Help! I Need More LC/MS Sensitivity!

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It seems like these days all LC/MS users are looking for the same thing – greater LC/MS sensitivity. Since most labs don't have the convenience of running out and getting the latest mass spec model, let's explore some additional options that won't require such a hefty investment.

Sample Prep

Let's talk about sample prep. I know that this can be a somewhat unpopular subject. Although it's easy to settle into liquid-liquid extraction or a simple protein crash, the goal here is to clean up your sample as much as possible. As everyone is aware, the dirtier the sample, the greater the ion suppression, the lesser the LC/MS sensitivity.

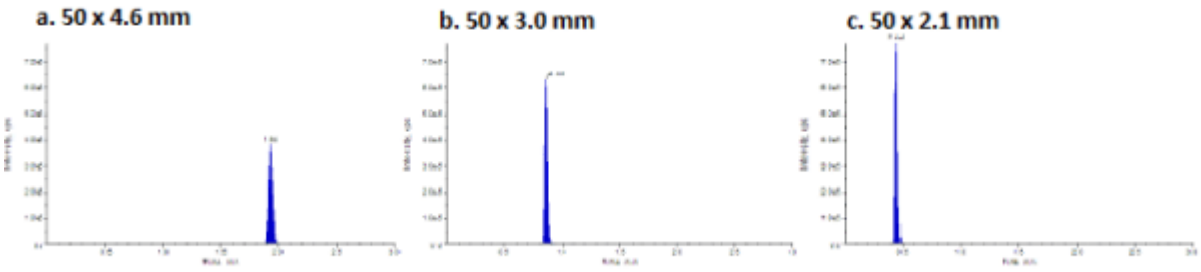
Choosing the most applicable sample prep product for your workload is probably just as important as the purity of the sample itself. There are QuEChERs, phospholipid removal products, protein crash filters, solid phase extraction (SPE), etc., the choices can become overwhelming. Not to mention the different formats that you have to choose from (spin columns, micro-elution plates, giga tubes, etc.).

Choosing the right one is dependent on your specific analytes, sample matrix, the amount that sample that you want to clean up, and the format of equipment available in your lab (vacuum manifold, liquid handler, etc.). For assistance in choosing the product that is right for you, I suggest checking out our Sample Prep Made Simple user's guide, or reaching out to one of our technical experts via our online chat.

***Special Note**: Since I support mostly pharmaceutical accounts, I want to comment that if you are working with any kind of biological matrix, you should be using some sort of SPE product. This sample prep step greatly increases the purity of your sample and will dramatically increase the sensitivity of your LC method.*

Column ID

Now that you have selected an appropriate sample clean-up method, let's discuss how the column affects sensitivity. We will start off by assuming that you have a standard C18 and are looking to increase sensitivity. The first thing that you can do is decrease your column id. For analytical methods, this is very obviously seen when scaling down from a 4.6 mm to a 2.1 mm, and is also seen when going from a 4.6 mm to a 3.0 mm (the dramatic difference here may surprise you).



With smaller column ids come decreased flow rates (and maintain the same linear velocity) due to smaller column volume, so make sure your system can support the slower flow rates.

Column Chemistry

Choosing the right column chemistry can affect ion suppression because it affects where your compounds elute. Keeping your compounds away from the two zones where ion suppression occurs the most often (the solvent front and the end of the elution gradient[1] will

ultimately improve your sensitivity). If you are working with polar compounds, for example, selecting a C18 column with some sort of polar selector (either a polar embedded or a polar end capped group) will give you additional polar retention and will "push" your compounds away from the solvent front.

You can also play with other column chemistries, such as a phenyl or pentafluorophenyl (PFP) phase and see how that affects your retention. If you are feeling extra creative with your method development, you can try a HILIC phase. My colleague, Scott Krepich, wrote a great blog about HILIC and its advantages. He touches upon why it's a good option for LC/MS. For the sake of keeping this article a reasonable length, I have included the link for his blog here for those of you who are interested in learning more.

Modifiers

Although trifluoroacetic acid (TFA) is a very popular and an effective ion pairing agent, it is also known to create ion suppression and therefore decrease sensitivity. More popular additives include formic acid, acetic acid, ammonium acetate and ammonium formate (for positive mode ionization). In a study comparing modifiers, TFA was found to be the worst additive under investigation in ESI, and formic acid was found to be the overall best[2].

It feels like we have only begun to discuss this hot topic of LC/MS sensitivity. If you are looking to dive deeper into this subject, please let us know! Feel free to comment, reach out to us via Live Chat or contact your LC Technical Specialist. We would love to hear from you!

1. Volmer, Dietrich A.; Jessome, Lori Lee. “Ion Suppression: A Major Concern in Mass Spectrometry”. *Chromatography Online*. 01 May, 2006. http://www.chromatographyonline.com/ion-suppression-major-concern-mass-spectrometry

2. Temesi, D.; Law, B. *LCGC* 17(7), 626 (1999)

3. “ Increasing LC-MS Sensitivity can be that Simple.” *Chromatography Today*. Labmate Online. 22 December, 2017. https://www.chromatographytoday.com/article/lc-ms/48/merck-kgaa/pyes-increasing-lc-msnbspsensitivity-can-be-that-simplep/2308

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