Good is Not a Number - Challenges in the Cannabis Extraction Manufacturing: Transitioning from Traditional Subjective to Modern QC/QA/PAT Chromatographic Analysis

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The cannabis plant has been used for centuries across the world for its supposed therapeutic and spiritual value. The traditional workflow from seed to shelf has been based on a subjective perception of value; i.e. is it good or bad? With the greater regulatory needs in countries that have legalised it, objective testing is essential for safety and efficacy for a range of possible formulations that are manufactured. With the greater regulated use of this therapeutic plant, the overall testing will improve from the requirements specified by an unregulated illegal market to those required by your local store in line with other nutraceutical products. With the acknowledgement that the market must have a safety-first mentality, the financial health of a company involved in the current cannabis market is also at risk without the use of modern testing technologies. The separation technology of chromatography provides this first step in being to identify what the analytical criteria should be to ensure the efficacy and the toxicity of the product is. This opinion piece was the subject of presentation given to a diverse audience of cannabis leaders in manufacturing, research and instrumentation.

Introduction

Marijuana mania has moved from the hushed whispers of smoke filled cafés to media headlines across the world. With the daily social media reports or reading about the health benefits/negatives in your local newspaper, it has become a prevalent feature of the times. Still with all this information overload, the general population is not well versed on the details of Cannabis Sativa L.

Please note that from this point forward I have omitted references to 'marijuana' or 'pot' or 'hemp' (or choose any other word that is not cannabis) and will simply refer to all plants as cannabis.

A large proportion of the traditional and illegal cannabis manufacturing industry is not regulated and hence product testing is not required. As a growing number of principalities have legalised it for specific conditions, this has changed dramatically. Laboratory services have come under more regulations themselves, such as ISO 17025, to assure the test results are correct, with the focus shifting from initially just the potency of the cannabis to also look at impurity profiling for pesticides, heavy metals and microbiological testing.

As in any industry the internal quality control and assurance results need to be validated. Historically the traditional manufacturing group sent out the sample when the product was ready for shipment. The profit margins were high enough and the regulations broad enough that passing the samples for shipment was easy.

With the number of plant shutdowns due to out of specification pesticide residues in samples, the dependence on outside third-party laboratories has become less favorable as a sustainable business model. Finding out about pesticides in products after they have been through the entire process is financially disastrous

Another driving force for internal laboratory testing is the maintenance of a mass balance and hence reducing the loss of material during processing. Mass balancing is simply accounting for knowing what amount of material you started with and ended with as well as every step in-between.

The following examples of extraction by supercritical carbon dioxide demonstrate the savings and advances that can be made by implementing even the simplest of separation science analytical testing.

A Typical Scenario for Consideration

You are the owner of a cannabis oil production company 'Sativa Products'.

It is busy Friday before a national holiday weekend in February, and you ask your manufacturing extraction manager, "How was the extraction and distillation output this week for hemp?"

Which answer would you like to hear?

1. "It was really good."

2. "We had some extractions that were better than others. The dewaxing, was good as well. The distillation was OK for most of them. We got some results back from Lab XYZ on the final product that had some better numbers than last week, but still inconsistent, as we have talked about before. Good news is they were below the limit of THCA/THC, so we are in good shape to ship the oil."

3. "From cultivation facility A, we received material that was between 15.5 to 17% CDBA, 3% CBGA and less than 1% CBC and less than 0.2% THCA/THC. We used the new decarboxylation method and captured more terpenes in cold traps. We had about 80% conversion of the CBDA to CBD. We used CO_2 extraction using Method L. After the extraction and collection in 4 collection vessels we had an 87% yield of CBD and THCA/THC is still well below the 0.3% limit. I do not have the yield after the dewaxing yet, but I will have those when we return from the holiday weekend."

4. "Based on the QC/QA lab results, the products from cultivation facility A were well within regulations for pesticides and the cannabinoid ratios were consistent with the results we have seen from this variety over the past 4 crops. The drying and decarboxylation were over the internal testing standards and were therefore passed to continue into the extraction lab. The extraction grind was consistent and the yields using method L were about 90%. These were passed to the dewaxing process and we are waiting for final tests before moving to the different formulation processes. We have received results back from our external service 'Laboratory Testing Services' that support that our internal testing is still valid with the state regulatory standards."

Reviewing these results and looking at the productivity as a basis for the health of the company, the fourth scenario is the best one to use. Is it possible to get those results without having to send out samples to local labs? The quick answer yes, but at what cost?

Few companies in the cannabis industry have laboratories in their facilities. (Yes, I know that 'few' is not a number). Listings of local licensed facilities in your area are available. Fewer companies have any protocols in place for testing all phases of the workflow from the planting to shelf life studies. The companies that have implemented at least some testing have realised that having this capability has paid for itself in a matter of a few weeks and others in just a matter of days. If you were to count return on investment in the first 'ah-ha moments', I have seen that in just a matter of minutes and the longest in a couple hours.

Those 'ah-ha moments' have been preventing those companies from joining the number of companies that have failed yet but could have been saved or made more consistent formulations by implementing simple testing. It has provided the opportunity for truly innovative companies to survive because they have cash flow - and as we all know cash is king. Companies quickly realised that, from the data on their processes, that the economics of testing were simple but ignoring the need for it is disastrous to the organisations wellbeing.

When working on a project I initially suggest to owners that some internal testing program is essential to their productivity, they immediately jump to the vision of a laboratory that cost millions of dollars to design, build and fill with expensive instruments run by PhD chemists, microbiologists and technicians. While there are some companies that have made this type of investment (typically over several years) that is not what is needed for everyone. The initial investment can be less than one hundred dollars, with a continued cost of under one thousand dollars a year to make a significant difference.

Chromatographic tools are available for analysis

Thin Layer Chromatography (TLC) is a great tool to start with. This is a simple and essential tool in synthetic chemistry laboratories providing quick and simple answers [1].

Gas Chromatography (GC) another simple analysis tool and can be acquired for between $20,000 and $80,000 depending on the capabilities and complexities of the instrument. GC, however will not allow the direct analysis of the acid forms of cannabinoids, as the heat used in GC will decarboxylate the natural compounds {2,3].

Liquid Chromatography (LC) another widely accepted chromatographic tool. This is more valuable than GC as it can measure the acidic and the neutral cannabinoids. This technology can be acquired in the $40,000 to $250,000 range depending upon the capabilities and complexities of the instrument and the required levels and precision and accuracy of analysis [4].

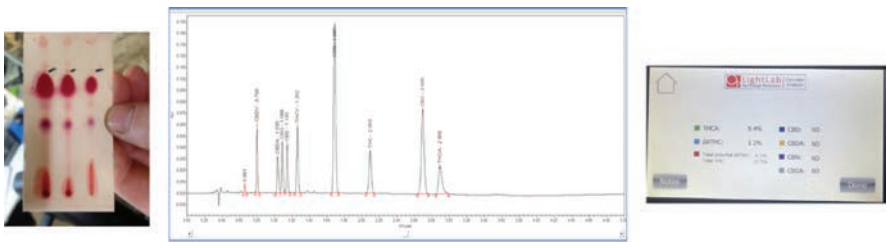

Figure 1. Comparison of typical TLC, Ultra High-Performance LC, Low Pressure Liquid Chromatography.

Supercritical Fluid Chromatography (SFC) is method that is being increasingly used in cannabis science because of the reduced sample preparation and transition into isolated compound collection. Recent work has compared the use of HPLC and SFC as techniques for Cannabinoid quantitation [5].

Remote Friendly Techniques to Use in Field and Laboratory

Many of the tools referred to above are designed for laboratory use. If testing at outdoor growing facilities is required a portable technique will be required. TLC is viable when looking for general non-quantitative results, and transportable GC and LC instruments are now becoming available.

Figure 2. Example of mobile chromatography system (permission of Light Lab, Orange Photonics).

The Need for Chromtographic Testing and Cannabis Productivity

Needed to determine production losses at every step.

In cultivation, when is the best time to harvest the plants? By testing the cannabinoid concentration each week, it possible to harvest at the optimal time rather than waiting. The optimal drying time for each of the plant varieties can be evaluated in the same manner.

Extraction of cannabis using supercritical fluid carbon dioxide (CO_2) is a simple process. With supercritical fluid CO_2 extraction, the yield is the challenge and is dependent upon on the pressure, temperature and flow rate conditions. Most extractions produce a yield of 90%.

There are subtle processing variations, but in its simplest workflow processing occurs after the plant has been harvested and dried. The plant is then ground to about the size of a typical coffee grind and the material is placed in a large vessel between 5 and 25 litres in size that hold between 2 Kg to 10 Kg of dried plant material. The vessel is pressurised to between 1,200 and 5,000 psi of CO_2. This pressure of CO_2 is sufficient for the cannabinoids to be soluble and move from the plant to the CO_2 stream passing through the bed and then transferred to collection vessel.

With such an easy process what could possibly go wrong?

The most common enemy in the process is channeling which can occur in any process and is best described as the CO_2 taking the path of least resistance through the bed. The yield, because of channeling, will never reach 100% as the CO_2 continues to flow down the path where material has already been extracted, leaving islands of the bed material unextracted.

Another common enemy is stopping the process before it is completed. This occurs for many reasons, such as a difference in the extraction ratio of cannabinoids and other components in the matrices such as terpenes, waters, waxes, etc. from one extraction batch to another.

The example shown in *Figure 3* after an extraction by flowing the CO_2 from the bottom of vessel and exiting the top shows the colour differential between the top and bottom of the bed. The lighter coloured material has been extracted and the upper material has not bee extracted to completion.

It is also important to note the lack of homogeneity of the bed material, again reducing the extraction efficieny and yield.

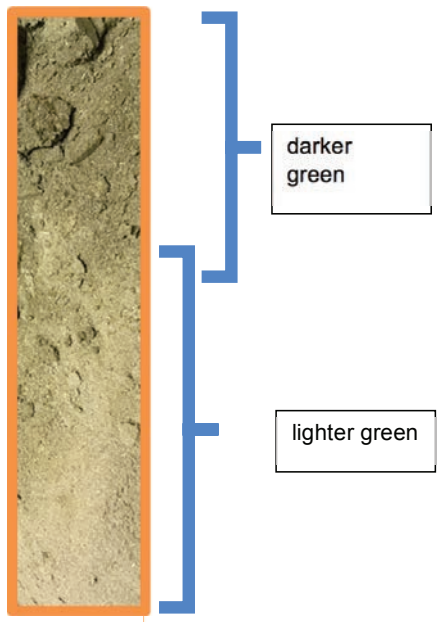

Figure 3. Post extraction photograph of the bed showing the colour of the bed material being lighter at bottom than the top.

By utilising in-house testing and taking samples, from locations within the different sections of the bed, it is possible to identify areas of poor CBDA extraction efficiency quantitatively. For example a starting material had an 18% CBDA potency prior to extraction. Samples were taken from nine different locations in the vessel. Results showing a significant amount of CBDA material still in the extraction vessel may be obtained as shown in *Figure 4*.

What is the challenge? The bottom third of the bed showed good extraction efficiency. From there the CO_2 found its way preferentially to the left side of the vessel resulting is an extraction difference on the left versus the right side. The top third of the vessel poorly extracted. With a starting 18% potency the bed is between 30% and 45% extracted.

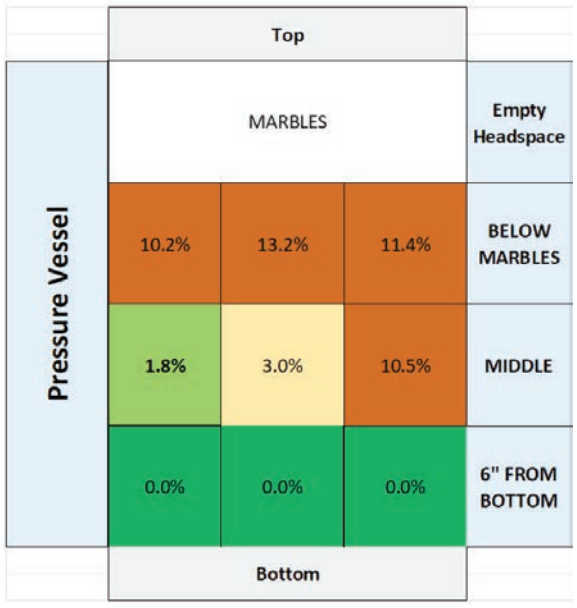

Figure 4. Test of eluent from CO_2 extraction. Showing variances depending on bed position.

Considerations for extraction efficiency improvements

The direction of flow, or the change of flow during the extraction process.

Is there Non-consistent flow throughout the vessel?

a. Is there a difference in the percentage from the bottom to the top? The extraction may not have run to completion. For example, there may be less than 1% CBDA left on the bottom and as much as 10% left in the top and 4% in the middle.

b. Is there a difference in the percentage between the three, with the middle having a higher percentage than the top and bottom? This would infer there may be channeling in the middle of the extractor, losing valuable material.

c. Is there a difference where material near the side at the bottom of the vessel is higher than the middle? The flow material into the vessel is not reaching the sides.

Was the flow consistent throughout the vessel?

a. CBDA values over 10% means the extraction was not run. In this case 50% of the CBDA remains in the starting material.

b. All tested values are less than 1% CBDA? The extraction was complete. This result provides a potential opportunity to reduce the extraction times (with this variety of plant) with a resulting daily output increase.

These analyses can then be performed for the dewaxing and distillation processes in the same manner by testing the feedstock prior to and after dewaxing and distillation.

A recent paper examined this experimental approach by utilising UHPSFC chromatography to monitor the extraction method and each phase of the workflow [6].

After changing the extraction conditions, the second experiment showed improved extraction efficiencies and reduced CBDA residue levels *(Figure 5)*.

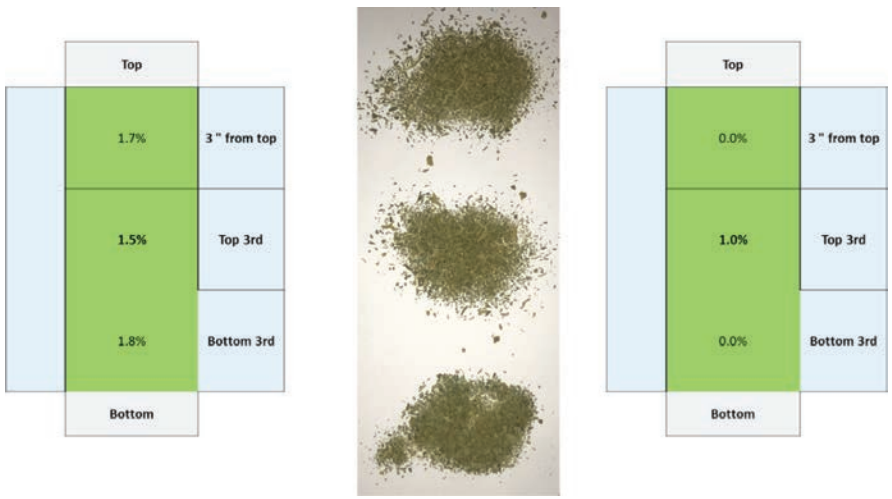

Figure 5. Testing of eluent after changing conditions. The table on the left shows some material still present in the extracted bed but within expectations. The table on the right shows no residual material therefore going to completion. The material in the middle looks the same.

Conclusions

There are many quotes about having real fact-based results versus general observations, most attributed to Dr W. Edwards Deming. I could not pick just one to summarise this article. So, I will leave conclude with my own, "'Good' is not a number.'" "'Fast' and 'Faster' are not official units of measure to accurately describe the rate of process." and "'A lot" cannot be used to accurately or precisely describe yield in a workflow."

There are more and more analytical tools being developed to permit the monitoring of efficiency and pesticide residue values throughout the workflow. Not having these in any facility results in an efficiency and financial loss.

There is a continued need for the expansion of applications in this area and the accompanying areas of natural products and dietary nutritional products.

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