Available online on 15.06.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Characterization of Sapropterin Dihydrochloride Tablet

Tapan Kumar Jena *, Rakesh Kumar Jat

Institute of Pharmaceutical Sciences, Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan – 333001

Article Info:

Article History:

Received 13 March 2024
Reviewed 27 April 2024
Accepted 20 May 2024
Published 15 June 2024

Cite this article as:

Jena TK, Jat RK, Characterization of Sapropterin Dihydrochloride Tablet, Journal of Drug Delivery and Therapeutics. 2024; 14(6):109-113

DOI: http://dx.doi.org/10.22270/jddt.v14i6.6583

*Address for Correspondence:

Tapan Kumar Jena, Institute of Pharmaceutical Sciences, Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan – 333001

Abstract

Characterization of Kuvan tablets involved thorough analysis of physical, chemical, and dissolution properties. Formulation development encompassed pre-formulation studies, feasibility trials, and process optimization. Kuvan tablets demonstrated variability in sapropterin dihydrochloride concentration but rapid dissolution across different media. Consistent mechanical strength, low impurity levels, and appropriate pH values were observed, ensuring efficacy, safety, and reliability.

Keywords: Sapropterin dihydrochloride, Hyperphenylalaninemia, Kuvan tablets

INTRODUCTION

In a typical diet, the body often consumes more phenylalanine than it needs. However, efficient mechanisms help maintain safe blood phenylalanine levels. These include using phenylalanine for protein synthesis, metabolizing it into other compounds, and excreting any excess. These processes ensure that blood phenylalanine levels stay within non-toxic limits despite the dietary surplus. Phenylalanine, obtained exclusively from dietary protein, is crucial for synthesizing tyrosine, which is necessary for neurotransmitter and thyroid hormone production. Normally, about 75% of dietary phenylalanine is converted to tyrosine by phenylalanine hydroxylase (PAH). Disorders in phenylalanine metabolism can lead to elevated blood phenylalanine levels, known as hyperphenylalaninemia (HPA). In normal conditions, phenylalanine is converted into neurotransmitters and protein components, a process involving key enzymes such as PAH, GTP-cyclohydrolase I (GTPCH), and pyruvoyl-tetrahydropterin synthase (PTPS). PAH facilitates amino acid and protein synthesis, while GTPCH and PTPS maintain normal levels of tetrahydropterin (BH4), essential for these metabolic processes [1-5].

Sapropterin's molecular structure features a pteridine nucleus with a keto group. The reduced pteridine nucleus includes an amino group and two hydroxy groups on the side, both part of chiral carbons. The drug has three chiral centers: two in the dihydroxypropyl side chain and one in the pteridone ring. This results in two stereoisomer forms, "R" and "S" configurations. The "R" configuration is the active form used to treat diseases, while the "S" configuration is inactive. Therefore, the drug's stereochemistry is crucial for its therapeutic activity [6, 7].

Sapropterin dihydrochloride is a drug used to treat hyperphenylalaninemia (HPA) in patients with phenylketonuria (PKU) and tetrahydrobiopterin (BH4) deficiency. It works by supplementing and aiding mutant phenylalanine hydroxylases, increasing phenylalanine clearance from the body. Sapropterin acts as a natural cofactor for enzymes like phenylalanine hydroxylase, tyrosine hydroxylase, tryptophan hydroxylase, and nitric oxide synthase. BH4, the cofactor for these enzymes, is essential for metabolizing phenylalanine and synthesizing neurotransmitters like serotonin, dopamine, and norepinephrine. Structurally, BH4 is a reduced form of a derivative of the pteridine nucleus, playing a crucial role in various physiological processes and neurotransmitter regulation [8-12].

The present study focuses on the characterization of immediate-release formulations of sapropterin dihydrochloride. This research aims to pave the way for the development of simulated tablet dosage forms using various excipients.

EXPERIMENTAL

Characterization of sapropterin dihydrochloride tablet (KUVAN TABLET) was performed to obtain information that can be used to link low-cost drugs to innovative drugs. It is done under the umbrella of variables. General description of medicinal product, moisture content, tablet dimensions, tablet hardness, change in dosage form weight, tablet disintegration time, percent friability, loss on drying, drug content or drug content homogeneity of the relevant drug component or substance, dissolution rate or rate of dissolution over time,

tablet pH in various solvents, and finally the reference product in both respects (qualitative and quantifiable form) 3D structure.

General Description

The patient information leaflet (PIL) and dosage form label of the reference medication, KUVAN TABLET, provided the general description of the product. The data was also provided by the product's patent paperwork.

Water Content

Karl Fisher reagent was used to titrate 30 millilitres of methanol. After precisely weighing between 100 and 200 mg of the powdered pill sample, it was quantitatively placed into the titration tank. Karl Fischer reagent was used to titrate it, and potentiometry was used to determine the end point.

Dimensions

Six tablets were collected at random, and each tablet's thickness, length, and width were measured using an Erweka TBH30MD tablet combination tester or manually with a Vernier Calliper. Every value should fall inside the range that the specification specifies.

Hardness

One official quality control test for tablets is their hardness. In this test, ten tablets are tested for hardness using the Erwika hardness tester. A tablet hardness tester is employed. The tester is subjected to pressure, and the device measures the force.

Weight variation

One official quality control test for tablets is their hardness. In this test, ten tablets are tested for hardness using the Erwika hardness tester. A tablet hardness tester is employed. The tester is subjected to pressure, and the device measures the force.

Disintegration Test

The disintegration apparatus limited the disintegration time (DT) of the prepared tablets. Within the apparatus, there are six baskets, and each basket holds one tablet. The device was operated for fifteen minutes with the assembly suspended in the beaker of water that was kept at a temperature of 37°C. The liquid was drained from the assembly. If all six tablets had crumbled, the tablets had passed the test.

Friability

Ten tablets are chosen at random and placed on a 1000-number sieve to test the friability of the material. The collected dust is then weighed to determine the amount of abrasive material present in the tablets. Each tablet was accurately measured and weighed as a group before being recorded (W1). To get rid of any dust, the inner side of the friability test apparatus's drum was cleaned with cotton or a piece of tissue paper.

Every tablet that had been weighed was put inside the apparatus's drum. After fixing the lid, the device was turned 100 times. With the aid of air pressure or brushing, the loose dust (slack dirt) was indifferent to the tablets placed from the drum on sieve number (1000). There should be no broken or cracked tablets. Collectively, all of the tablets were accurately weighed (W2) and percentage of friability was calculated.

Loss on drying

A glass-stoppered shallow weighing bottle that had been dried for thirty minutes at 105°C was weighed. One to two grammes of the sample were added to the bottle, and a glass stopper was used to cover it. Accurate weight measurements were made of the sample and the glass-stoppered bottle. The sample was dispersed as evenly as possible to a depth of approximately 5 mm by gently shaking it sideways.

The sample was dried for three hours at 105°C by placing the filled bottle in the drying oven and removing the stopper. Following drying, the weighing bottle and stopper were removed from the oven and drying area, and they were left to stand in a desiccator until they reached room temperature. After covering the weighing bottle with the stopper, the bottle was weighed and percentage of loss on drying was calculated.

Assay of sapropterin dihydrochloride

The study prepared a buffer solution by dissolving 17 grams of diammonium hydrogen phosphate in 1000 mL of water, adjusting the pH with ortho phosphoric acid, and stirring with an ultra sonicator before filtering through a 0.45 µm membrane. The mobile phase used was a 20:20:60 mixture of water, acetonitrile, and buffer solution, and the diluent was an 80:20 mixture of acetonitrile and water.

A stock solution of sapropterin dihydrochloride (500 ppm) was made by dissolving 50 mg of the reference standard in the diluent. Tablets were powdered, and a portion containing 12.5 mg of sapropterin dihydrochloride was sonicated in 180 mL of diluent, adjusted to 250 mL, and filtered through a 0.45 µm PVDF filter. This solution was further diluted from 5 mL to 50 mL for analysis.

Ultra violet detection in the isocratic mode of high pressure liquid chromatography was carried out using the chromatographic parameters mentioned below. Waters Spherisorb SCX (10µ, 250 × 0.46 cm) was the column used for the analysis. It had an ultra-violet detector at 272 nanometer sand a flow rate of one millilitre per minute. The column's temperature was kept constant at 40 degrees Celsius.

Dissolution Test

In the vessel of the USP dissolution apparatus type (Paddle), 900 mL of 0.1 N hydrochloric acid was used as the dissolution medium, and the temperature was kept at 37±0.5°. Once positioned, a single tablet was turned on at 50 revolutions per minute. A sample of the specimen was taken out at predetermined intervals. Aliquots of the dissolving medium were added to the removed specimen sample amount at 37±0.5°. The technique outlined in section 4A.10.2 was used to analyse the specimen samples assay.

Tablet pH

For five minutes, a single tablet was submerged in 250 millilitres of water and repeatedly shaken using a sonicator. A pH metre was used to measure the solution's pH, and the result was recorded. Six tablets were used in total, each with a different strength, and the mean of the measured value was computed.

Qualitative and quantitative composition of reference product

The reference listed drug (RLD) labelling, patents, and pertinent literature have all been consulted in order to gather information or literature about the excipients of Kuvan tablets. The observations were tallied for use as a future point of reference when studying these medications in different formulations, and the difference can be computed then.

RESULT AND DISCUSSION

Kuvan tablets, containing Sapropterin dihydrochloride, have revolutionized the treatment landscape for phenylketonuria

(PKU) as the first FDA-approved therapy for this condition. Manufactured by BioMarin Pharmaceutical Inc., these tablets play a vital role in addressing the needs of PKU patients. This evaluation focuses on key quality attributes and performance parameters to ensure the efficacy, safety, and consistency of Kuvan tablets.

Table 1: Quality Targeted Product Profile (QTPP)

Attributes	Target
Route of Administration	Oral
Dosage form	Tablet
Strength	100 mg
Appearance (colour & shape)	Round, off-white to light yellow, tablets
Therapeutic moiety	Sapropterin Dihydrochloride
Weight of tablet (mg)	300 mg
Diameter (mm)	9.5 mm
Friability	Not more than 1.0% w/w
Assay	Not less than 90.0% and not more than 110.0% of the labeled amount of Sapropterin dihydrochloride.
Dissolution profile	USP-II, 50 RPM, 0.1N HCl, 900mL (Time points - 5,10,15 and 20 min) Not less than 85% of the labeled amount shall be dissolved in 15 min
Biopterin (Impurity-I)	NMT 0.15%
Tetrahydro biopterinsulphate (Impurity-II)	NMT 0.15%
Tetrahydro pterindihydro chloride (Impurity-III)	NMT 0.15%
Maximum unspecified degradant impurity	NMT 0.15%
Total impurities	NMT 1.0%
Label Claim	Each tablet contains 100mg Sapropterin dihydrochloride.

Table 2: Water content (% w/w) in Kuvan tablets

Batch	Weight of sample (mg)	Weight of water consumed by 1 mL KF reagent (mg)	Burette reading (mL)	Water content (% w/w)
Frist	200	1.1	2.3	1.35
Second	200	1.0	2.2	1.24
Third	200	1.2	2.2	1.28
Mean of water content (% w/w)				**1.29**

The assay analysis of Sapropterin dihydrochloride reveals variability in its concentration across six batches, with mean values ranging from 98.96% to 100.13%. This variability underscores the importance of rigorous quality control to ensure that each tablet contains the specified amount of the active ingredient, critical for therapeutic efficacy.

The dissolution test demonstrates rapid and complete drug dissolution within 30 minutes across different media, including 0.1 N HCl, purified water, and apple juice. Consistent dissolution characteristics in various physiological environments indicate robust performance and predictable drug release kinetics, ensuring reliable therapeutic outcomes.

The friability test assesses tablet mechanical strength, with results showing mean friability values within acceptable limits (0.35% w/w). Consistent friability percentages across batches indicate uniformity in manufacturing and packaging processes, contributing to product quality and stability during handling and transportation.

Table 3: Dissolution profile of the Kuvan tablets

Time in min	% Released drug		
	0.1 N HCl	Purified Water	Apple Juice
0	0	0	0
5	78	75	76
10	92	86	88
15	96	93	94
20	98	96	97
30	100	100	100
45	101	100	100

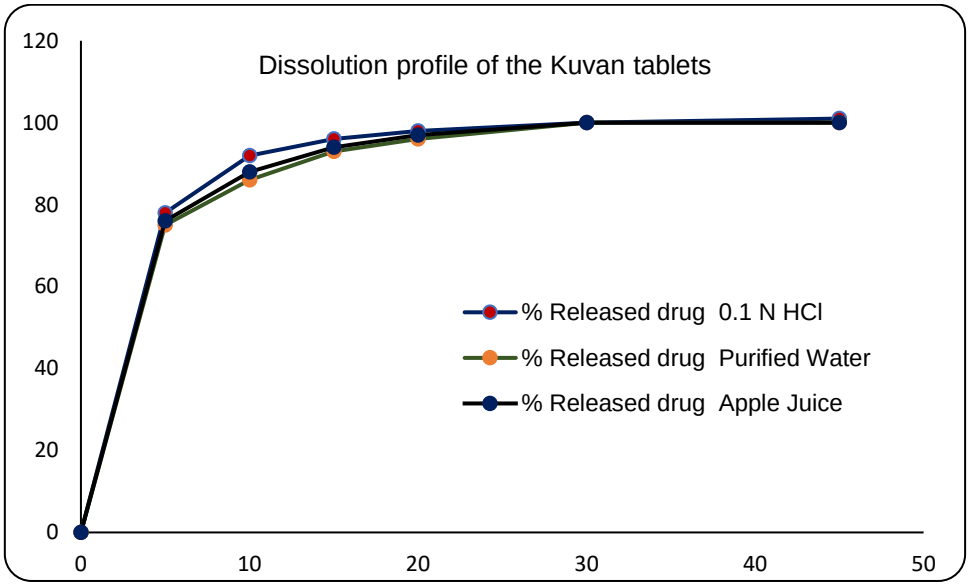

Figure 1: Dissolution profile of Kuvan tablets (100 mg)

Analysis of related substances confirms impurity levels well below specified limits, with total impurities not exceeding 0.261% w/w. Stringent quality control measures during manufacturing minimize impurities, enhancing drug safety and reducing the risk of adverse effects.

Tablet pH evaluation indicates consistent pH values ranging from 3.4 to 3.6, with a mean pH of 3.47. Maintaining consistent pH levels is crucial for optimal drug performance and gastrointestinal tolerability, ensuring compatibility with physiological conditions.

In conclusion, the evaluation underscores the adherence of Kuvan tablets to stringent quality standards and performance criteria. With consistent assay results, rapid dissolution, satisfactory mechanical strength, low impurity levels, and appropriate pH levels, Kuvan tablets offer effective, safe, and reliable treatment for PKU patients. Continued quality control measures are recommended to uphold pharmaceutical quality standards and ensure consistent therapeutic outcomes.

CONCLUSION

Kuvan tablets demonstrate high quality and reliability for treating phenylketonuria (PKU). The evaluation shows consistent dosage with minimal variability in Sapropterin dihydrochloride concentration across batches. The tablets dissolve rapidly and completely within 30 minutes in various media, ensuring predictable therapeutic effects. They exhibit strong mechanical strength with low friability values, indicating stability during handling and transportation. Impurity levels are significantly below specified limits, enhancing the drug's safety profile. Additionally, the consistent pH levels ensure compatibility with physiological conditions and gastrointestinal tolerability. These findings confirm that Kuvan tablets provide effective, safe, and reliable treatment for PKU, supported by stringent quality control measures.

REFERENCES

1. Rodwell, Victor W., and Robert K. Murray. "Biochemistry & Medicine." Harper's Illustrated Biochemistry, 31e Rodwell VW, Bender DA, Botham KM, Kennelly PJ, Weil P. Rodwell V.W., & Bender D.A., & Botham K.M., & Kennelly P.J., & Weil P(Eds.), Ed 26, 2003, 255.

2. https://pubchem.ncbi.nlm.nih.gov/compound/Phenylalanine

3. Tripathi, K.D. (2013) Essentials of Medical Pharmacology. 7th Edition, Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, 816-835. https://doi.org/10.5005/jp/books/12256

4. Angela T. S. Wyse, Tiago M. dos Santos, Bianca Seminotti & Guilhian Leipnitz, Insights from Animal Models on the Pathophysiology of Hyperphenylalaninemia: Role of Mitochondrial Dysfunction, Oxidative Stress and Inflammation, Molecular Neurobiology 2021;58:2897-2909. https://doi.org/10.1007/s12035-021-02304-1 PMid:33550493

5. Ekenna IC, Abali SO, Comparison of the use of kinetic model plots and DD solver software to evaluate the drug release from griseofulvin tablets, Journal of Drug Delivery and Therapeutics. 2022;12(2-S):5-13 https://doi.org/10.22270/jddt.v12i2-S.5402

6. Daniel A. Hussar et al; New Drugs: Nebivolol hydrochloride, nilotinib, and sapropterin dihydrochloride; 2008; Journal of the

American Pharmacist Association; https://doi.org/10.1331/JAPhA.2008.08509 PMid:18359737

7. Dennis J. Cada; 2008; Sapropterin Dihydrochloride Tablets Hospital Pharmacy, Volume 43, Number 4, pp 307-314. https://doi.org/10.1310/hpj4304-307

8. Nenad Blau; Sapropterin dihydrochloride for phenylketonuria and tetrahydrobiopterin deficiency, Expert Review of Endocrinology & Metabolism; 2010;5(4):483-494, https://doi.org/10.1586/eem.10.39 PMid:30780801

9. Deniz Kor, Berna Şeker Yılmaz, Fatma Derya Bulut, Serdar Ceylaner and Neslihan Önenli Mungan; Improved metabolic control in tetrahydrobiopterin (BH4), responsive phenylketonuria with sapropterin administered in two divided doses vs. a single daily dose; J Pediatr Endocrinol Metab; aop; 2017 DOI https://doi.org/10.1515/jpem-2016-0461 .

10. Lunan Pharmaceutical Group Co.; 2019; Preparation and in vitro/in vivo Evaluation of Sapropterin Dihydrochloride Immediate Release Tablets; CJPH; 50(08): 883-889; DOI: https://doi.org/10.16522/j.cnki.cjph.2019.08.010 .

11. Emanuela Scudellaro, Luciana Tartaglione, Fabio Varriale, Carmela Dell' Aversano and Orazio Taglialatela-Scafati, HPLC-Based Analysis of Impurities in Sapropterin Branded and Generic Tablets, Pharmaceutics 2020;12:323; https://doi.org/10.3390/pharmaceutics12040323 PMid:32260076 PMCid:PMC7237990

12. https://www.trc-canada.com/product-detail/?T795613 (accessed on 23.08.2022).