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Article

Formulation and Optimization of Immediate Release Tablet of Sapropterin Dihydrochloride by Dry Granulation Process

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Abstract

The research aims to develop and evaluate an immediate-release dosage form of sapropterin dihydrochloride to improve efficacy, stability, and patient acceptance in treating hyperphenylalaninemia (HPA), ensuring rapid therapeutic action upon administration. Formulation development began with a pre-formulation study to evaluate drug-excipient compatibility, solubility, and compressibility, followed by feasibility trials to create a prototype formulation. Dissolution tests and optimization methods, including DoE and OFAT, were employed to refine the formulation based on critical quality attributes. Process optimization involved identifying and fine-tuning critical parameters through sequential unit operations and risk assessments, ensuring uniformity and quality during scale-up for commercial production. The prototype formulation development for a tablet product based on the reference product Kuvan involved strategic excipient selection to meet critical quality attributes (CQA) and mitigate concerns like mottling. The formulation deviates from the reference by using LH 21 as a binder, colloidal silicon dioxide as a glidant, and omitting anhydrous dibasic calcium phosphate, with Mannitol SD (Pearlitol 200) chosen for its flowability and compressibility. The feasibility trial aimed at achieving pharmaceutical equivalence to Kuvan tablets, focusing on bioequivalence, stability, and API distribution, and involved top spray fluid bed granulation with roller compaction and blending identified as high-risk steps. Optimization of tablet formulation considered drug substance particle size, blend ratios, and excipient selection, with adjustments in intra and extra-granular ratios significantly impacting tablet characteristics.

Keywords: Immediate Release, Sapropterin Dihydrochloride, Dry Granulation Process

INTRODUCTION

Hyperphenylalaninemia, including phenylketonuria (PKU), is a metabolic disorder characterized by elevated phenylalanine levels due to defects in the enzyme phenylalanine hydroxylase (PAH). This enzyme converts phenylalanine to tyrosine, a precursor for neurotransmitters and hormones, with the cofactor tetrahydrobiopterin (BH4). Untreated PKU can lead to severe neurological damage, including intellectual disability and developmental delays, due to toxic byproducts and disrupted neurotransmitter synthesis. Early detection through newborn screening and dietary management is crucial, with recent advances in pharmacological therapies providing additional treatment options. Lifelong management strategies are essential to prevent neurological complications and maintain overall health [1, 2].

The limited availability of sapropterin dihydrochloride drug products in the market, combined with issues such as poor tablet hardness, stability, and high cost, highlights the need for a superior dosage form. Current formulations face challenges due to the highly crystalline and hygroscopic nature of sapropterin dihydrochloride, which impacts quality during direct compression and transportation. The proposed research aims to develop an advanced, cost-effective dosage form using a different composition and process, improving therapeutic efficacy, patient compliance, and safety. Key challenges include selecting a suitable antioxidant, ensuring drug stability, and optimizing the manufacturing process, with a focus on dry granulation and roll compaction to achieve higher process yield and product quality.

The present study aims to formulate immediate release tablets of sapropterin dihydrochloride using the roll compaction method with different excipients than those used in marketed products. The primary goal is to design and evaluate a synthetic form of the naturally occurring R-diastereomer of tetrahydrobiopterin (BH4) for treating hyperphenylalaninemia (HPA). Key objectives include ensuring drug-excipient compatibility, focusing on quality target product profile (QTPP), critical quality attributes (CQA), critical material attributes (CMA), and critical process parameters (CPP), utilizing design of experiments (DoE) and statistical methods to optimize formulation and process variables, and proving the new formulation's efficacy and safety. The study also involves creating a single-layer tablet for immediate release, enhancing patient compliance and acceptance, and assessing the in-vitro effects and chemical stability of the drug throughout its shelf life.

The use of super-disintegrating agents like cross-linked polyvinylpyrrolidone, sodium starch glycolate, and carboxymethylcellulose in immediate release tablet formulations ensures rapid disintegration and drug release. This review article covers the properties of these agents, formulation techniques, and evaluation parameters for

immediate release tablets [3, 4]. Calcium orthophosphate, a biocompatible and bioactive salt found in biological systems, holds promise for biomedical applications. Particularly, dicalcium phosphate monohydrate (CaHPO4·H2O) stands out for its advantageous properties and is extensively utilized as an excipient in tablet technology within the pharmaceutical field [5]. The study observed a decrease in aspirin levels across all samples, with average yields ranging from 66.5% to 80.0% at study completion. The effectiveness of moisture-proof polymer coatings on slightly hygroscopic cores was found to be limited, as evidenced by the decrease in aspirin levels. In some cases, such coatings may even accelerate the degradation of solid dosage forms [6].

To address the urgent need for better treatment for patients with hyperphenylalaninemia (HPA), including those with phenylketonuria (PKU) or BH4 deficiency, an immediate release dosage form of sapropterin dihydrochloride is being developed and optimized for commercial use. This dosage form aims to improve patient well-being and will utilize immediate release technology to ensure rapid therapeutic action. The proposed formulation will also ensure chemical and physical stability, providing a more effective and reliable treatment option for these patients.

EXPERIMENTAL

Pre-formulation study

Drug-excipient compatibility studies were conducted to assess the physical and chemical compatibility of sapropterin dihydrochloride with various excipients under accelerated storage conditions, ensuring adherence to the intended formulation protocol for treating phenylketonuria. Solubility testing involved dissolving the drug in different solvents and determining its solubility through chromatography after filtration and dilution. Particle size analysis of sapropterin dihydrochloride was conducted using the Malvern master-sizer. The sample was dispersed in a medium, and continuous monitoring was employed to achieve an obscuration level between 10 and 30%. Measurements were taken twice, and the average was calculated for stable obscuration levels. The compressibility index of the drug powder was calculated using tapped density and bulk density measurements. Tapped density was determined by mechanically tapping 20g of the powder in a cylinder until saturation, while bulk density was measured by filling a cylinder with 10g of powder. Powder microscopy involved spreading a small amount of powder on a slide and examining it under a microscope for homogeneity.

Formulation & Optimization of Immediate Release Tablet

Excipient selection for the tablet formulation of sapropterin dihydrochloride was based on the composition of the reference product Kuvan tablet. Excipients were chosen considering drug-excipient compatibility studies, prior knowledge, and compatibility with stress conditions. Ascorbic acid, cross-povidone, anhydrous dibasic calcium phosphate, mannitol, riboflavin, and sodium stearyl fumarate were selected for their respective roles in the formulation. A feasibility trial was conducted to formulate tablets with different ratios of excipients and sapropterin dihydrochloride. Steps included sifting, blending, roll compaction, pre-lubrication, lubrication, and compression, with each step evaluated for its impact on blend uniformity and critical quality attributes (CQAs). Dissolution testing was performed on the formulated tablets to assess their release characteristics, following the protocol outlined for the reference product.

Formula optimization for sapropterin dihydrochloride tablets involved maximizing various factors using a predefined formula and the roll compaction process. Excipients were carefully selected and their ratios optimized for specific functions. Parameters such as drug particle size, granular ratio, crospovidone grade and level, and antioxidant selection were studied during optimization using Design of Experiments (DoE) and One Factor at a Time (OFAT) methods.

The process optimization for formulating sapropterin dihydrochloride tablets involves accurate dispensing of ingredients, premixing for homogeneity, roller compaction for granule formation, pre-lubrication and lubrication to aid compression, compression into tablets, and finally, packing for distribution and storage.

RESULT AND DISCUSSION

Pre-formulation study

The drug-excipients compatibility study aimed to evaluate the physical and chemical compatibility of the drug substance with various excipients under accelerated storage conditions. Excipients were selected based on a careful formulation strategy and reference product compositions. The ratios between the API and excipients were determined through literature review and considerations of excipient functionality and drug potency. The study integrated prior knowledge and scientific literature to ensure a well-informed approach to excipient selection and formulation development. Overall, the investigation provided insights into excipient-drug interactions and stability issues, contributing to the development of a robust formulation strategy.

Sapropterin dihydrochloride demonstrates pH-dependent solubility in aqueous media, with higher solubility in acidic conditions and a decrease in solubility with increasing pH, indicating its classification as highly soluble according to the Biopharmaceutics Classification System (BCS) over a pH range of 1.2-7.4. The particle size of Sapropterin dihydrochloride, assessed using the Malvern Mastersizer, influenced various quality parameters of tablet dosage forms such as dissolution rate, disintegration time, content uniformity, and hardness. The tapped density of the powder ranges from 0.717 to 0.735 mg/mL, while the bulk density ranges from 0.463 to 0.481 mg/mL, with average values of 0.726 mg/mL and 0.474 mg/mL, respectively. The compressibility index, calculated as 34.62%, indicates the degree of powder compressibility.

Formulation & Optimization of Immediate Release Tablet

The composition of the immediate-release tablet of Sapropterin Dihydrochloride, formulated via the dry granulation process, comprises distinct components serving various functions in the tablet formulation (Table 1). The intragranular core part contains Sapropterin dihydrochloride as the active pharmaceutical ingredient (API), combined with Mannitol SD (Pearlitol 200) as a filler, Ascorbic acid in fine powder form acting as an antioxidant, and a minute quantity of Riboflavin as a colorant. On the other hand, the extra-granular part includes additional Mannitol SD (Pearlitol 200) to further contribute to the tablet's bulk, Crospovidone XL as a disintegrant to aid in tablet breakdown upon ingestion, Low substituted Hydroxy propyl cellulose (LH 21) as a binder, and Colloidal silicon dioxide for its anti-caking properties. Furthermore, Sodium stearyl fumarate is incorporated as a lubricant to facilitate tablet manufacturing processes. Each tablet is formulated to contain a total weight of 300.00 mg, with precise quantities of each ingredient meticulously determined to ensure the desired pharmaceutical attributes and performance of the final dosage form.

Table 1: Composition of Immediate Release Tablet of Sapropterin Dihydrochloride by Dry Granulation Process

Ingredients	Quantity of ingredient (mg/tab)
Intragranular core part	
Sapropterin dihydrochloride	100.00
Mannitol SD (Pearlitol 200)	93.90
Ascorbic acid (fine powder)	3.00
Riboflavin	0.10
Extra-granular Part	
Mannitol SD (Pearlitol 200)	66.00
Crospovidone XL	25.00
Low substituted Hydroxy propyl cellulose (LH 21)	6.00
Colloidal silicon dioxide	3.00
Lubricant	
Sodium stearyl fumarate	3.00
Total weight	**300.00**

The immediate release tablets of Sapropterin Dihydrochloride exhibit different characteristics across three batches: hardness ranges from 5.5 to 8.1 kp, thickness varies between 4.00 and 4.25 mm, friability ranges from 0.11% to 0.15%, and disintegration time spans from 3.20 to 4.15 minutes (Table 2).

The dissolution profile of the formulated tablets reveals efficient drug release across three media types - 0.1 N HCl, purified water, and apple juice - over a 45-minute period. In all media, complete dissolution is achieved by 30 minutes, indicating good solubility and consistent kinetics. Notably, a slight increase in drug release at 45 minutes suggests potential sustained release, highlighting the tablets' versatility and suitability for various physiological conditions (Table 3).

Table 2: Evaluation Parameters of Immediate Release Tablet of Sapropterin Dihydrochloride

Batch No	Hardness (kp)	Thickness (mm)	Friability (%)	Disintegration Time (min)
1	5.5-7.5	4.12-4.17	0.11	3.30-3.50
2	5.7-7.6	4.00-4.25	0.15	3.20-4.05
3	5.5-8.1	4.00-4.20	0.12	3.40-4.15

Table 3: Dissolution profile of the Formulated tablets

Time in min	% Released drug		
	0.1 N HCl	Purified Water	Apple Juice
0	0	0	0
5	65	76	74
10	80	88	84
15	94	94	92
20	97	97	96
30	100	100	100
45	101	101	100

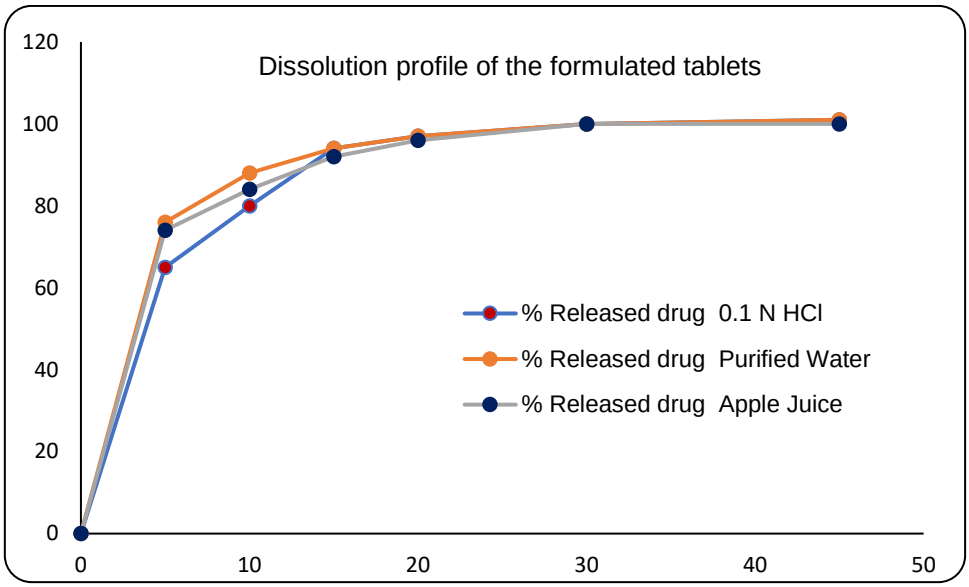

Figure 1: Dissolution profile of the Formulated tablets

CONCLUSION

In conclusion, the study underscores the commitment to producing high-quality sapropterin dihydrochloride tablets for phenylketonuria patients through rigorous evaluation and optimization efforts. Adherence to stringent quality control measures and continuous optimization will be crucial for maintaining pharmaceutical standards and ensuring consistent therapeutic outcomes. Moving forward, the establishment of In Vitro-In Vivo Correlation (IVIVC) sets the stage for commercializing the immediate-release tablet, offering a viable treatment option for hyperphenylalaninaemia patients. Future recommendations include conducting in-vivo bioequivalence studies to validate IVIVC results and scaling up production to ensure accurate batch calculations.

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