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WHITE PAPER

CANNABINOIDS

Therapeutic effects and the advantages of soft capsules as appropriate dosage form

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1 HISTORY

Cannabinoids, a historical review

The history of cannabis is almost as old as humanity itself (1,2). Cannabis or hemp plant has grown in almost all parts of the world, but its use has been limited to the manufacture of textiles and rope (3).

The geography plays an important role in the usage and spread of cannabis as a curative plant. As the content and the ratios of the cannabinoids in the resin do vary with the sun exposure, only highly exposed and humid regions had the right pharmacologically active drug content.

Knowledge and therefore spreading of the use seems to have started in the Himalayan region of central Asia, going to India, Asia Minor, North Africa and across the desert to sub Saharian Africa and the rest of the African continent (4,5,6). In India the plant was used mainly for social (during family celebrations like marriages and birth, to induce a relaxing mood and to induce appetite) and religious reasons (most notably the festival of Durga Puja). Also the way of usage was different: *bhang* was taken by mouth whereas *ganja* was smoked. The strongest preparation *charas* (known elsewhere as hashish) was not socially approved and the users where regarded as “bad characters” or outcast.

Therapeutic use of cannabis

In India cannabis was also used in the traditional Indian medicine and many of the therapeutic uses were similar to the claims made today: sedative, relaxant, anxiolytic and anticonvulsant actions, all of which also made it useful in the treatment of alcohol and opiate withdrawal, analgesia, appetite stimulation, antipyretic and antibacterial effects, and relief of diarrhea (7).

The introduction of the drug effects on cannabis into Europe started in the 19th century. Whereas in England the pharmacological effects where predominant, in France there was more interest in the psychoactive effects. To mention is the “Club des Haschichins” which served the famous French psychiatrist Moreau de Tours as subjects for experiments on the effect of hashish in their writings (8, 9). Writers like Baudelaire, Gautier and Dumas seem to have used hashish as routes to aesthetic self-realization, as did Ginsberg and others in the Unites States over a century later.

In the meantime, in the UK cannabis was scientifically tested. O’Shaughnessy (10), who did work as a British physician in India sent supplies of cannabis to a pharmaceutical company in London. This supplies were used for clinical trials in cholera and “hydrophobia” (rabies) which led to the adoption of cannabis in the British Pharmacopoeia and later into the US Pharmacopeia, and were widely used in the English-speaking world as sedative, hypnotic and anticonvulsant agents in the late 19th and early 20th centuries (11,12). The fact that the plant material was too variable in composition, it’s shelf life too short and that pure opiates or new synthetic drugs were being invented led to the exclusion of cannabis from the British Pharmacopoeia in 1932 and the US-Pharmacopeia in 1941 (13). By that time its clinical use had disappeared, and its formal banishment was accepted.

2 REGULATORY

Cannabinoid products, rules and regulations

In the last decade medical cannabis has seen an exponential market growth over all five continents. Unfortunately, the regulatory framework has not been able to keep up with the widespread of cannabis and its uses. Whereas there is still a social component to the matter (the consumption of cannabis related products is still seen as not acceptable, depending on the geography and cultural roots) the medical benefits are undisputable.

The medical and therapeutic potential of Cannabis is recognized in 2020

The year 2020 has ended with two great news for the world of cannabis. First, a new judgment by the Court of Justice of the European Union (CJEU) on November 19 where the court ruled that cannabidiol (CBD) "cannot be regarded as a narcotic drug" and therefore the distribution and marketing of CBD should not be prohibited within the EU territory (14).

December 2, 2020, the United Nations voted on the recognition of the medicinal and therapeutic potential of cannabis and urged to remove this substance from Schedule IV of the Single Convention on Narcotic Drugs which includes the most dangerous substances with limited or no medical value, such as heroin (15).

Thus, from now on, cannabis should only be classified under Schedule I of the afore mentioned Convention, which includes substances that are addictive, are not so harmful to health and have a therapeutic value. However, this change in the classification will not have a great impact in terms of legalization since this reclassification simply means that the UN recognizes the therapeutic benefits and uses of cannabis.

Cannabis as a pharmaceutical product: regulatory frameworks

The framework for regulating cannabis as a pharmaceutical product varies widely across the world, though increased clinical research into cannabis products means more approvals are likely under way. It is currently a complex patchwork of approaches which are born out of national legislation rather than an overarching EU or European Medicines Agency framework. The same approach is valid for the United States, where states are passing medical marijuana legislation independent of federal action. Additionally, Canada has its own regulatory framework for defining and governing medicinal cannabis products.

Under international drug control treaties, the use of cannabis in the European Union is limited to scientific and medical purposes, and medicines are authorized through a number of different procedures.

Also, individual member states have different schemes for allowing patients to access unapproved medicines under medical supervision.

Under the current EU regulatory landscape, medicinal cannabis can go through one of three pathways. To become a licensed medicine, products must go through a Marketing Authorisation Application (MMA) process, which requires drug sponsors to demonstrate quality, safety and efficacy. Products can also be accessed under the compassionate/exceptional use process. This process may be used for magistral or extemporaneous products – classifications akin to compounded product - which must be prescribed by a specialist on a named patient basis. The third pathway is an expanded use scheme, which is specifically for patients with unmet clinical needs to allow them to access to medicines still in development. Meanwhile, EU member states have enacted various pieces of legislation to legalize medicinal cannabis use, with the Netherlands leading the way in 2003 and Ireland not passing legislation until 2019. But many regulatory challenges remain, including determining who can prescribe these medicines, how prescribing guidelines will be updated, and how patients will be monitored.

Cannabis as “novel food”: the discussion about the approval process

Cannabis products complexity does persist or is even more pronounced in the nutritional field. On December 2, 2020, the health division of the European Commission notified the European Industrial Hemp Association (EIHA) their decision that CBD may qualify and be regulated under food category, as the association explained the next day in a press release. However, this change in the criteria has not been officially published yet on the EU Official journal website by the European Commission, and cannabidiol is still included in the new foods catalogue or ‘novel foods’, a list of products that require a safety evaluation and official control before they can be marketed. Actually, as of today, it is indicated that there are applications for ‘novel foods’ in process.

Food supplements that do not require an approval process must be made exclusively from hemp seeds in the form of oils, hemp proteins or flours made with sativa strains with less than 0.2% THC (dependent on the state of manufacture and sale).

Currently in the United States, 33 states, including the District of Columbia, have legalized medical marijuana and 10 states, including the District of Columbia, have legalized recreational use. These laws contradict US federal law, where cannabis and CBD are considered a schedule I substance by the US Drug Enforcement Administration. The Farm Bill of 2018 removed cannabis and cannabis derivatives with very low THC content from the definition of marijuana in the Controlled Substances Act. If cannabis is going to marketed as having a therapeutic effect it must be approved by the US Food and Drug Administration for safety and efficacy. Dietary supplements go through a separate process and it is illegal to have a food supplement with CBD added or to market CBD as a dietary supplement. In July 2020, the US Food and Drug Administration issued draft guidance for industry on clinical research into cannabis and cannabis-derived compounds. Cannabis under the 0.3% delta-9 THC limit may be used for clinical research, according to the guidance.

Even if the current regulations are partly misleading, there is a clear path forward for pharmaceutical purposes: the development of cannabinoid drugs for medical use. For synthetic or natural cannabinoids with a clear origin and set specifications the pathway through clinical trials for well defined indications has the highest rate of possible success.

3 ENDOCANNABINOID SYSTEM

How cannabinoids influence the human body

The phytocannabinoids of the cannabis plant work in a similar way to our naturally produced endocannabinoids. The endocannabinoid system (ECS), unlike the central nervous system (CNS), peripheral nervous system (PNS), and circulatory system, is one of the most understudied systems in the human body. It has been documented that ECS is directly involved with various roles in apoptosis, neurotransmitter levels, and homeostasis (16).

ECS is a unique system in multiple dimensions. To begin with, it is a retrograde system functioning post- to pre-synapse, allowing it to be a “master regulator” in the body. Secondly, it has a very wide scope of influence due to an abundance of cannabinoid receptors located anywhere from immune cells to neurons. Finally, cannabinoids are rapidly synthesized and degraded, so they do not stay in the body for very long in high amounts, possibly enabling cannabinoid therapy to be a safer alternative to opioids or benzodiazepines.

The way endocannabinoids interact with the human body is a lock-key mechanism which interacts in different parts of the body or body functions, whereas the lock is the cannabinoid receptor (CBR) and the key the cannabinoid (CB).

Depending where the cannabinoid receptor (CBR) may be located it can influence different functions of the human body (see Figure 1).

Human endocannabinoid system

The most well-known cannnabinoid receptors, CB1 and CB2, are proteins that are imbedded in the membrane of cells. These surface proteins are then attached to another protein that determines the signaling direction activation or inhibition.

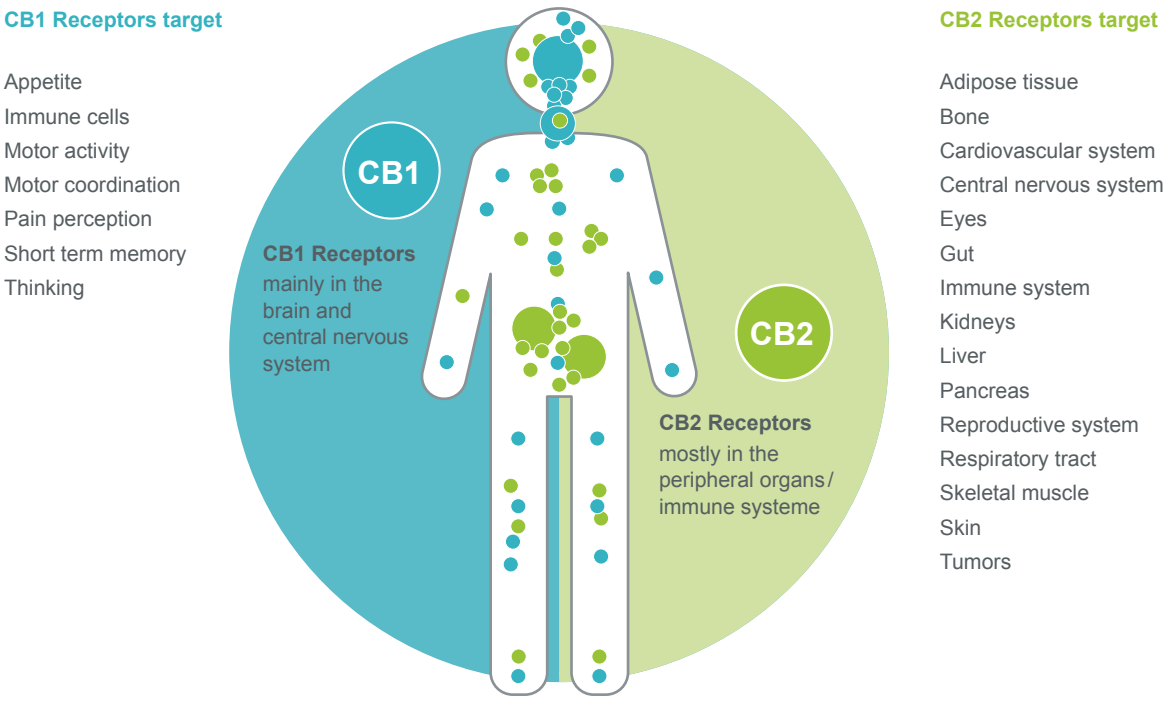

Figure 1: Human endocannabinoid system (Graphic: Aenova)

A big distinction is made between CB1 and CB2 Receptors. While the first are primarily found in the brain and CNS, CB2 Receptors are mostly in the peripheral organs especially cells associated with the immune system.

The ECS role is to maintain our body's ability to function normally by influencing the functioning of other systems. It plays a critical role in our nervous system and regulates multiple physiological processes. This includes the adjustment of our response to pain, appetite, digestion, sleep, mood, inflammation, and memory. The ECS does have multiple functions and it is one of the most underrated mechanism of our body. It also influences seizure thresholds (i.e. in epilepsy), coordination, and other processes such as the immune system, heart function, sensory integration (touch, balance, sense of space), fertility, bone physiology, the central stress response system (the HPAA), neural development, and eye pressure.

It is undisputed that the effects of the cannabinoids on the ECS are diverse and still unexplored. The more research will be performed the more insights we will get into the interaction of the cannabinoids with the human body. That is the reason that medical research will be always in the driving seat of the exploration of the unmet potential of future drug compounds.

4 CANNABINOIDS IN CLINICAL TRIALS AND ON THE MARKET

To date, there is no approved marketing application for cannabis for the treatment of any disease or condition. This comes from the fact that cannabis per se is a complex and hard to characterize mixture. Approximately 120 different cannabinoids are present in the Cannabis sativa, Cannabis indica, and Cannabis ruderalis. Only 2 out of the mixture are well characterized: cannabidiol (CBD) and tetrahydrocannabinol (THC).

CBD is a psychoactive cannabinoid, yet it's non-intoxicating and non-euphoric, meaning it won't get you "high". It's often used to help reduce inflammation and pain. It may also ease nausea, migraine, seizures, and anxiety.

THC is the main psychoactive compound in cannabis and is responsible for the "high" that most people associate with cannabis. Different plants and strains of cannabis do produce THC and CBD in variable amounts. Only after extraction from the plant and purification these compounds can be used for clinical trials or to manufacture drug products. CBD and THC in really high purity can also be synthetically produced.

Up to now, the FDA has approved only one cannabis-derived drug product: Epidiolex (cannabidiol), and three synthetic cannabis-related drug products: Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone). These approved drug products are only available with a prescription from a licensed healthcare provider. Importantly, the FDA has not approved any other cannabis, cannabis-derived, or cannabidiol (CBD) products currently available on the market. Sativex, a further cannabis-derived drug product was approved in Canada in 2005 and has been marketed in several European countries (Figure 2).

Marketed Drug	Indication	Dosage Form	API Molecule	Drug Strength
Epidiolex®	Myoclonic seizure	Oral Solution	Cannabidiol	100 mg/mL
Marinol®	Nausea and emesis associated with chemotherapy	Softgel Capsules	Dronabinol	10 mg
Syndros®	Nausea and vomiting associated with cancer	Oral Solution	Dronabinol	5 mg/mL
Cesamet™	Nausea and vomiting associated with cancer	Oral Capsule	Nabilone	1 mg
Sativex®	Neuropathic pain from Multiple Sclerosis (MS) and for intractable cancer pain	Buccal Spray	Cannabinidol; Dronabinol	25 and 27 mg/mL

Figure 2: Approved cannabinoid drugs (Table: Aenova)

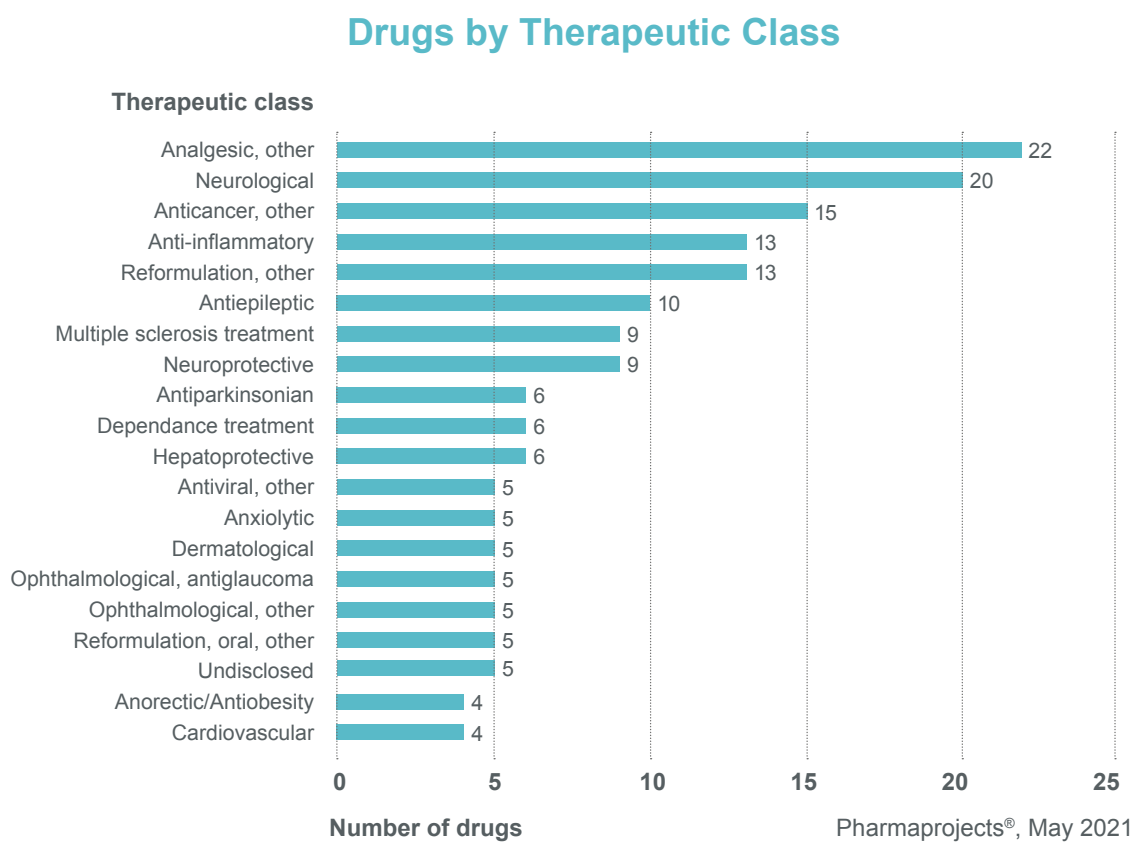

Figure 3: Clinical trials being performed on cannabinoids indicated by therapeutic area. Data obtained out of the Informa Pharma Intelligence database

From clinical trials to the market

The potential of cannabinoids for the treatment of several diseases is also proved by the number of clinical trials ongoing. Actually over 100 clinical trials are ongoing and more are in the planning. Out of these trials the major indications are in oncology, CNS in general and anti-inflammatory indications (Figure 3).

Almost half of the trials are in the US, but also Canada, where the main producers of cannabis are heavily represented. The other trials are evenly distributed in Europe, with a clear predominance of the UK (Epidiolex was developed by GW Pharmaceutical) (Figure 4).

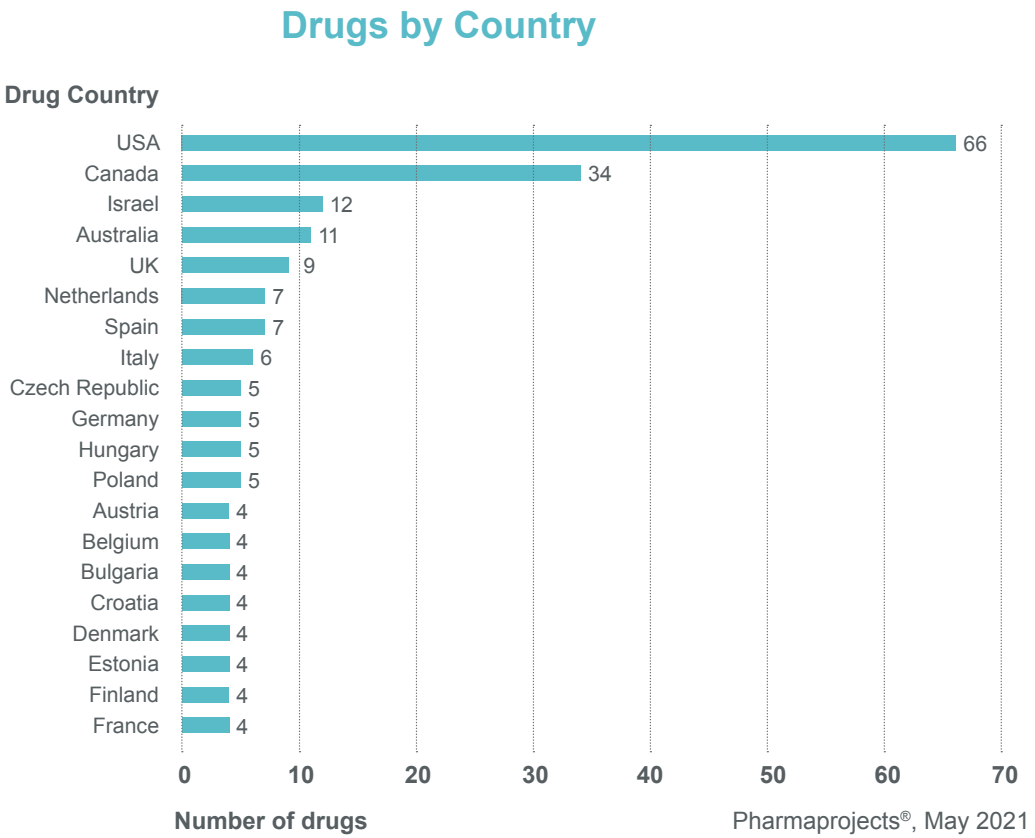

Figure 4: Clinical trials being performed on cannabinoids indicated by geographical location. Data obtained out of the Informa Pharma Intelligence database

5 CANNABINOIDS AND SOFT-GEL CAPSULES (SGC)

Soft gelatin capsules as the formulation of choice for cannabinoids

For pharmaceutical purposes, several different delivery routes have been considered for the formulation of cannabinoids: oral, nasal, sublingual, transcutaneous, rectal, etc. (17). All different formulation types have advantages and disadvantages, but oral delivery is often preferred because of ease of use and lower regulatory hurdles.

Based on the Developability Classification System (DCS) cannabinoids fall into the Class II, meaning that they have good permeability and poor water solubility. Out of this category the Class IIA represent those drugs where absorption is limited by the dissolution rate, while Class IIB the drug's intrinsic solubility is the limiting absorption factor (18, Figure 5). Whereas for Class IIA particle size reduction can lead to an increased bioavailability, for the cannabinoids (compounds Class IIB) the drugs have to be presented to the gastrointestinal tract in an already solubilized form.

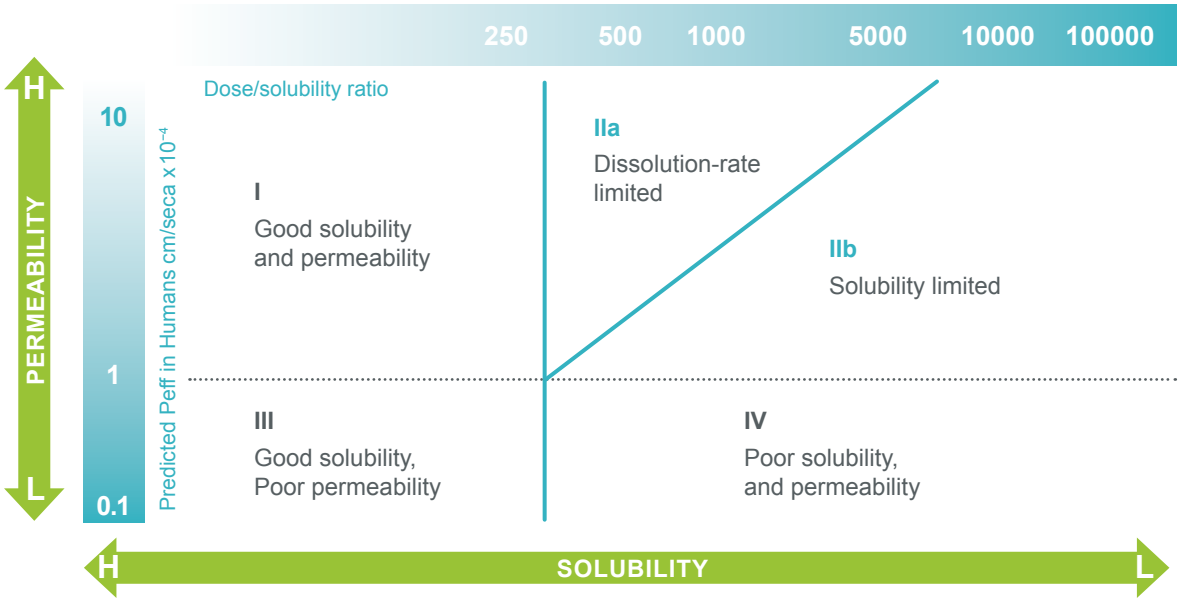

Figure 5: Drug Developability Classification System (DCS)

Furthermore, the poor bioavailability is not only due to the poor gastrointestinal solubility but also to a significant first path metabolism that occurs in the liver following gastrointestinal absorption. This is the main reason that cannabinoids are ideal for lipid-based drug delivery systems (LBDDS) in soft gelatin capsules. Some recent studies have shown that THC and CBD oral bioavailability have increased 3-fold (from 3-8% to almost 30%) (19) thanks to the use of LBDDS.

Once the soft gelatin capsule is ingested by the patient, the capsule ruptures within 5 to 10 minutes and the cannabinoid is released in the GI tract and absorbed into the blood stream. The absorption process can be influenced either by the diet of the patient or/and by the excipients of the capsule. By choosing the right lipid excipients the digestion, by the lipases and bile salts, can lead to mixed micelles that are absorbed through the enterocytes.

Another possibility is to add surfactants in the capsules, which, at rupture, create self-emulsifying drug delivery systems (SMEDDS). This is again a method of increasing the bioavailability. As already stated, some cannabinoids exhibit a really high first path metabolism, which leads to poor bioavailability. To bypass the liver the use of long chain fatty acids and lipids can lead to the formation of chylomicrons with the cannabinoids, which are absorbed into the lymphatic system and favorably increase bioavailability.

6 ADVANTAGES OF CANNABINOID FORMULATIONS IN SGC

There are several reasons that do speak for cannabinoid formulations in Soft Gelatin Capsules (SGC):

Protection of APIs sensitive to light and oxidation by the capsule shell
THC like Dronabinol is sensitive to oxygen and represent an ideal candidate for SGC formulation. As cannabinoids have a similar chemical structure they will benefit as well from such protection.

Increased patient compliance of SGC due to ease of transport and dosage
Most of the CBD products are in liquid form, either as drops or as liquids to be dosed by a syringe, going along within inconvenient (syringe) handling. SGC present a handy formulation easily administered “on the go”.

Dosage range easily adjustable
With soft gelatin capsules you do have the possibility either to adapt the concentration in the same sized capsule or to change the size of the capsule. By changing the color you can add a clear distinction factor for the different strengths.

Better bioavailability by SGC
Increased GI solubility, intestinal permeability and enhanced lymphatic absorption can be reached with SGC formulation.

Chewable SGC can be used for sublingual applications
This would be the case if you do need the API to be absorbed in the mouth, rather than going through the GI tract and avoiding first path metabolism at the same time.

Wide range of SGC shapes and sizes
This makes the soft gelatin capsule the ideal formulation for elderly people or children. Older patients will find a soft gelatin capsule easier to swallow while our youngest will be delighted by the colors and forms.

Marketing advantages due to elegant appearance of SGC
Soft gelatin capsules are just good to look at. With the wide ranges of colors, shapes and sizes they can be used to add significant value to any brand portfolio.

Efficient smell and taste masking of SGC
If you ever tried CBD drops you know how awkward the taste is. Also in this case soft gelatin capsule could be of help. You could even coat the capsule with a flavor, so increasing the palatability of the product.

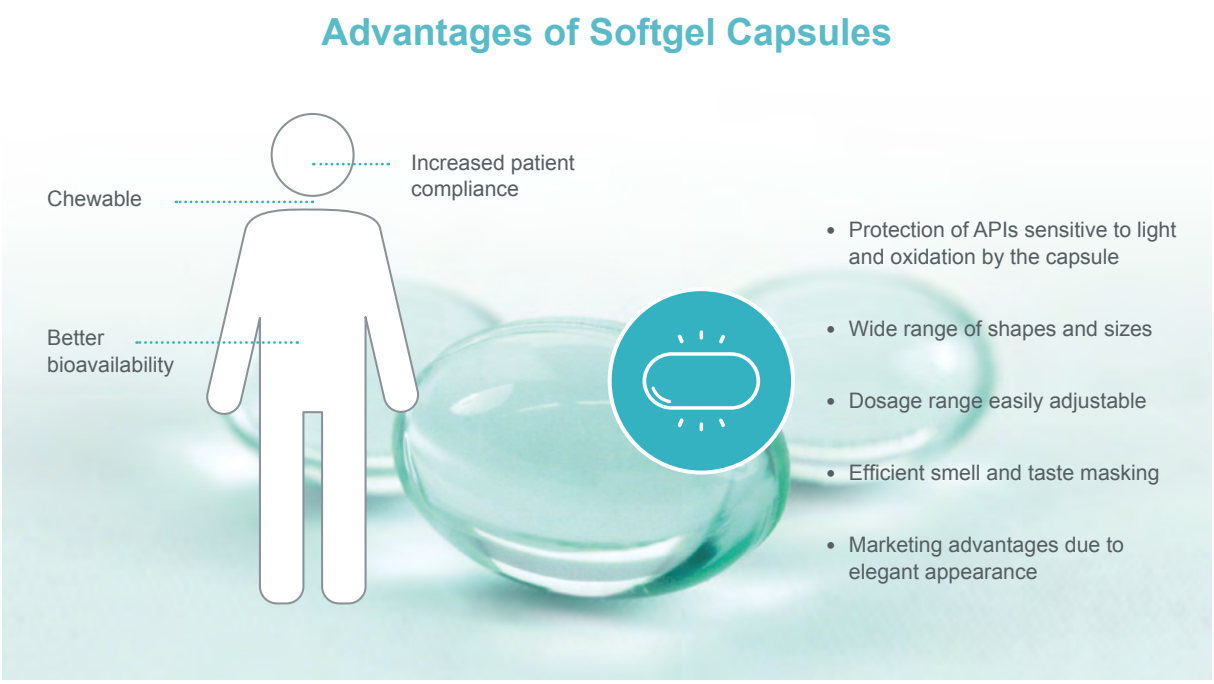

Figure 6: Advantages of Softgel Capsules (Graphic: Aenova)

7 CONCLUSIONS

Cannabis and cannabinoids do represent a significant business opportunity for life science companies. There is substantial interest of consumers and patients for cannabinoid products with proven safety, efficacy and quality. Challenges are certainly the regulatory requirements as well as a solid business model for financing.

Nevertheless cannabis has undoubtedly significant medical benefits that are still to be discovered. Cannabinoids in soft gelatin capsules are undoubtedly one of the most suitable formulations for these compounds. Optimal bioavailability, protection of the API and increased patient compliance are just a few reasons that do speak in its favor.

8 YOUR COMPETITIVE ADVANTAGE WITH AENOVA

SGC development, technologies and manufacturing from one hand

Aenova has more than 35 years of experience in the formulation, analytical development and production of soft gelatin capsules.

Our production facilities are equipped with state-of-the-art equipment to process any formulation and any capsule design, color and size.

Aenova worldwide #2 in the production of softgel capsules

With development and manufacturing capacities including high potent active pharmaceutical drugs at our Center of Excellence in Kirchberg/Switzerland and OTC and consumer healthcare products at our cost competitive manufacturing site in Cornu/Romania, we offer a complete service for softgel capsules, also in vegan form, from formulation to marketing with specific brands available for our customers.

The Aenova site in Kirchberg, Competence Center Soft Gelatin Capsules, Business Unit Softgel Capsules, has special expertise in the development, production and analytical testing of pharmaceutical soft gelatin capsules, including high potent APIs.

The Kirchberg site has inhouse experience on successful pharmaceutical and analytical development, registration and market supply of cannabinoids formulated in soft gelatin capsules. The site is holding a narcotic license and installed tailored innovative equipment to allow safe handling of cannabinoids in totally inert atmosphere to ensure maximum product stability.

In our competence center for pharmaceutical soft capsules, we apply decades of know-how and state-of-the-art infrastructure to deliver flawless quality to our customers worldwide.

With our innate Swiss reliability, we always deliver our products on time. Hand in hand, our experienced team works with passion to find innovative solutions for demanding customer needs. Our high service standards are the driving force for long-term, successful partnerships with our customers.

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10 THE AUTHORS

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Dr. Mario Arangio holds a Ph.D. in Analytical Chemistry from the university of Saarland, Germany. After a short period in the USA working for a biotech company in the Boston area he worked for Pfizer in Italy in the oncology field as a group leader. After that he covered different positions up to business unit leader in the pharmaceutical and diagnostic field. Dr. Arangio leads the pharmaceutical development group at Aenova Kirchberg since November 2018.

Dr. Christian Luftensteiner

Dr. Christian Luftensteiner holds a Ph.D. in Pharmaceutical Technology from the University of Vienna, Austria. After postdoctoral research on oral peptide delivery and bioavailability enhancement at Aventis in collaboration with technology leaders, he worked several years for Novartis Pharma in leadership roles in Technical Research and Development and Pharmaceutical Operations. Subsequently he hold senior positions in innovation and development at Bayer and Actelion prior joining Aenova. Dr. Luftensteiner leads Aenova's site in Kirchberg as Managing Director since 2017.

ABOUT THE AENOVA GROUP

The Aenova Group is a leading global contract manufacturer and development services provider for the pharmaceutical and healthcare industry. Our services include end-to-end manufacturing and development of all dosage forms and potency levels (ranging from nutraceuticals to high-potents) out of 15 production sites in Europe and the US.

With our comprehensive know-how, many years of experience, well-trained staff of around 4.300, innovative technologies and highest quality standards we are a reliable, long-term partner to pharmaceutical and consumer health care customers around the world, both in the human and veterinary healthcare market.

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