Industrialization and Scale-up of Cannabis and Hemp Processing Using Sub- and Supercritical Fluids

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1. Introduction

The cannabis and related hemp industry have a significant impact as measured in terms of revenue to national and local municipalities. In 2021, $24 billion of sales of cannabis and hemp products were realized in the USA and $3.8 billion in Canada. [1] Over the last decade the scaleup of this industry has grown exponentially particularly with respect to the magnitude of the greenhouse- and field-grow operations resulting in tactically and strategically different approaches to extracting and processing cannabis-hemp, e.g., over 2000 SC-CO_2-based extractors of different scales and design to serve the above needs (over 25+ new companies have originated in this time period to fulfill these production requirements). This presentation is based on this researcher's consulting and educational activities in this field from 2014-2022. [2]. This presentation will cover the following topics:

- Innovative approaches employing sub- and super-critical fluids utilizes in the extracting and downstream processing of cannabis and hemp
- Scaling of the processing extraction equipment commensurate with the scale of cannabis and hemp biomass being processed
- Approaches to address synthesis, isolation, and purification of new "minor" cannabinoids such as Δ^8THC, Δ^{10}THC, CBN, CBG, CBC, CBDV, THC-O and THCV
- The resultant cannabinoid end-products that can be achieved, including cannabinoid mixtures having specific physiological benefits as well as combinations with other SFE natural products

2. Materials and Methods

The choice of extraction media to apply in cannabis/hemp processing has centered on the "big three": extraction solvents: propane-butane, CO_2, and ethanol [2-5]. Each of these media produce industrially marketable extracts or eventual products; CO_2 because of its merits is widely cited on marketable end-products. However other solvents have been applied in cannabis extraction, namely DME [6], R134A, chlorofluorocarbon options, and water - which may have certain advantages. Use of R134 (fluoroform) can for example, extracts 100-fold less co-extracted lipids relative to the "big three" solvents. The use of water whereas might seem to be inconsistent based on solute-solvent solubility considerations, however it has been applied in several extraction formats, in part because it allows in-situ decarboxylation of the acidic forms of cannabinoids [7], emulates the steam distillation of terpenes and allows the room temperature separation of the resultant aqueous phase from the immiscible extracted phase. These aqueous-based formats include subcritical water extraction, PSE, and continuous biomass feed systems, such as the spinning disc reactor and potential of the applying the Dox/Hivex ™ system – which is based on subcritical water.

The non-specificity of the "big-three" extraction media tends to produce an extract having a high content of non-polar co-extractives, i.e., lipids, waxes, naturally-occurring pigments. To overcome this problem, companies selling extraction units have resorted to improved extraction conditions aided by incorporation of in-situ adsorbent beds to enrich the cannabinoid/terp content of the extraction critical to the appearance and effectiveness of a "full spectrum extract". This is the basis of the Green Mill Corporation's "Real Time Winterization™" methodology where specific extraction conditions allow the production of an extract not requiring post-extraction remediation. In-situ adsorbents, within the extraction vessel, i.e., the process analogue of MSPD as well as segmented sorbent beds in series with the extraction vessel permit color improvement in the result extract.

Aside from traditional cannabinoid biosynthesis and decarboxylation of the cannabinoid acid forms, new so-called "minor cannabinoids" can be generated from cannabis or hemp extracts [8]. Isomerization of

Δ^9THC to Δ^8THC is incurred in acidic media + heat; similarly isomerizing Δ^9THC under basic conditions yields the two diastereomers of Δ^{10}THC which can be further separated by chiral-based chromatographic procedures. Of keen interest if the isomerization of CBD in hemp extracts to Δ^8THC under acid conditions resulting in a quasi-legal product of lower potency than Δ^9THC. The well-known conversion of Δ^9THC to cannabinol (CBN), accelerated by oxygen and light can be modulated under appropriate temperatures to provide a mixture of Δ^9THC + CBN, including in-situ decarboxylation from Δ^9THCA.

In addition to integrating adsorption media into the SFE of cannabis/hemp, supercritical fluid chromatography (SFC) has been successfully applied to isolate specific cannabinoids (CBG, CBC, CBD) at high purity using CO_2 + co-solvents [9]. A number of large-scale chromatographic techniques have been applied to produce purified cannabinoids, specifically our research has demonstrated the feasibility of ethanol-modified normal phase chromatography. Elution in these chromatographic methods can be correlated with the cannabinoid logP values. [10, 11].

3. Results and discussion

Utilizing the techniques described in the Materials and Methods section, cannabis/hemp processors today employ multiple extraction methods such as: propane-butane + CO_2, ethanol + CO_2 and butane + ethanol to provide different extracts for the end user. One example is the Vantage Hemp facility in Greeley, CO consisting of 60,000 ft^2 total production space which has 6-2 columns- CO_2 extractors and a separate 25,000 ft^2 facility for hydrocarbon-based extractors (2units-6 columns), which realizes the processing of 5.5 tons of hemp biomass/day. A similar large scale processing facility (100,000 ft^2/$65-million-dollar investment) at HempRise in Jeffersonville, IN is scaled to process 3.5 million kg of biomass annually.

A variety of new products types/compositions have resulted from the methodology previously noted. For example, extract-products have been produced containing both pure (Δ^8THC Δ^{10}THC, CBG, CBN, THCV, HHC), mixed cannabinoid content as CBD + Δ^8THC, CBC + Δ^8THC, CBD + CBG, CBD +CBN, CBDA + CBD, Δ^9THC + Δ^8THC, THCV + Δ^8THC, CBN + Δ^8THC, CBG + Δ^8THC and 3- and 4-component mixtures such as CBD + CBG + CBN; CBD + CBC + CBG + CBDV. These are produced by the aforementioned reaction chemistries or purified usually by chromatographic methods such as SFC.

The high CAPEX costs associated with supercritical fluid extraction equipment suggests its use can be optimize by applying it for non-cannabinoid-containing extracts, particularly those utilized in combination with cannabis or hemp extracts in final product formulations. For example, the use of sub- and super-critical carbon dioxide can be used to extract seed oils, essential oils, natural antioxidants, etc. that are used in the formulation of the final cannabis or hemp derived product. Pertinent examples include rosemary, turmeric, ginger, curcumin, lavender, omega fish oils, COQ-10, etc. will be cited along with both commodity and specialty TG-based oils. These can be accomplished at CO_2 pressures < 340 bar consistent with the pressure imitations “newer” extraction equipment vendors offer for sale [7].

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