspace analysis, which considers the fast detection of unstable substances from the model network without requiring a ton of arrangement, are used in this technique [6]. We might accomplish strong NDMA detection and quantitation at the following levels by combining this technology with Channel MS, an express and exceptionally sensitive mass spectrometric method [7]. In addition to improving throughput, our integration of headspace analysis with Channel MS protects the exactness and precision expected for regulatory compliance [8].

A few essential forward leaps were made in the development of the HS-Channel MS approach, for example, optimizing headspace conditions to increase the appearance of NDMA from drug structures and fine-tuning Channel MS borders for designated ionization and detection [9]. In addition, fastidious technique validation was conducted in accordance with ICH recommendations to guarantee the method's dependability and repeatability for different drug formulations [10]. The method's appropriateness for routine quality control and regulatory submissions was demonstrated by the careful assessment of validation boundaries like linearity, (LOD), (LOQ), exactness, precision, and robustness [11].

Furthermore, by drastically cutting down on the time and resources required for NDMA analysis, the high-throughput capability of HS-Filter MS addresses the industry's expanding requirement for effective screening of large quantities of medicinal items [12]. Pharmaceutical firms are supported by this methodological innovation in maintaining the safety of their goods while complying with strict regulatory requirements [13]. HS-Filter MS is a major development in pharmaceutical analysis that promotes improved medication safety and quality assurance by providing a streamlined and appealing alternative for NDMA quantification [14].

An important step in the correct direction for analytical science has been the invention and validation of the HS-Filter MS technique for NDMA quantification in medicinal products [15]. This novel approach offers a potent, sensitive, and high-throughput means of identifying a fundamental contaminant in pharmaceuticals by fusing the advantages of headspace sampling with the sophisticated capabilities of Filter MS [16]. This method's successful application highlights its potential as a crucial instrument for the pharmaceutical sector, guaranteeing the continuous protection of public health through improved monitoring of medication safety [17].

2. MATERIALS AND METHODS

2.1. Chemicals, Standards, and Samples

2.1.1. Samples of Drug Products

Technique development is the primary focus of this evaluation, with proof-of-concept preliminary work on a small number of pharmaceutical goods following closely after. It should be emphasized that although though the drug goods metformin and valsartan are from reviewed clusters, the studies presented here were completed well beyond the item expiration dates, thus the data cannot be compared and distributed from the hour of review. Therefore, the results achieved here have no bearing on the item as originally presented, but instead show the headspace-SIFTMS approach's potential. In this way, in request to evaluate the quantitative adequacy of the Channel MS method of treatment, information collecting using both LC and Channel MS has been done concurrently for the latest metformin survey. For Filter MS analysis, 300 mg of the medication item was utilized, and for LC-MS/MS analysis, 400 mg, unless otherwise specified.

2.1.2. Standards and Chemicals

A laboratory water purification device was used to produce ultrapure water. Sigma Aldrich provided the methanol (HPLC grade) and formic corrosive (>98% virtue).

Preparation of NDMA calibration standards was completed using a 5000-µg mL−1 standard in methanol.

2.2. SIFT-MS

2.2.1. SIFT-MS Analysis

A proactive explanation of the SIFT-MS analytical approach with detailed explanations has already been provided elsewhere. In this assessment, a business SIFT-MS device running on helium transporter gas was utilized. Under customary factory settings, the SIFT-MS device worked at 0.7 mbar for the ion source, 0.8 mbar for the transporter gas pressure in the flow tube, 120 ◦C for the flow tube temperature, 25 V for the static potential on the tube, and around 25 standards cubic centimeters each minute (sccm) for the model flow rate.

The SIFT-MS analysis performed by NDMA is previously illustrated. Analyte sensitivity to SIFT-MS can be measured by looking at the reaction rate coefficient, or k. Nitrosamines are more sensitive than other volatile organic compounds (VOCs) due to their high limit, which means they could accumulate more k-values than other gases. This survey found no issues with any of the frameworks that were tested.

High lingering solvent concentrations may impact SIFTMS concentration estimations due to the unnecessary consumption of reagent ions. In this case, the NO+ reagent ion is usually more potent than H3O+ and O2 +• since it is considerably less weak to common solvents like ethanol or isopropyl alcohol (due to their different reaction rate coefficients).

2.2.2. Automated Analysis of Headspace-SIFT-MS

An MPS, or multipurpose autosampler, was included with the SIFT-MS device. The experiments were incubated in a virtual twelve spot agitator, which was made out of two genuine six-place agitators, before the headspace was analyzed and injected into the SIFT-MS instrument using a septum-less sampling head (GERSTEL).

The headspace analytical conditions for both the single measurement and MHE were prepared by incubating 10 mL vials at 60 ◦C for 30 minutes. At a rate of 100 µL s−1, a 2.5

mL portion of headspace was removed and injected into the model inlet of the SIFT-MS instrument using a gas-tight syringe that had been warmed to 150◦ C. The overall flow into the instrument was ensured to be 25 mL min−1 by syphoning high-prudence nitrogen make-up gas through the warmed inlet (120◦ C). The syringe was quickly flushed at 200 mL min−1 without air after a model was injected.

Calibration takes this into consideration since model dilution at the inlet occurs in situations like test measurement. The evaluation of each model took one hundred seconds. The fine-grained concentrations represent the typical quality achieved during injection, which takes around forty to sixty seconds.

2.3. Autonomous LC-MS/MS Evaluation

The LC-MS/MS method has been approved for use in the examination of metformin-containing medicinal products by a couple of irbesartan and metformin pharmacological substances. There was 0.2% formic acid in both of the elution solvents, which started with 95% water and 5% methanol.

Holding for one minute followed by ten minutes of sloping to 95% methanol, followed by five minutes of holding. The procedure included dissolving 400 milligrams of programming interface in 5 mL of water. Regardless, once completion, this approach caused gel formation with the metformin pharmaceutical items, making case analysis more difficult. After being mixed for two minutes at 2000 rpm on a Quick Blend (GERSTEL), the samples were centrifuged for five minutes at 4500 rpm to separate the supernatant from the other excipients.

3. RESULTS

Important NDMA detection performance by headspace-SIFT-MS and results comparing it to a supported LC-MS/MS method are provided here, along with results demonstrating the invention of the MHE-SIFT-MS technology. There were not enough readily available instances to warrant the use of the progressive changing stages to analyze various pharmaceutical substances containing NDMA.

3.1. Headspace-SIFT-MS Analytical Performance of NDMA Analysis

The most important steps in developing the technology were finding the (LOQ) for headspace analysis and making sure the NDMA linear detection worked. Because NO+ is only moderately sensitive to acetone and significantly less sensitive to methanol, the NO+ ion's bent was linear in comparison. To try to stimulate a non-linear response in NO+, the last choice was used as a buffer in the low concentration region; nonetheless, NO+ was still strong. The effect is much the same regardless of whether the solvents are from the calibration blend or a medicine stuff.

Table 1: (LOD), (LOQ), and (S/N) measurements for gas stage SIFT-MS examination of NDMA delivered into a 2.5 mL aliquot at a rate of 100 µL s−1.

NDMA Reagent Ion—Product Ion Pair	Signal-to-Noise Ratio (S/N)	Theoretical LOD Based on 3:1 S/N (ng)	Theoretical LOQ Based on 10:1 S/N (ng)
H3O+ 75	24.9	1.34	2.2
NO+ 74	16.4	1.52	2.8

O2+• 74	6.10	2.4	5.5

3.2. Method Development for Tablet Formulations Quantitative SIFT-MS Analysis

It is feasible to quantify outright concentrations in condensed stages independent of the network by using multiple headspace extraction (MHE). For a fruitful MHE to give a decent match to the decay of the VOC signal, analysis all through a dynamic range of around two significant degrees is needed. Starting with a larger test volume (100-500 mg) as suggested by static headspace analysis (at harmony; Figure 1) is the first order of business. For ranitidine testing, the NO+ signal characteristics suggest using 500 mg of the prescription item. When the conventional region-under-the-bend approach fails to adapt to calculating the total concentration in the drug item, it is possible to include the concentration data from the various injections. Thing 2's final concentration was inferred using the standard region under-the-bend approach, whereas Thing 1's quality was obtained by combining injections 1-6. Both pharmaceutical items R1 and R2 fell within the range reported to the US FDA for ranitidine preparations, with NDMA strengths of 68 and 328 ng g−1, respectively.

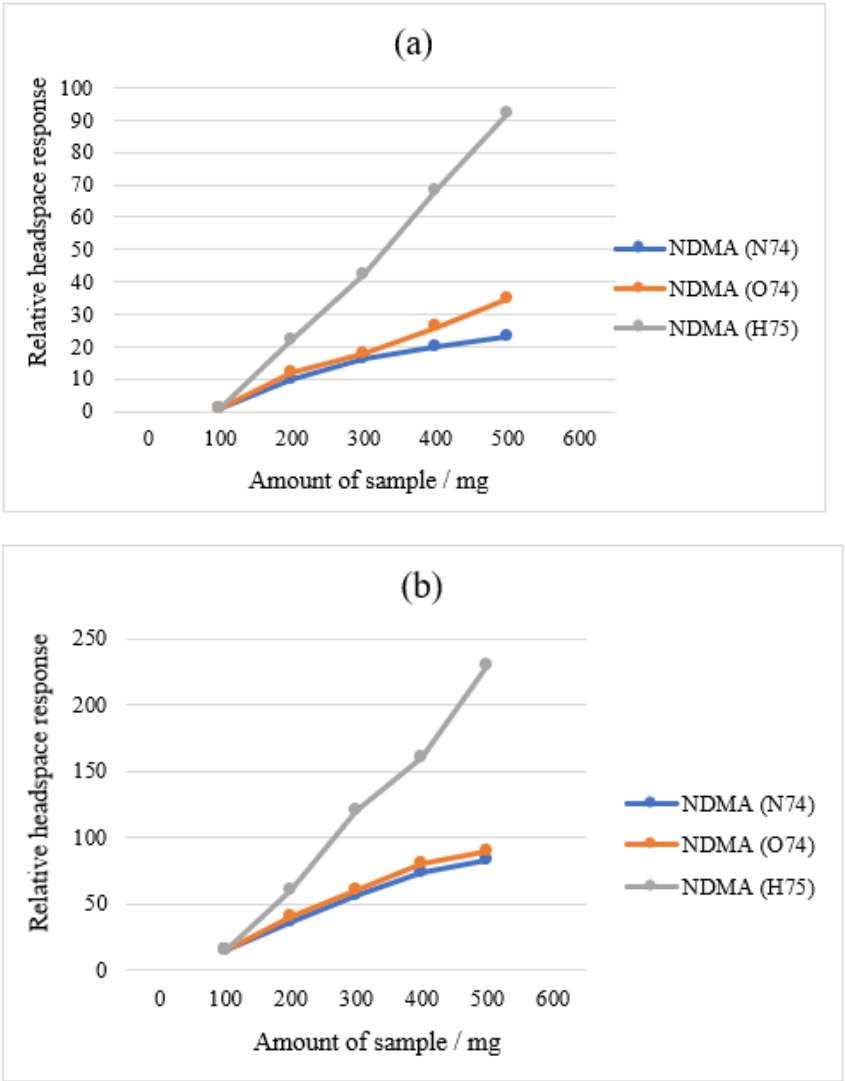

Figure 1: NDMA headspace response for the ranitidine drug products (a) R1 and (b) R2 was estimated as a function of test mass using SIFT-MS.

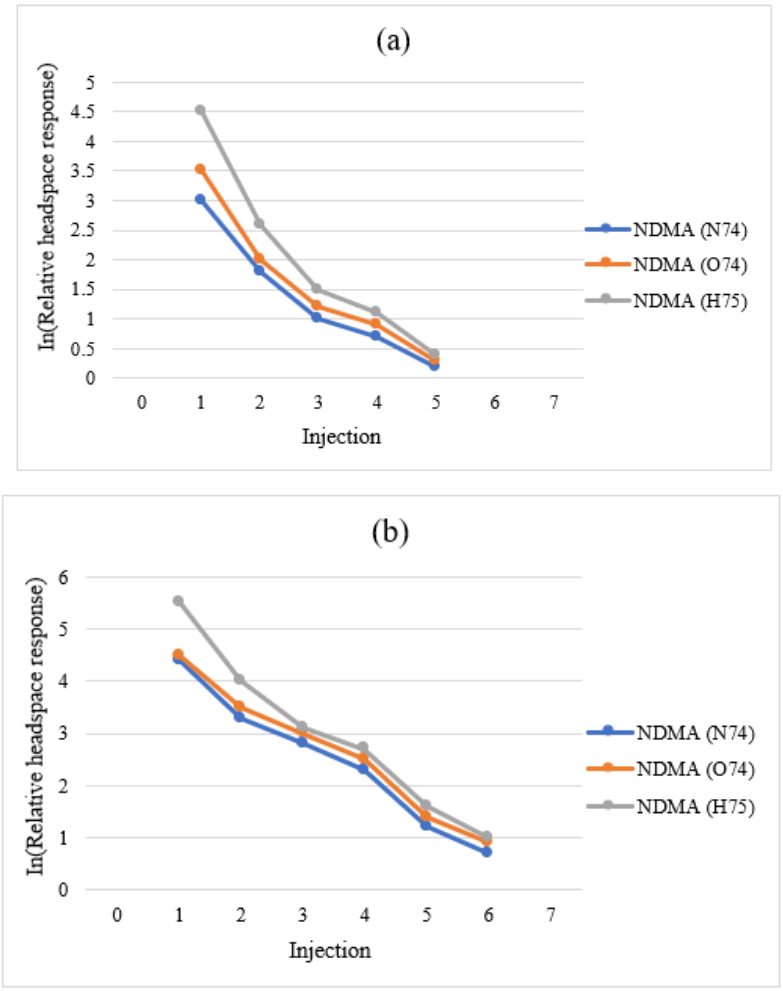

Figure 2: R1 and R2, which reflect the natural logarithm of headspace concentration as a function of injection number, provide MHE-SIFT-MS data for NDMA in 500 mg tests of ranitidine pharmaceutical items.

Using the natural logarithm, some MHE bends do not exhibit a linear relationship with injection number, even though the results are completely repeatable. Two products, R1 and R2, were tested at 300 mg with three-crease measurements; RSDs for R1 were 1.5-2.7% and RSDs for R2 were 3.6-5.5%. This exemplifies the remarkable reproducibility of the SIFT-MS method, even when applied to less-than-ideal cross sections.

Using a single headspace injection instead of full MHE for each case is made possible by the excellent repeatability, which is demonstrated for MHE-SIFT-MS analysis of polystyrene, where the last decision is repeatably associated with the main injection. The model headspace should be harmonic with respect to the entire MHE, therefore keep that in mind.

A single valsartan pill was also used to evaluate the significance of the recently simplified MHE method for ranitidine products. Despite the fact that their expiration value has not been determined by the producers, it should be emphasized that this value pales in comparison to the documented potential gains of up to 22 µg per tablet. When it comes to drug things R1 and R1, the necessary injection is close to 0.60, however when it comes to drug things V1 it is only 0.16. Calibration using MHE is considered standard procedure for several drug thing

systems. Compared to the ranitidine offshoots, this medication has a reduced headspace partitioning.

3.3. LC-MS/MS Head-to-Head Comparison

To analyze NDMA in powdered pharmaceutical items, an MHE-SIFT-MS methodology was developed, as mentioned in the previous subsection. Although they weren't compared to other established chromatographic techniques, the findings of the method development demonstrate that the methodology reports the correct significant level. Table 2 provides a summary of the results, and Figure 3 illustrates the external association. The ion signals in the LC-MS/MS study were suppressed for two examples (M5 and M6) due to the lattice. Keep this in mind. Finding out how to quantify these models required more LC-based technique development, which was beyond the scope of the current study, hence no data is accounted for. Although the two methods approached test preparation and analysis in completely different ways, they still managed to get highly congruent results for the four models they identified. In addition, while the study results were obviously past their expiration dates, several of the characteristics shown here were within the appropriate concentration range of 60 to 190 ng per pill that the US FDA discovered in May 2020. With headspace-SIFT-MS, the item screening process can be accelerated.

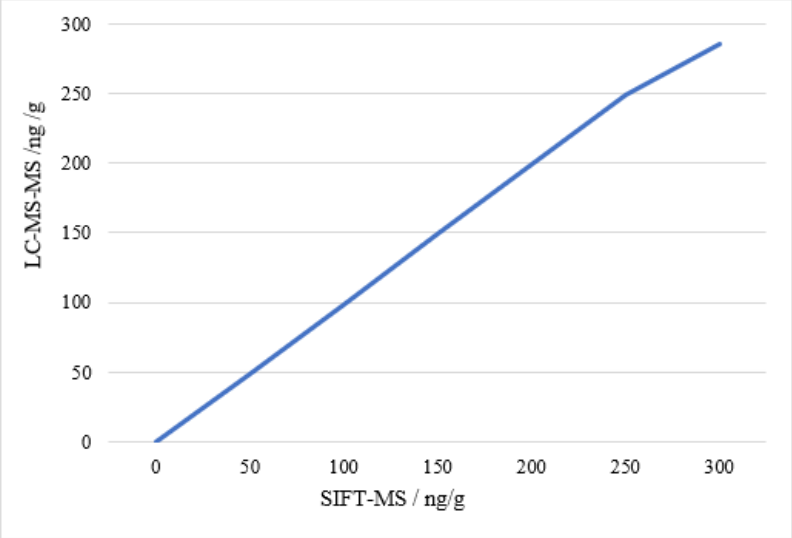

Figure 3: correlation between the outcomes of the dissolution-LC-MS/MS and MHE-SIFT-MS techniques for four metformin samples. Measured data is shown by the blue triangles.

Table 2: NDMA concentrations reported for the dissolution-LC-MS/MS and MHE-SIFT-MS techniques in the metformin products.

Sample	SIFT-MS	LC-MS/MS
M1	269	220
M2	242	268
M3	79.3	58
M4	157	143

M5	132	*
M6	56.2	*

4. DISCUSSION

The consequences of creating an MHE-SIFT-MS technique to quantify NDMA in pharmaceuticals without dissolving them in solvent (i.e., from the headspace above powdered examples) were nitty gritty in the past section. Besides, a conventional LC-MS/MS system was utilized to look into the methodology. With an accentuation on the methodology's truly wide pertinence, this section examines the results and the potential benefits and disadvantages of the recommended MHE-SIFT-MS approach contrasted with the old methodology [18].

Notwithstanding the immensely different model preparation and analytical methodologies utilized by the SIFT-MS and LC-MS/MS systems, Table 2 and Figure 3 show that for the models that were up for evaluation, there is a significant level of agreement between the methods. With SIFT-MS, you might lessen model preparation while increasing model analysis throughput. In request to abstain from doing the tedious full MHE approach for each case, the last and most significant option is to "breakdown" the methodology to a single headspace analysis. In the limited ranitidine test set, the equivalency between products from two manufacturers using different remaining solvents was generally excellent (Figure 2); both R1 and R2 had MHE calibrations of 0.589 and 0.599, separately, for the principal injection to the amount of the six MHE injections. Table 3 shows the results of the six metformin tests. In these models, the RSDs for the MHE calibration were under 12% and for the slant of the MHE fit, it was 14%. These outcomes recommend that MHE calibration is appropriate across products, as this calculation is done for four distinct items or gatherings from one manufacturer, and for metformin from three separate manufacturers. In view of this reason, it would be reasonable to expect that it could be utilized less significantly the entire day, or even longer, given the consistent outcomes saw with formaldehyde in a gel grid [19].

Table 3: Metformin NDMA analysis using MHE-SIFT-MS parameters (linear fit slope and initial injection to total procedure ratio).

Metformin Sample and Statistical Parameters	**First MHE Injection to Total MHE Ratio**	**Slope of the Linear Fit with Six Injections of MHE**
M1	1.1233	−1.2277
M2	1.1246	−1.2302
M3	1.0925	−1.1631
M4	1.1282	−1.2366
M5	1.1120	−1.2031
M6	1.1071	−1.1895
Mean	**1.1146**	**−1.2084**
Standard Dev.	**1.0136**	**1.0287**
RSD (%)	**12.9%**	**14.8%**

In any case, it is acknowledged that the MHE-SIFT-MS method won't be beneficial all the time. For instance, unless the MHE-SIFT-MS calibration is strong over a longer timeframe (e.g., week by week calibration), the arrangement time for LC-MS/MS for extremely concise model runs will probably be unrivalled. Note that this needs to be examined in a subsequent report since it could not be evaluated here due to restricted drug-thing tests. For some grids, quantitative analysis with SIFT-MS may be impossible due to persistent solvent levels in headspace or because solvents themselves interfere with analyte measurement [20]. In any event, subsequent DMF interference was effectively changed in the three medicinal items under investigation here. In conclusion, given that chromatography is eliminated, it is conceivable that the headspace composition of a few medicinal items is too mind boggling for SIFT-MS to ascertain, as it doesn't give a meaningful separation of analytes. This will become clear as soon as the approach is developed. However, it should be mentioned that chromatographic methods are not impervious to framework effects. For example, in this evaluation, ion suppression prevented the LC-MS/MS strategy from analyzing NDMA in two of the metformin tests, but headspace-SIFT-MS quickly and accurately evaluated each of the six cases utilizing the developed methodology. Furthermore, the recently developed distributed extraction approach has to be significantly modified in order to be used with metformin products rather than water-solvent programming interfaces. However, the comparable SIFT-MS method has shown to be applicable to a variety of medicinal products that have three APIs.

5. CONCLUSION

The results demonstrate that SIFT-MS can detect low levels of NDMA pollutant in pharmaceutical products containing the three active pharmaceutical ingredients metformin, ranitidine, and valsartan. When NDMA reacts with NO+, it forms the m/z 74 thing ion, which SIFT-MS uses to provide express analysis for qualifying ions in these networks. Getting explicitness and doing away with chromatography requires the ability to use several item ions simultaneously in a single continuous analysis. The results of SIFT-MS were compared well with those of an authorized LC-MS/MS method. While SIFT-MS isn't designed to provide a definitive response for every drug cross-section, the results suggest that it should be investigated further for the investigation of NDMA in various systems and other non-specific nitrosamines in relevant pharmaceutical items. To provide system independent quantification, the new SIFT-MS method employs the MHE technology to directly quantify from the headspace of the powdered drug item. This accounts for the entire multiple-injection technique's speedier analysis, which could bring about a day to day test throughput that is generally 200% bigger than the LC-MS/MS method. One way or another, the MHE-SIFT-MS framework genuinely must be completely approved. SIFT-MS's continuous analysis may likewise be beneficial for situations involving in-process NDMA monitoring.

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