
CRITICAL EQUIPMENT QUALIFICATION PARAMETERS AFFECTING THE HOMOGENIZATION PROCESS OF MEDICAL CANNABIS SEMI-SOLID PHARMACEUTICALS

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Abstract: The medical cannabis has been used for many of years for medicinal purpose, in different pharmaceutical formulation, mostly as a magistral preparation for the relief of pain in cancer patients or chronic painful diseases. Over than 540 substances were found from which more than 100 that have been found to be cannabinoids due to their similar chemical structure. The component with the most psychotropic action is Δ^9 -tetrahydrocannabinol (Δ^9 -THC), and the major non-psychoactive ingredient is cannabidiol (CBD). Δ^9 -tetrahydrocannabinol firstly was isolated in 1969 by Robert Mechoulm and Yechiel Gaoni. In 2003 World Health Organization put Δ^9 -tetrahydrocannabinol in Schedule IV of the convention. Several therapeutic indications relate to the Δ^9 -THC and CBD as analgesia, inflammatory and neurodegenerative diseases, and many other cases. In some studies, there are reported safety concerns about the registered side effects of Δ^9 -THC as a psychoactive. For that reason, the legal usage of cannabis for medicinal purposes and for recreational use is regulated differently. The most relevant explanation is related to the not enough sufficient results and data obtained from the pharmacokinetic studies and research in pharmacological behavior. Extracts of cannabis was used from many years ago. Nowadays in pharmaceutical industry as the development of technology there are many dosage forms in where extracts, cannabinoids, flower are used. Medicinal cannabis products can come in many different forms, including capsules, drops, chewable, creams, crystals, flower, lozenges, oil (most common), oro-mucosal sprays, tinctures and many more. Also, there are synthetic analogs to nature cannabinoids in pharmaceutical market. In this study will be discussed about production of semisolid pharmaceutical forms obtained from medical cannabis. They are produced in pharmaceutical grade equipment, high-pressure homogenizer mixer. In this study it will be discussed about the process of equipment qualification. Firstly, by the user requirement specification, design qualification protocol was approved. Then factory acceptance test was performed in production site of equipment and site acceptance test was performed in customer's site. Then installation qualification protocol was look through and then operational qualification protocol also. All the qualification protocols were approved by both sides. In different qualification protocols, different tests were performed, and they are explained separately. During the qualification process, there are considered some of the parameters which later during the production process can affect in the quality of finished products. These parameters are called critical process parameters and accent will be put on this process parameters that are with a critical effect on quality of the final products. This critical process parameters were considered and concluded from qualification protocols where all the parameters that can affect quality of the product were separately examine.

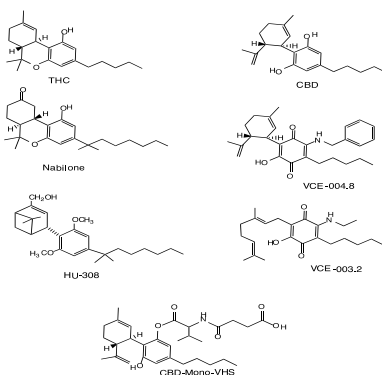
Keywords: medical cannabis, semisolids, qualification, critical process parameters

1. INTRODUCTION

The use of medical cannabis has recently received a lot of attention due to changes in laws in many countries worldwide and according to recently obtained medical and pharmaceutical studies on its use and effects in many diseases and diagnosis. The legislation changes are one of the first steps to enable access to medicinal cannabis containing pharmaceutical active compounds (API) for therapeutic uses, under certain conditions.

Cannabis plants, different varieties, has a different and large number of compound contents which are identified chemically, and the most active and main compounds are cannabinoids. Cannabis plant has special secretory cells called trichomes which are secretory type of glands and there is where the synthesis of phytocannabinoids is happen. Unfertilized female type of cannabis flowers has a higher yield before senescence (Russo, 2011). According to the chemical identification (structures in Fig.1), there are isolated more than 120 different phytocannabinoids (Elsohly and Slade, 2005), and Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD) are the most examined. In the cannabis plants beside the two most abundant phytocannabinoids, several polyphenolic compounds (called flavonoids) are produced.

Figure 1. Structure of the principal cannabinoids



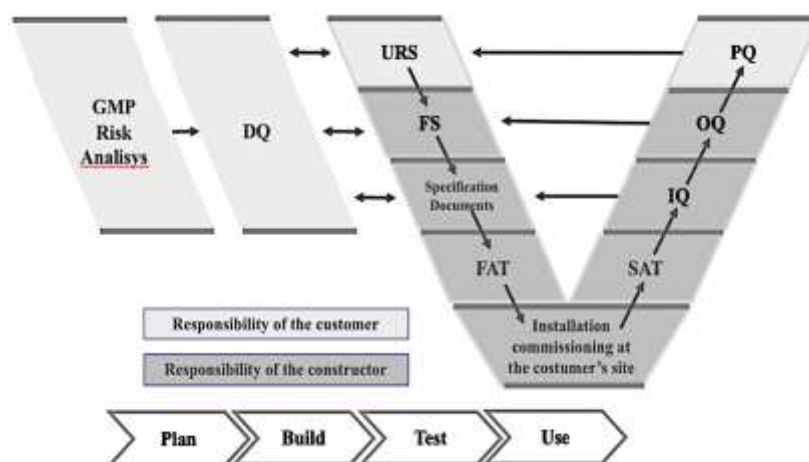
Each country has its own laws and regulations regarding the cultivation, processing and production of final pharmaceutical forms derived from medical cannabis. Cultivation of medical cannabis is always in special production sites where no cultivation chemicals are used and pesticides, heavy metals, microbial and mycotoxins are minimized and defined. To produce adequate pharmaceutical forms, it is very important to obtain starting material with well-controlled parameters that guarantee quality, because medical cannabis is used by patients with serious conditions and diseases, and therefore it is important to achieve medical quality. Published clinical studies (Ruhul and Declan, 2019) show that medical cannabis has possible and potential benefits for several diseases. The cannabis flowers are used as active pharmaceutical ingredient and as starting material in a aim to produce different finale dosage forms. In some countries, the flower itself is used, prescribed, and can be bought in pharmacies or cannabis-based medicinal forms can be prepared (Romano and Hazekamp, 2019). The dried flowers of medical cannabis are also used to produce extracts such as full-spectrum oils, distillates, pure active substances such as THC and CBD that form the active part of any pharmaceutical form. Due to the mode of use and availability, many these pharmaceutical dosage forms are in the semi-solid dosage form (Stella et al. 2021). Semi-solid formulation containing cannabinoids has been proposed for skin diseases, as the treatment of psoriasis, some types of acnes (Sheriff, Lin, Dubin, & Khorasani, 2020). Several current OTC products containing CBD are on the market in the US, Europe, Canada, and Australia a in compliance with their regulations (Markus, V, 2022).

Semi-solid pharmaceutical dosage forms are often used because the administration of the drug through the skin is easily, especially when properly produced active component and its good absorption. They are carriers of active medicinal ingredients that are delivered locally through the skin and all the mycosis membranes trough the body. Semi-solid pharmaceutical forms are complex formulations, with complex ingredients and type of production, no matter they seem simply to produce (Maqbool, Mishra, Pathak, Kesharwani, & Shambhunath, 2017) and usually they are made from two or more components and are homogeneous (Patel and Holley, 2018). Mixing is a process where different components are laying closely and are in contact with each particle between them. These may be mixtures of solids, semi-solids, or liquids (Maqbool, Mishra, Pathak, Kesharwani, & Shambhunath, (2017). There are important physical parameters that must be all od them achieved, and if not the whole process of producing can give a final form that will have a poor quality. During the production cycle each step must be monitored to ensure the quality of the final dosage forms and to be sure if the patients use this product that in every time they applied it, it will have a same concentration until the expiry date of the product. Homogeneity is one of the key properties that is necessary to be achieved for the pharmaceutical formulation to have a homogeneous appearance. The homogeneity is always proportional to the distribution of all the ingredient, and it must be uniform in all final closure systems. (Maqbool, Mishra, Pathak, Kesharwani, & Shambhunath, 2017). If the homogenization process is with poor quality, there is a problem in the final formulation of the drug that affects its quality, especially its stability. Inadequate homogenization of the preparation can lead to the formation of lumps or globules, which are the result of insufficient or incomplete mixing of the oil and water phases. This can affect in dosage that is applied to the patient, not proper dose will be applied.

The homogenization process is where two or more ingredients are mixed. Almost always this are immiscible phases and through use of homogenization process in some vessels and mixers the final homogeneity needs to be achieved. Homogeneity is only one of the factors that affects the quality and effectiveness of semi solid products. Particle distribution, spread ability, level of grit, and use of surfactants are all important factors in determining the quality and the shelf life of semi solids. And all of them can be controlled for or guarded against during the manufacturing process. These machines are controlled by computer systems, and they are always validated in the aim to ensure precises control of mixing parameters like speed, temperature, pressure etc. (Nwoko and Valentine, 2014).

This systems for producing a semisolid, and all the equipment in pharmaceutical industry, must achieved the requirements of Good Manufacturing practices (GMP). All the equipment must be properly qualified and validated. In quality assurance guidelines there is special part about qualification. Qualification must be done in all the buildings where pharmaceutical dosage forms are produced and that is not just machines but that is all the systems and facilities, and the main aim is to be sure that all the systems work properly and give always same results. Every GMP qualification contain four phases: Plan, Build, Test and Use (Fig. 2).

Figure 2. Applied so called V-Model of Qualification



An essential part in the manufacturing of semi-solid products and APIs are the machines and the overall equipment in the production site. All the machines must be specially designed and placed in suitable places, they must have a required size, there must be maintenance part that is easily available and for cleaning. All this must be done to not interrupt the production process. The equipment should be constructed so that the surfaces in contact with the raw materials, semi-products or APIs do not change their quality according to established protocols and specifications (Stella et al. 2021). Qualification of the equipment includes several steps related to each other:

1. **User Requirement Specification (URS)** -This is all the parts that buyer asks to be achieved. Here are described all the technical needs of the machine from size, use, maintenance, utilities, documentations etc. This document is written by buyer and send do producer.
2. **Design Qualification (DQ)** – In this document is described all the deign parts that machine needs to satisfy.
3. **Factory Acceptance Test (FAT)** – This is test that is done in the factory that equipment is produced and here are done all the test and are compared the URS requirements and the machine that is produced by the constructor. The aim is to be sure that what we purchase that we receive.
4. **Site Acceptance Test** – This is the test that is done after the FAT test is approved and this test is done in customer's site.
5. **Installation Qualification (IQ)** – This test verifies that equipment as properly installed. Here we can see what the critical parameters are.
6. **Operational Qualification (OQ)** – This test verifies that operational properties are satisfactory and critical parameter are concluded.
7. **Performance Qualification (PQ)** – This test needs to demonstrate production process and the main aim is to see that system work by its performance use.

Both the machine constructor and machine buyer have a same responsibility for the equipment qualification and for the accuracy of the results from the tests that are made. Some of the test can be done just by the user like DQ. Some of tests like IQ for an equipment that has more simple use can be done by the user, but some equipment with more complex parameters must be done from both sides together. OQ can be done by the producer and by the user. PQ test must always be done by the user because the producer doesn't know production process, and this should be done daily so it is necessary to be done by the user (Reddy, Reddy, Navaneetha and Reddy, 2014).

The goal of this study was to determine critical process parameters during homogenizer qualification processes. Through the knowledge and implementation of these critical parameters can improve the production process and ensure the quality of the final product for which it will guarantee.

2. MATERIAL AND METHODS

Homogenization mixer

In our study the homogenization mixer of producer OmniProjekt, Serbia was used (Fig. 3), machine for producing a semi solid dosage form. The design of the mixer and the selected mixing processes are determined by the nature of the material used for mixing, in our case products containing cannabinoids. This homogenization mixer is with double wall full fill with water system for heating and cooling and it is working under pressure and vacuum. All the materials that are in contact with pharmaceutical form are made of ASI 316 and certificates are given by the producer, also for all parts of the equipment.

Figure 3. Homogenization mixer of producer OmniProjekt installed in our production site



The **qualification process** itself was implemented in the following order:

- Drafting of **URS** (User Requirements Specification) is made, sent, and approved by both parties, and **DQ** (Design Qualification) is performed where URS requirements are approved by both parties. All customer requirements specific to the products include GMP requirements.
- **FAT (Factory Acceptance Test)** was realized in Serbia production site, followed by **SAT (Site Acceptance Test)** test on site in our production site. The following tests were performed as integral parts of the FAT and SAT protocols: Equipment identification, documentation verification, main and spare parts of equipment, electricity, compressed air, heating system, cooling system, dosing system, software, mechanical parts, and safety. During these tests, all parts successfully passed the qualification protocols.
- With the execution of the **Installation Qualification (IQ)** protocol, we ensured that the equipment is properly installed, and that the documentation is properly prepared. In this protocol, the following tests were performed: identification of equipment, verification of documentation, schemes, equipment drawings, verification of positioning of equipment in the production room, main and spare parts of equipment, measuring equipment, electricity, compressed air, heating system, cooling system., training, materials in contact with the dosage form and tools to carry out this protocol. During this test, all parts successfully passed the qualification protocol.
- The **Operational Qualification (OQ)** protocol was implemented to confirm that the equipment works correctly with previously set parameters. In this protocol, the following tests were performed: verification of documentation, electromechanical testing, testing in case of emergency, verification of the homogenization and mixing process, verification of dosing, verification of alarms. During this test, all parts successfully passed the qualification protocol.
- In the realization of the **Performance Qualification (PQ)**, we had to ensure that using the protocols from the manufacturer, the homogenizer produces a product with the required quality. This is very important for the preparations containing cannabinoids because these active components have certain properties, such as easy degradability during changes and elevated temperatures, the presence of oxygen, UV light and other things that significantly affect their stability.

3.RESULTS

Medical cannabis producing process must be done under GMP area because the final dosage forms are pharmaceuticals. The Good Agriculture and Collective Practices (GACP) are for producing the plants, and after that

all the post-harvest processes must be done under GMP. There is still complex situation for cannabis flowers as active ingredients that is intended to be written in prescription and given to the patient by the pharmacies and authorities in the European market. Each country has different laws for cannabis flowers, for their production, active ingredients, final dosage forms etc. (Markus, 2022). The machines, facilities, processes that are done by GMP must be qualified according to EU GMP guidelines.

During the process of equipment qualification, we have concluded which are the critical process parameters (CPPs). These parameters can both be some characteristics of the process and of the equipment and they can critically affect in the final dosage form quality. This can be temperature, speed of mixing, but also can be some final dosage form characteristic like viscosity, melting point, homogeneity. This Critical Process parameters with their variability in the process of production can affect on a critical quality attribute (CQA) and because of that during qualification process of the equipment they must be specially controlled and monitored (Reddy et al., 2014). Every semi solid final dosage form has a different characteristic and use and because of that we must concluded for us which will be this critical process parameters and attributes that need to be monitored. During the performing of the tests, qualification protocols, we tested the following critical steps: Temperature, Speed of homogenization and Speed of mixing.

Process Temperature: Temperature is the one of the parameters for cannabis plant quality during vegetative, flowering phase and for post harvesting processes like trimming, drying. Cannabinoids are very sensitive compounds, and this is the most critical point of the production that must be controlled and monitored because too much heating can lead to cannabinoids degradation. But also, the cooling can affect because if the product is not homogenized good, the cooling can result in making of precipitation.

- a) If we heat the product slowly there can be poor yield from evaporation.
- b) If we heat to rapidly also the contact material homogenizer/product can be burnt.
- c) If we cool to rapidly also, we can make precipitation of the product and the viscosity will be changed.

Cannabinoids are stable in temperature under 150 °C (4).

Our process of homogenization was realized on temperature range under 90 °C. But in anyways this is critical parameter especially because of the ability of degradation of THC to his analog cannabiol (CBN) which is considered to be the key cannabinoid to show the step of degradation of THC and also it is the key parameter in stability studies as the marker for shelf life of the product. In our homogenizer there are two temperature measuring's. One is inside the double wall filled with water that is controlling the temperature inside the vessel. And the other is inside the vessel that is measuring temperature inside the semisolid probes.

In SAT and FAT test temperature ranges that were examined were at 35°C,50°C,75°C and 85 °C. The temperature was set on PC panel in the way that the temperature that is inside the double wall it is concluded that needs to be 5-7°C higher than the temperature inside the vessel in the way to achieve a working temperature. All the temperature ranges where set, achieved and approved successfully.

In Operational Qualification protocol there is test for „Verification of function of homogenization and mixing “for the purpose to prove the set and achieved parameters. The steps were to:

- Set a temperature for heating – it was set 45°C
- Set a speed of mixing – it was set 20 rpm
- Set a speed of homogenization- it was set 2000 rpm

These parameters where set with time range of 1 minute. All the parameters that where set, were achieved and approved successfully.

Mixing Methods and Speeds

Semi-solids are generally not stable formulations and mixing and homogenization as process parameters are very important during production. For maximum yield and quality of the production process it is very important to set the optimum parameters like mixing speed, mixing time, temperature heating and time, also cooling. For each step of the production cycle, it must be set mixing speed and time. The process of dispersing is in very close touch to the mixing speed because very low mixing speed can lead to low disperse and the viscosity will not be achieved. Homogenization is performed at a maximum speed of 2800 rpm, and mixing is performed with a mixer at a maximum speed of 35 rpm. The goal is always to achieve uniformity in the dosage forms that are produced. For this purpose, different parameters are set to see which of them are the best to obtain a product that is stable and uniform. The time of mixing is set in a way the minimum time that is need to the product to start to dissolve and the maximum time before the product changes it's characteristic like viscosity.

4.DISCUSION

The product that we produce must be manufactured, stored in facility that has implemented GMP requirements. The process of validation of equipment or facility ensures that always we will get a same result. If we want to validate some

process, equipment etc. it is very important that all the parts are previously GMP qualified. With qualification in our case for homogenizer can be proved that as a machine it can produce semi solid forms with expected quality and characteristics. Qualification always begins with defining the purpose, continues with assessing and documenting whether the equipment is fit for purpose.

As previous is told temperature, mixing speed and time and homogenization speed and time are critical parameters. If the production batch is smaller the mixing and homogenization are done more easily. But as the batch is bigger this process is more complex. One time passing through the homogenization pump is not enough to produce a uniformity. Always there is a need for specific number of cycles and time of homogenization, and that must be set correctly by experiments. The homogenization process is not important just for uniformity of final dosage form but also for some physical characteristics like droplet size, particle size.

To produce a quality semisolid product the temperature is also very important. This process can affect particle distribution, homogeneity and if the cannabis extract is heated properly, it can be better dissolution in the product and that has impact on viscosity (Patel and Holley, 2018). But if the temperature is too high cannabinoids can degrade and terpenes can evaporate. Special accent on this parameter must be put on in the way to ensure product specification and to reduce some negative effects in final dosage form (Nwoko and Valentine, 2014).

5.CONCLUSION

This study was realized to show how the homogenization process and its critical parameters affect the quality of the finished product, as well as to be a starting point for the validation of the process itself. This phase of work is important to observe all the critical parameters in that process, and so that the finished product is always of the same quality, without any deviations in every production cycle. The obtained results based on our qualifications and those from the literature will help us to have better control over all these parameters and over the production process itself. Continuous improvement, implementation and knowledge of these parameters are essential to meet GMP requirements while ensuring higher levels of process quality. Equipment qualification is a very important process that demonstrates the quality of systems and equipment and is an integral part of the GMP quality system. There is a relationship between raw materials and their physicochemical properties, process parameters, control of critical process parameters and the final product. We can rightly conclude that the qualification and validation of the equipment, and therefore the knowledge of the critical parameters, is a live problem and must be done in a way to achieve the best quality of our products.

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