



Advantages of
Soft Gelatin Capsules Dosage Form,
in the Manufacture Of Cannabis-based Products.

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Introduction

Cannabis-based products are manufactured, mainly, from oils obtained from a synthetic way as Dronabinol or obtained from plants of genus Cannabis, as Cannabidiol (CBD) oils [1]. The oils of medicinal-grade cannabis can be delivered using different dosages forms such as: tinctures; inhalant; pills, liquids gel, oils, creams, patch; Chewing-gum; capsules, among others [2, 3]. Selecting the appropriate dosage form plays an important role in the success of the drug product because the dosage form selected should be able to protect the drug substance during all the shelf life and also facilitate its handling and administration to the patients [4]. This paper refers to Cannabis-based products manufactured in soft gelatin capsules. First, the paper shows a brief information of cannabis base product and then the characteristics of the Soft Gelatin Capsules (SGC) as dosage form and its advantages to be used as the primary dosage form to develop cannabis-based products.

Cannabis-Based Products

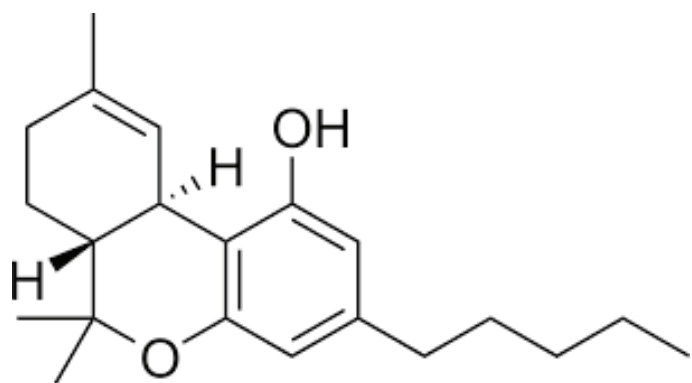


PLANTS OF CANNABIS

Plants of genus *Cannabis* (Family Cannabaceae) have two primary species: *Cannabis sativa* (Hemp) and *Cannabis Indica* (Marijuana) [5]. Marijuana is a controlled substance used as a recreational drug, while hemp is an industrial material used in the industry of textiles, paper, among others [6]. Although, scientific commonly accepted *Cannabis Sativa* as the scientific name for all cannabis species [7], they have differences in the chemical composition, specifically in the proportion of delta 9-tetrahydrocannabinol [THC] that they present.

DELTA 9-TETRAHYDROCANNABINOL AND CANNABINOIDS

THC is the intoxicating compound of marihuana, responsible to get the user high and to generate the psychoactive effects [8]. In the USA, the Agriculture Improvement Act of 2018 uses the difference in the proportion of THC to separate marihuana (controlled substance, schedule I) from hemp (not controlled substance) [9]. This Act defines hemp as a cannabis and cannabis derivatives with very low concentrations (no more than 0.3% on a dry weight basis) of THC [9]. However, these limits change for each country, for example, while Italy and Sweden [10] use more restrictive levels of THC (0.2%), other countries such as Colombia [11] and Ecuador [12] use wider limits (1%). 9-tetrahydrocannabinol [THC] that they present.



CANNABIS-BASED PRODUCT COMMERCIALIZED

Table 1 shows a summary of the current Cannabis-based Product Commercialized. This table includes the dosage form, the main active ingredient and the country which is commercialized. Additional products can be found in [13] and [14]. Additional information about regulatory requirements of Cannabis-based Product can be found in the 2020 Global Report on Cannabis Policy - World Law Group [15]



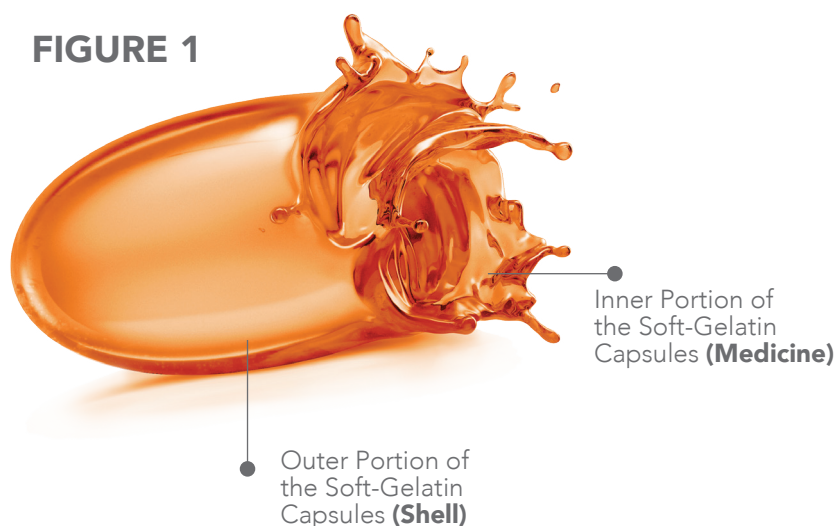
TABLE 1

DESCRIPTION	CANNABIS-BASED	USES	COUNTRY	DOSAGE FORM	COMPANY
Marinol® (dronabinol)	Synthetic Δ-9-THC	Anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS). Nausea and vomiting associated with cancer chemotherapy	USA	Capsule (Soft capsule)	AbbVie
Dronabinol	Synthetic Δ-9-THC	Anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS). Nausea and vomiting associated with cancer chemotherapy	USA	Capsule (Soft capsule)	Manufactured by PROCAPS for Akorn, Inc
SYNDROS (Dronabinol)	Synthetic Δ-9-THC	Anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS). Nausea and vomiting associated with cancer chemotherapy	USA	Solution	Insys Therapeutics, Inc
Cesamet® (nabilone)	Synthetic Δ-9-THC	Anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS). Nausea and vomiting associated with cancer chemotherapy	USA; Canada; Europe	Capsule (Hard Capsule)	Bausch Health US LLC
Epidiulex (cannabidiol)	Cannabidiol from plants	Treatment of seizures associated with Lennox Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC)	USA	Solution	Greenwich Biosciences, Inc.
Sativex (Delta-9-THC/ cannabidiol)	Cannabidiol from plants	Indicated as treatment for symptoms improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS).	Approved in more than 20 countries (UK; Europe, Canada, Latin America, etc)	Spray	GW Pharma (International)
Neviot	Cannabidiol from plants	Indicated for the treatment of seizures associated with Lennox Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC)	Colombia	Solution	Procaps

ADVANTAGES OF SOFT GELATIN CAPSULES DOSAGE FORM, IN THE MANUFACTURE OF CANNABIS-BASED PRODUCTS

Compared with other dosage forms, SGC is the best option to deliver non aqueous vehicles [16], such as those needed for Cannabis-based products. This is due because SGC's offer a high number of advantages such as [16, 17]: bioavailability of a poorly soluble compound; protects the encapsulated compound against oxygen and light; improves swallowability, masks odors and unpleasant tastes, improves the accuracy of the dose, is a tamper-evident product which difficult its counterfeit and finally it can be coated with suitable exterior coating agents to obtain an enteric release.

FIGURE 1



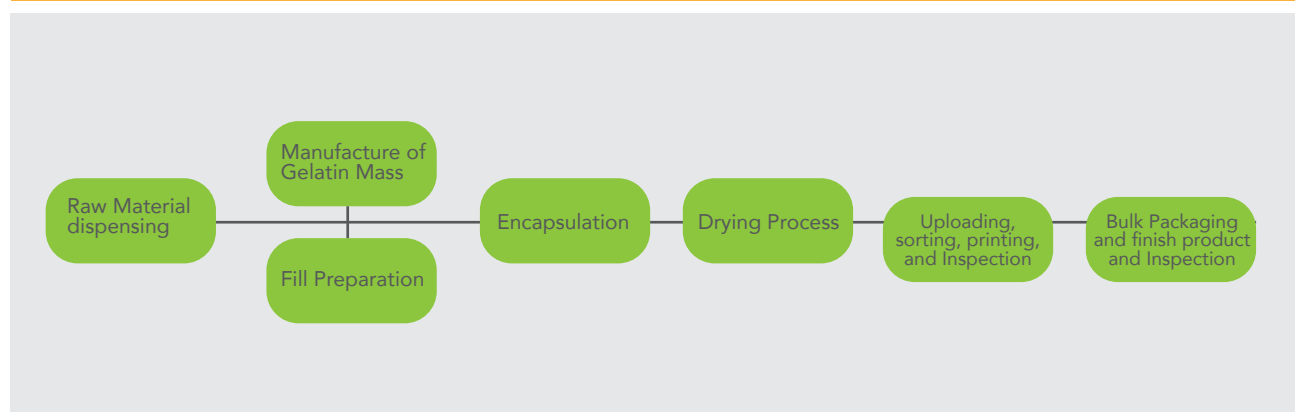
A SGC (See Figure 1) is a one-piece of capsule hermetically sealed containing liquid, suspension or semi solids fill [16, 18]. It is a dosage form that is formed by an outer portion, the shell and an inner portion of Medicine (fill of the soft gelatin capsule). The shell is formulated with gelatin, a plasticizer and water. In addition, the shell also can contain additives like colorants or flavors. The Medicine contains the APIs and the excipients needed to prepare the solution, suspension or emulsion, which are the fills typically used in SGC.

One of the advantages of using SGC for Cannabis-based products is its capacity to protect the cannabis oil from oxidation and other factors such as light, during the manufacturing process and during its shelf life. Figure 2 shows the manufacturing process of SGC. In SGC, the shell formula and especially the plasticizer source and concentration should be adjusted to improve the characteristic as water vapor permeability, oxygen permeability and volatile solute permeability [16], which are indispensable to protect the Cannabis-based products, overall oils which are very sensitive to oxidation.

Cannabis oils and other oils used in the manufacture of SGC are very sensitive to oxidation and therefore, it should be protected, from the oxygen, during the processes that include raw material dispensing; fill preparation and encapsulation. For dispensing, a glove box could be used to remove the air and use an inert gas (i.e. nitrogen or argon) to perform the dispensing process. This minimizes drug substance exposure to the oxygen and therefore the oxidation process. For other raw materials, such as the other oils used in the manufacturing process, the dispensing process could be performed using a blanketing or purging with an inert gas (i.e. nitrogen or argon) to perform the dispensing process.

This minimizes drug substance exposure to the oxygen and therefore the oxidation process. For other raw materials, such as the other oils used in the manufacturing process, the dispensing process could be performed using a blanketing or purging with an inert gas. This is used to remove the air over the raw material reducing the oxygen exposure. On the other hand, fill preparation should be performed protecting the raw materials (mainly the drug substance) from oxygen exposure. For this, drug substance premix and/or blanketing or purging with inert gas can be used. In addition, to minimize the oxidation risk, a hermetically closed reactor tank should be used and the fill should be transferred from the manufacturing reactor tank to the storage tank using a closed system to avoid oxygen exposure. Finally, during the encapsulation process, a closed system should be used to transfer the fill from the storage tank to the hopper of the encapsulation machine. The hopper should be equipped with a level sensor to fill it automatically once the fill achieves a specified level. In addition, a blanketing or purging with inert gas should be used in the hopper to avoid oxygen exposure.

FIGURE 2. MANUFACTURING PROCESS OF SOFT-GELATIN CAPSULE



On the other hand, it is widely known that Cannabinoids are metabolized in the liver [19, 20], for this reason the manufacture of oral dosage form offers a big challenge because it should avoid the first pass effect in its metabolism of the drug product. This is one of the most important advantages of SGC in the manufacture of Cannabis-base products. Using SGCs it is possible to formula the drug substances using Lipid Based Formulations as self-emulsifying drug delivery systems (SEDDES) and Self-microemulsifying drug delivery systems (SMEDDS) [21]. SEDDS and SMEDDS can be formulated using for example surfactants, co-surfactant and lipids which could contribute to the overall improvement in oral bioavailability via promoting the lymphatic transport and avoiding the first pass effect in its metabolism.

Another advantage SGC's offer is its versatility, since it can be modified to get other commercial characteristics which could be favorable for specific groups of population, some of these modifications that we can offer are:

- Versagel™ (Vegetarian soft capsules)
- Enteric Coated Soft Gelatin Capsules
- Twist-off Soft Gelatin Capsules
- Chewgels (Chewable softgels)
- Unigel™

VERSAGEL™

Compared with other dosage forms, SGC is the best option to deliver non aqueous vehicles [16], such as those needed for Cannabis-based products. This is due because SGC's offer a high number of advantages such as [16, 17]: bioavailability of a poorly soluble compound; protects the encapsulated compound against oxygen and light; improves swallowability, masks odors and unpleasant tastes, improves the accuracy of the dose, is a tamper-evident product which difficult its counterfeit and finally it can be coated with suitable exterior coating agents to obtain an enteric release.



ENTERIC COATED SOFT GELATIN CAPSULES

The best way to stabilize acid-sensitive drug products, to improve tolerance, to delay onset of action and to reduce aftertaste.

- Protect acid-labile APIs

Avoids gastric irritation and reflux because the API is not delivered in the stomach (especially desirable for APIs like fish oil or garlic oil)

Target drug delivery in the small intestine which is preferred to treat intestinal disease

TWIST-OFF SOFT GELATIN CAPSULES

A soft gelatin capsule with twist-off cap allows access to a measured dose. It can offer more accurate dosing than sublingual and oral products administered using a dropper with a marking at a specific volume (usually 0.5 ml or 1.0 ml).

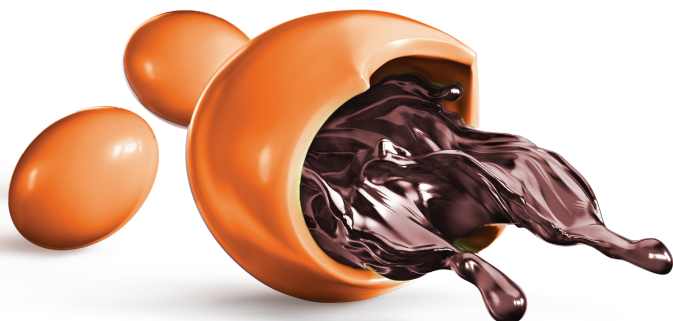


CHEWABLE SOFTGELS

With new ingredients, special shapes and flavors, this new concept in Chewable softgels as a solution and line extension to existing products.

Characteristics:

- Conveniently administered **without water**.
- Portable dosage form that **eliminates messy liquids**.
- Pleasant tasting helps **mask tastes and odors**.
- Can be formulated in a **range of textures**.
- Increasing acceptance by **patients, adults and especially children**.



UNIGEL™

Unigel™ is the only patented technology for fixed dose combinations that incorporate the benefits of soft gelatin capsules.

Benefits of Unigel include:

- Single or Multiple active ingredients with different release profiles (sustained and immediate) and release sites (gastric and intestinal).

- Multiple active ingredients with chemical incompatibility concerns.

- Multiple active ingredients where at least one is a liquid or a semisolid.

- Any combination of the above.

- Reduces the number of drug intakes, increasing patient compliance.

- Patent challenge opportunities in a new dosage form.

- Life cycle management extensions.

- Highly differentiated consumer product appeal.

- Available in different sizes and shapes



Conclusions

Soft Gelatin Capsule can be one of the most important dosage forms to be used in the administration of cannabis-base products, because SGC's offer extra protection during the manufacturing process and during the shelf life to protect it from stressing condition and the oxidation by air. In addition, the versatility SGC's offer allows the preparation of a portfolio of products with different SGC technologies useful to cover different markets and different groups of population. However, the most important advantage is that the product in SGC can be formulated to avoid the first pass effect in its metabolism and improve the bioavailability of the cannabis-based products.

Finally, but no less important is that Procaps have more than 43 years developing SGC in all its presentations (Versagel®; Enteric Coated Soft Gelatin Capsules; Twist-off Soft Gelatin Capsules; Chewgels® and our patented technology Unigel®. In addition, Procaps have experience developing and manufacturing Rx and OTC products for highly regulated markets such as USA, Europa, Canada, etc, including cannabis-based products.

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