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Short communication

Drug product quality attributes in designing of 20% CBD solution for oral use

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Introduction

Cannabidiol (CBD) is secondary metabolite obtained from Cannabis Sativa plant and has substantial therapeutic potential in indications such as anxiety, schizophrenia, addiction, post-traumatic stress disorder, graft-versus-host disease, cancer and inflammatory bowel disease. Its development as an effective drug is hindered by intrinsic characteristics such as low bioavailability, low water solubility and variable pharmacokinetic profiles. In order to be successfully utilized as a medicine, it is paramount to identify and overcome the inherent challenges that hinder CBD's effective delivery, particularly through the oral route, which is the most preferred route for drug delivery by patients (Millar et al., 2020). Sublingual administration of CBD allows it to bypass digestion and the drug can be absorbed directly into the bloodstream thus resulting with 20–30% higher bioavailability and a 50% higher Cmax when compared to the oral route (Lucas et al., 2018).

In the past few years pharmaceutical industry is highly encouraged to apply Quality by design (QbD) approach in the product development. According to ICH Q8(R2) (2009) QbD covers definition of the quality target product profile (QTPP), identification of potential critical quality attributes (CQAs) of the drug product, followed by risk assessment and linking critical material attributes (CMA) and critical process parameters (CPP) to CQAs, development and optimization of the product and manufacturing process and design and implementation of control strategy.

The aim of the study was to design a CBD oil solution (2000 mg/ 10 mL) for sublingual application with the QbD approach, by defining QTPP and identifying the CQAs in the first stage of development.

Materials and methods

QTPP of CBD oil solution (2000 mg/10 mL) was defined in relation to product quality, safety and efficacy considering its route of administration, dosage form, strength, bioavailability, stability and container closure system, while CQA were identified and justified accordingly from the product quality attributes (QA) using official guidelines and prior knowledge and understanding of the drug product in question and manufacturing process.

Results and discussion

QTPP were established in accordance to reference listed drug product physico-chemical properties, its packaging insert and labeling. Dosage form should be oil solution with a strength of 2000 mg/10 mL for sublingual administration (3 drops under the tongue held for at least 60 sec. before swallowing), with plasma Cmax reached in 15 min, shelf life of at least 12 months, packed in dark glass vial with dropper as primary container closure system, and carton box as secondary packaging with included package information leaflet.

Drug product QA that are a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality are presented in Table 1. Identified and appropriately justified CQA are also presented in Table 1.

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Table 1. Drug product quality attributes

Drug product QA	Target	Method	Is it CQA / Justification
Appearance	Light yellow viscous liquid with characteristic cannabis odor	(Visual)	No / Color is not directly related to the safety and efficacy
Identification-	Positive on cannabidiol (CBD) Positive on Δ9-THC- Tetrahydro -cannabinol (THC)	(HPLC) (UV-VIS spectrophotometry Eur. Ph. 2.2.25)	Yes / Identification is critical for safety and efficacy.
Deliverable volume	Not less than 10mL	(USP, <698>)	No / Deliverable volume is not directly related to the safety and efficacy.
Relative density	0.946-0.956	(Eur. Ph. 2.2.5)	Yes / Relative density has critical influence related to the stability of oil.
Content: Δ9-THC- Tetrahydro cannabinol (THC) Cannabidiol (CBD)	< 0.2% (w/w) 180-250 mg /mL or 90-125%	HPLC (Eur. Ph. 2.2.29)	Yes / Content will have influence upon safety and efficacy.
Residual solvents: Ethanol	< 500 ppm	(Eur. Ph. 2.4.24)	Yes / Residual solvents will have significant influence.
Related substances cannabinol (CBN)	Not more than 3%	HPLC (Eur. Ph. 2.2.29)	Yes / Related subst. will have influence

Table 1. Drug product quality attributes (continued)

Drug product QA	Target	Method	Is it CQA / Justification
Microbiological quality			
TAMC	$\leq 10^4$ CFU/g	(Eur. Ph. 5.1.8)	Yes / Microbiological quality is critical for safety and efficacy.
TYMC	$\leq 10^2$ CFU/g	(Eur. Ph. 5.1.8)	
Escherichia coli	absent /g	(Eur. Ph. 2.6.31)	
Salmonella	absent / 25g	(Eur. Ph. 2.6.31)	
Bile tolerant gram-negative bacteria	$\leq 10^2$ CFU/g	(Eur. Ph. 2.6.31)	

Conclusion

Quality target product profile and quality attributes were defined and critical quality attributes were determined during first stage of development of CBD oil solution for sublingual administration. The next stage would comprise identification of critical material attributes and critical process parameters and their linking to CQA, followed by development of design space and implementation of adequate control strategy in order to enable easier management of product during its life cycle and hence product continual improvement.

References

Eur. Ph., 2022. European Pharmacopeia 11th edition, Volume I. Council of Europe; Strasbourg, France

ICH Q8(R2), 2009. ICH Harmonised Tripartite Guidline - Pharmaceutical development

Lucas, C.J., Galettis, P., Schneider, J., 2018. The pharmacokinetics and the pharmacodynamics of cannabinoids. British journal of clinical pharmacology, 84(11), 2477-2482. https://doi.org/10.1111/bcp.13710

Millar, S.A., Maguire, R.F., Yates, A.S., O'Sullivan, S.E., 2020. Towards better delivery of cannabidiol (CBD). Pharmaceuticals, 13(9), 219. https://doi.org/10.3390/ph13090219

USP 43–NF 38, 2020. United States Pharmacopeial Convention