The cannabis industry exists in a Wild West environment, where state law-abiding scientists and fringe characters operate under a variety of conflicting regulations. This article describes that world and provides advice to formulators on the science of developing medicinal cannabinoid products.

For ages, cultures all over the world have recognized the medicinal value of cannabinoids and they were widely used that way in the USA until about 1937. Yet in recent years, both medicinal and recreational cannabinoids have become a growth industry. How, why, and when things changed is beyond the scope of this article, which instead discusses some of the scientific considerations of formulating cannabinoids into tablets and capsules.

As you probably know, the human body has endocannabinoid receptors that respond to phytocannabinoids and synthetic cannabinoids. The market seems to have similar receptors because today cannabinoids are a big growth industry in the USA, one many people liken to the Wild West. That is an interesting analogy and somewhat true. There are good guys—that’s us on the pharma side—and outlaws. Several high-tech companies are providing excellent products with filed intellectual property to support them. The outlaws include black
market actors and fly-by-night peddlers of formulations made without scientific work and promoted with false claims. In addition, the regulations governing the industry vary from state to state.

So the cannabis industry is a hybrid, growing where the nutraceutical and pharma markets overlap and where regulations conflict. That suits me because I like to be where the action or growth is, so after 25-plus years working in mainstream pharma, I leapt into the world of cannabis. I now work for a company that is striving to make better products that are proven by science in order to secure market share. What follows is some of what I’ve learned.

Some facts about the active

Let’s start at the beginning, the active pharmaceutical ingredient (API). What is its nature? By today’s standards, it’s a fairly ordinary one: Insoluble (1 to 2 micrograms per milliliter) [1], with poor absorption, and available in a variety of physical states ranging from stable oil at about 55 to 65 percent purity to 99.9 percent pure crystalline material that is subject to degradation from air and light.

There are too many cannabinoids to address here, but a couple popular ones are delta-9-tetrahydracannabinol (THC) and cannabidiol (CBD). A popular API form of cannabis is a 65 percent pure mixture of THC and CBD, with the balance (35 percent) being terpenes, plant waxes, other plant compounds, etc. As anyone working in the nutraceutical arena knows, there are a variety of issues with plant extracts, including their very sticky nature and hydrophobicity. Isolating the oil from the plant is commonly done by supercritical fluid extraction (SFE) using CO₂ or by ethanol extraction. The oil is then processed to remove the plant waxes and decarboxylated to convert the acid forms of the phytocannabinoids to more usable forms.

Formulating tablets and capsules

So, we have the API in an oil form that’s pretty easy to fill into capsules, right? Well, kind of: Once I got to talking with long-time contacts in the capsule area, I hear, “We can’t do business any longer,” due to the nature of my company and API. Nothing personal, they tell me, they just don’t want any assets frozen or taken by the federal government. “Oh, and good luck.”

But we did find companies that would do business with us, and after buying some capsule shells and liquid capsule fillers, we’re all set, right? Not exactly. While the majority of THC capsules are indeed simply filled with oil, there is room for improvement. For that, we turn to a variety of materials and strategies to enhance absorption.

One approach is to make an emulsion or a self-emulsifying drug delivery system (SEDDS). I’m not at liberty to divulge the specifics of our formulation methods, but even people with no experience in this area could figure out some strategies after searching the literature.

What about capsule leakage? Although most cannabis-based capsules on the market today use straight THC-CBD oil, few cannabis manufacturers, I suspect, have a capsule bander and have likely never heard of one. And that’s OK if your formulation is a semi-solid capsule like ours and not prone to leakage. Other companies dilute the THC-CBD oil with medium-chain triglycerides (MCTs) such as coconut oil or with polyethylene glycol (PEG) to improve the filling characteristics. Yet others add powder to the oil and market their products as leak-free. At the other ends of the spectrum are full-fledged pharma formulations with a list of chemicals that the average cannabis customer doesn’t recognize and formulations that use pure plant materials with no additives, which a variety of patients prefer, even though there are many safe, effective additives that would enhance absorption.

So much for capsules. How about tablets? First, let’s specify the API load. But there is no agreed-upon dosage of cannabinoids for a tablet or a capsule. It varies from state to state and country to country. That’s what you get when states take jurisdiction from the federal government for a Schedule 1 substance. Odd, isn’t it? In New York, my home base, 10 milligrams (mg) is the maximum allowable dose for cannabinoids. Tablets are the same dose in Colorado and because Colorado law caps the amount of cannabinoid per package at 100 mg, they market 10 of these 10 mg tablets in a bottle. Other states have different laws, so it gets complicated. (We got our capsules to market after undergoing a review by the New York government and without sending a truckload of paperwork to the FDA.)

Fortunately, 10 mg of API (about 17 mg of oil) is not too tough to deliver. Or is it? At about 65 percent purity,
cannabis oil is a bit viscous, but nothing that a little heat won't cure. And while loading oil into powders is certainly not mainstream, it's nothing new. Any formulators worth their weight in microcrystalline cellulose should be able to load 17 mg of oil into a tablet that people can still swallow. In fact, a variety of materials are a perfect fit for the task, including specialty silicas, cellulosics, and even lactoses. Just don't hit the formulation too hard on the tablet press or you will express the oil right out of the tablets and make a mess.

**Modifying the API**

Are we happy to have formulated a stable 65 percent pure oil into a tablet? Sure, but once again there's room for improvement in solubility/absorption, tablet size, etc. The first step is to purify the API. Who wants 35 percent of miscellaneous compounds in their API, especially compounds that haven't been identified and may not do anything in the formulation? Actually, a lot of people want just that, seeking what's been dubbed the “entourage effect” [2].

The idea here is that those non-API compounds work together to provide superior therapeutic results. That has not been scientifically proven for this plant extract or any indications, but the people we know as “label readers” in the nutraceutical market believe it's the way to go. Regardless of your thoughts on “natural versus chemical,” when it comes to plant compounds, we must make some effort to purify the API. For $100,000, I can get a wiped-film evaporator and distill my API to better than 90 percent purity, which we call distillate.

THC and other cannabinoids at 90 percent purity are very viscous liquids or semisolids at room temperature. Distillate is often preferred for its clarity and purity and is still a candidate for a SEDDS formulation. Heated to near 100°C, the distillate's viscosity decreases and it becomes more liquid, but keep in mind that heat and oxygen promote degradation. For insight on mitigating that, break out your excipient handbook or call some colleagues to reacquaint yourself with preservatives and stability enhancement. As with oil, distillate can—with difficulty—be loaded directly into capsules or, preferably, diluted with coconut oil, other medium-chain triglycerides, or liquid PEG and handled as a viscous liquid.

Making tablets by loading this very viscous API into a powder, however, is not widely practiced. But where there is a will—or significant incentive—there is usually a way. Just don't expect it to happen in your production V-type blender.

With increasing purity comes smaller dosage forms. If we're filling capsules, we just go to a smaller capsule. But be quick about filling them so you don't expose the API too long to high temperatures because it may degrade. For 10 mg tablets, which I don't consider “low dose” in the usual sense, you still need to pay attention and use a sensible approach. That includes using materials that blend well so you can use low-dose and geometric blending techniques. Also consider using a very, very wide particle size distribution to help stabilize your content uniformity.

**Formulating with CBD**

Because CBD does not have the legal implications of THC—it has no psychoactive implications—many more formulation strategies are available. CBD exists as an oil at lower purities, a wax at higher purities, and a crystalline solid at its highest purity. Much of the CBD found on the market is isolated from hemp instead of cannabis, so it contains much less THC and other cannabinoids. Purified CBD crystals are commercially available as a 99.9 percent pure material. This is great if your state’s regulations allow you to source and use these materials. At my company’s New York operation, we cannot use any cannabinoids unless we isolate them directly from plants that we ourselves have grown at a state-approved facility. Any additives we use must meet USP/NF standards.

Formulating CBD tablets can be straightforward if you use the crystalline form of the API. Here again, higher purity may equal lower stability depending on your formulation, so use conventional stability enhancement methods and sensible packaging.

Many people are interested in formulating particular cannabinoid profiles, and many of the formulations on the market have THC-to-CBD ratios tailored to offer certain effects or meet specific indications. Ratios such as 1-to-1 or 1-to-15 are thought to offer benefits for certain indications or prevent psychoactive effects while remaining effective. If local regulations allow, you can add crystalline...
CBD can be formulated in many ways, including tablets, capsules, tinctures, sublingual sprays, and 'vape' cartridges. Inhaling the vapor emitted from heated oil formulations—is a popular alternative to smoking. SEDDS-based products and liposome-based sublingual sprays also provide rapid onset. **A word about regulations**

Cannabinoid regulations are complicated because every state has its own rules. Federal law prohibits the transport of cannabinoids across state lines, so any company that plans to reach markets beyond its home state must install production equipment locally. It is not possible to manufacture and distribute from a central facility.

As a result, manufacturers must build a suite in each state they seek to serve. This can get expensive fast because it means buying five production-scale encapsulation machines instead of one. In addition, not all markets embrace all dosage forms, and it’s the customer who ultimately dictates what products get formulated and what they include.

I’ll conclude with this fact: From 1911 to 1933, more than half the states in the USA passed laws banning cannabis. But the federal government took no action over that period. Today, the same states that were first to ban cannabis are the first to legalize it and many allow a recreational market even while a federal ban remains.

**Beyond solid dosage**

There is a variety of cannabis products that aren’t tablets or capsules in both the medical and recreational markets. As a medicine, cannabis is available only with a recommendation or prescription from a physician. In recreational markets, anyone can get cannabis. Both markets have standards for impurities and residual chemicals, such as pesticides and hydrocarbons. Edibles are very popular in the recreational market but require significant dosing due to the pharmacology of cannabinoids. Most other products, regardless of the market, are liquids and include tinctures, sublingual sprays, and “vape” cartridges. Inhalation is probably still the most popular method of taking cannabis. Many people smoke the flowers, but that is not an option for some patients. As with tobacco, many people opt not to inhale smoke into their lungs, even though inhalation offers the most rapid onset and makes it easy to control dosing. That’s why vaping—

**References**


David Schaible is the senior product development and formulating chemist at PharmaCann. E-mail: david.schaible@pharmacann.com. Prior to his work in cannabis, Schaible spent more than 25 years in the generic, drug delivery, and excipient industries. He has been invited to speak domestically and abroad about excipients and cannabis. He holds several patents and is the author of several articles, posters, and papers.