WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 1, 591-602. Review Article ISSN 2277–7105

A REVIEW ON PROCESS VALIDATION OF EXTENDED RELEASE BI-LAYERED TABLET CONTAINING DAPAGLIFLOZIN, SITAGLIPTIN & METFORMIN HYDROCHLORIDE

Priya Kant*, Rita Saini and Shivanand Patil

Department of Pharmacy, Shree Dev Bhoomi Institute of Education Sciences & Technology, Dehradun, Uttarakhand, 248007.

Article Received on
10 November 2024,

Revised on 30 Nov. 2024,
Accepted on 20 Dec. 2024

DOI: 10.20959/wjpr20251-35116

***Corresponding Author**
Priya Kant
Department of Pharmacy, Shree Dev Bhoomi Institute of Education Sciences & Technology, Dehradun, Uttarakhand, 248007.

ABSTRACT

This article provides a detailed exploration of process validation of Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended release bi-layered tablets, encompassing its introduction, life cycle, stages, and various types. The primary focus of the study is to demonstrate that process validation plays a pivotal role in instilling a high level of confidence that the products manufactured will consistently meet established specifications and quality attributes throughout the entire manufacturing process. Central to this confidence is the validation study, which rigorously evaluates critical parameters such as accuracy, sensitivity, specificity, and repeatability of the manufacturers approved and documented test procedures. Consequently, validation emerges as an essential component of quality assurance, ensuring that the products not only comply with regulatory requirements but also adhere to the highest standards of quality. The article further emphasizes the significance of employing objective measures, robust statistical tools, and thorough analyses in the validation process. These elements are crucial for understanding and managing variability, which is inherent in manufacturing processes. By focusing on the detection and control of such variability, process validation provides assurance of consistent quality and productivity throughout the product's life cycle. This review meticulously examines the different approaches, processes, and critical steps that must be continuously monitored during the manufacturing phase, highlighting the necessity of pharmaceutical validation. By addressing these various aspects, the article aims to reinforce the integral role of validation in maintaining product integrity,

reliability, and compliance within the pharmaceutical industry, ultimately contributing to enhanced patient safety and therapeutic efficacy.

KEYWORDS: Dapagliflozin, Sitagliptin, Metformin hydrochloride and Process validation.

INTRODUCTION

Dapagliflozin, Sitagliptin, and Metformin are key components in managing type 2 diabetes mellitus (T2DM). Dapagliflozin, an SGLT2 inhibitor, reduces glucose reabsorption in the kidneys, leading to increased glucose excretion, which helps lower blood sugar levels and can aid in weight loss and blood pressure reduction. Sitagliptin, a DPP-4 inhibitor, enhances incretion hormones, boosting insulin secretion and decreasing glucagon levels, thereby improving glycemic control post-meals. Metformin, the first-line treatment for T2DM, decreases hepatic glucose production and enhances insulin sensitivity, effectively lowering blood glucose levels with a favorable safety profile.

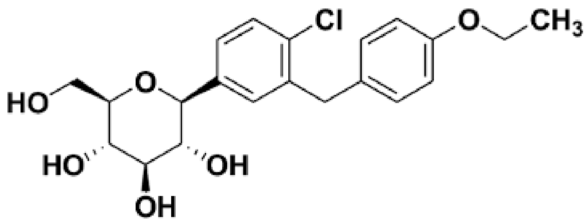
The bilayer tablet formulation combines these agents, offering comprehensive blood glucose control through multiple mechanisms, while simplifying the dosing regimen to improve patient adherence.

In terms of manufacturing, process validation is essential for ensuring consistent production of these tablets. It guarantees uniformity in size, weight, and dosage across batches, meets quality standards for attributes like dissolution and hardness, and ensures regulatory compliance through documented proof of reliability. Furthermore, it identifies inefficiencies to enhance process performance and confirms the safety and efficacy of the tablets for patient use. Overall, process validation is crucial for maintaining product consistency, quality, and compliance in tablet manufacturing.[1]

Drug profile

Dapagliflozin: S-odium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin was the first to receive FDA approval. recommended as a type 2 diabetic treatment. When combined with diet and exercise, dapagliflozin improves adult glycemic control by inducing glycosuria, or the suppression of glucose reabsorption in the proximal tubule of the nephron. Research has examined dapagliflozin as a monotherapy or in conjunction with other oral hypoglycemic drugs such as insulin.[2]

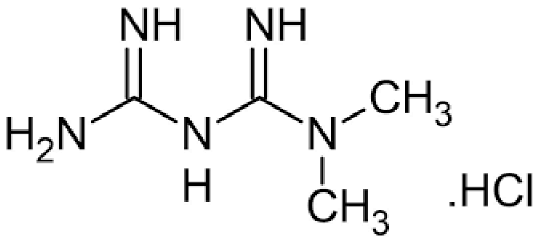
Structure



Chemical formula- $C_{21}H_{25}ClO_6$

Metformin hydrochloride: Metformin is the first-line treatment for type 2 diabetes and is classified as an antihyperglycemic medication because it lowers blood sugar levels without causing low blood sugar (hypoglycemia). It works as an "insulin sensitizer," meaning it helps the body use insulin more effectively and lowers insulin resistance. Metformin is particularly suitable for overweight individuals with type 2 diabetes because it can also help with moderate weight loss.[3]

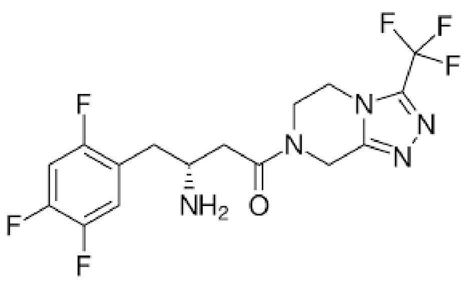
Structure



Chemical formula- $C_4H_{12}ClN_5$

Sitagliptin: It is an oral inhibitor of dipeptidyl peptidase-4 (DPP-4), is designed to help individuals with type II diabetes mellitus better control their blood glucose levels. It is used in addition to exercise and diet. By lowering glucagon and raising insulin in reaction to glucose, this medication enhances blood sugar management.[4]

Structure



Chemical formula-$C_{16}H_{15}F_6N_5O$

Types of validation

Validation often comes in four main forms. They are listed below.

- Process validation
- Equipment validation
- Analytical method validation
- Cleaning validation

Process validation

One of the well-thought-out requirements of a quality management system is process validation. The most important and widely accepted criterion of modern excellent manufacturing practices is process validation. Producing goods consistently matched to their intended purpose is the aim of a quality system. A crucial element in ensuring the achievement of these criteria and goals is process approval.[**Error! Reference source not found.**,6]

- Retrospective validation
- Prospective validation
- Concurrent validation
- Revalidation

Process validation approch

General consideration

Process validation is critical element to assuring dependability and quality of manufacturing processes, regardless of whether an improved or conventional technique is used to manufacture a therapeutic item. A product's production method needs to be approved before it can be sold. Concurrent consent might be given in some extraordinary circumstances. The validation process must confirm that the control method is suitable for both process design and the quality of final product. This includes all strengths produced and all manufacturing sites involved in creating the sold product. Using a bracketing method may be suitable when variations in potencies, quantities, or package sizes are present. Every recommended location must be considered during the verification process. Data must be validated to prove that the production process is effective for each product at every manufacturing location. If the file does not indicate otherwise, these documents must be stored at the originating site and readily accessible for examination.[7]

Process validation approach for product

Process validation is a systematic approach aimed at gathering and analyzing data to scientifically demonstrate the capability of a manufacturing process to consistently produce high-quality products. This comprehensive evaluation spans from the initial process design phase through to commercial production. The process validation activities encompass three key stages, as outlined below:[8]

Stage 1 – Process design: The initial steps involve a meticulous layout of the commercial production process. The knowledge acquired from developmental & scale-up activities influences design of the process. The objective is creating consistent production process to ensure quality products.[9]

Stage 2 – Process qualification: At these steps, a comprehensive evaluation of process is designed to carried out assess of its suitability for consistent commercial manufacturing. To make sure that the procedure regularly satisfies predefined quality standards and requirements, a number of parameters and variables are evaluated. Verifying that the production process can reliably produce goods of appropriate quality is the aim.[10]

Stage 3 – Continued process verification: During regular production, this steps is continuously monitored to evaluate the validated process which stays under control. The process is ensured to continue producing goods that fulfill the necessary quality requirements by ongoing observation and analysis. To maintain quality of final product, any deviations or differences are promptly addressed to safeguard the process's integrity.[11]

Comparison studies between Latest and Existing studies

The study on Metformin Hydrochloride immediate-release tablets employed a systematic wet granulation method, validating the manufacturing process for 500 mg, 850 mg, and 1000 mg film-coated tablets through optimized critical parameters, ensuring consistency and quality. In contrast, the latest validation study of Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended-release bilayer tablets involves a more complex formulation with multiple active ingredients, requiring extensive monitoring of drug interactions and release profiles. While both studies focus on process validation and quality assurance, the Metformin study is simpler and more straightforward, whereas the bilayer approach introduces additional challenges related to maintaining therapeutic efficacy and stability across multiple components.[12]

The study on Metformin hydrochloride 500 mg tablets focused on prospective process validation, examining critical parameters during sifting, blending, and compression for a batch size of 200 tablets. It confirmed that the manufacturing process meets predetermined specifications and quality attributes, aligning with ISO 17025 standards. In contrast, the latest process validation for Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended-release bilayer tablets involves a more complex formulation with multiple active ingredients. This requires a comprehensive evaluation of drug interactions and release profiles, adding complexity to the validation process. While both studies emphasize quality assurance, the Metformin study is more straightforward, whereas the bilayer validation addresses additional challenges related to combination therapies.[13]

The study on Metformin hydrochloride 500 mg tablets focused on prospective process validation for a small batch size of 200 tablets, assessing critical parameters during sifting, blending, and compression to ensure compliance with ISO 17025 standards. It demonstrated that the manufacturing process meets specified quality attributes. In contrast, the latest validation study for Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended-release bilayer tablets involves a more complex formulation with multiple active ingredients, requiring comprehensive evaluation of interactions and drug release profiles. While both studies emphasize quality assurance, the Metformin study is simpler and more direct, whereas the bilayer validation faces additional challenges related to combination therapy.[14]

The research on Metformin hydrochloride 500 mg tablets focused on concurrent process validation, emphasizing the importance of controlling critical parameters throughout manufacturing to ensure quality. Three consecutive batches were evaluated, with successful calibration of instruments and verification of raw materials. Key metrics during granulation, drying, blending, and compression met specifications, confirming a properly validated process.

In contrast, the latest validation study for Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended-release bilayer tablets involves a more complex formulation that necessitates thorough assessment of interactions and release profiles. While both studies stress the need for quality assurance, the Metformin study is more direct and simpler, whereas the bilayer validation must address additional challenges related to the combination of multiple active ingredients.[15]

Issues regarding process validation of dapagliflozin, Sitagliptin and Metformin hydrochloride extended release bi-layered tablets

1. Resource intensive

The process of validating involves the extensive expenditure of time, labour and cash. Pharmaceutical companies may find the extended and comprehensive processes of documentation, testing, and monitoring as expensive. Specifically, smaller firms may experience difficulties in allocating limited resources towards validation exercises, which could lead to delays in the validation processes or weak validation protocols.

2. Rigidity

There's speedy development and continuous improvement of production technologies in the pharmaceutical sector. Nevertheless, rigid implementation of process validation impedes organizational dynamics as penned. The validation process ensures assurance and integrity while limiting pharmacies to alter and amend their validated processes. Such rigidity hinders the introduction of enhancements, and the inability to accept some technologies in the production process aimed at improving efficiency and product quality may result in losses.

3. Complexity of processes

These typically involve several processes with multiple variables. However, validating these complicated processes can be time-consuming since there are some situations which can hardly be taken into account. Unforeseen fluctuations may happen when undertaking normal production activities and the result is an effect on product quality. However, it remains a daunting task to account for such fluctuations when conducting a validation that may only reflect limited variations associated with practical manufacturing situations.

4. Inadequate risk management

Process validation is meant to prevent problems in product quality, but there are certain instances when such events cannot be avoided. Divergences in manufacturing may result due to a lack of risk assessment and handling. Such departures may impact on product quality and safety. Failing to consider some risk factors or insufficiently comprehending the consequences of deviation, if any, may lead to invalidation.

5. Regulatory compliance challenges

Adherence to strict regulation by the pharmaceutical industry remains imperative in the approbation of products and securing the marketplace. It is not an easy feat, however, to meet and sustain such standards as they grow more rigorous over time. Changes in regulations could mean that validation protocols have to be changed which is a complex issue. Keeping up with regulatory changes helps a manufacturer to avoid not being compliant such as postponing the product approval and recall.

6. Documentation burden

Documentation is vital in demonstrating compliance with process validation and regulatory standards. This is comprehensive documentation with protocols, reports, SOPs and every step in the validation process. Ensuring that these records are stored, updated, and maintained can be very demanding. Too much paperwork may shift focus from core areas of medication production and may be inaccurate or miss out on recordings.

7. Human error

Despite thorough testing and verification mechanisms, man-made mistakes can contribute to problematic occurrences. 3 Process validation will not work if there is inadequate training, deviations from established procedures or lack of attention. Validation should consider human factors in the design of training programs, the establishment of standardized procedures, and constant monitoring to ensure that errors will not compromise the process.

8. Supply chain variability

Raw materials and components that are essential for the pharmaceutical industry worldwide. This implies that, if the supplier provides poor quality or characterised materials it interferes with the entire manufacturing process. When dealing with multiple suppliers, it is difficult to ensure that there is consistency in the quality of the inputs. The validation process may be subjected to uncertainty in that issues such as changes in suppliers or variations in the quality of raw materials may undermine the reliability of the manufacturing processes.

METHODOLOGY

Research design

In research, a "compass" through this intricate path of planning and conducting explorations is the research methodology. Consequently, it shows the steps used by investigators to determine the purpose, the problem, as well as the solution based on the information collected over an investigation period (Melnikovas, 2018). This process necessitates a research fashion that provides an organised framework for the research endeavour. It is imperative to decide on a direction towards the initial end of the design phase of this exercise; by doing so, the kind of relevant information that should be accrued to achieve the intended goal of this task is specified (Sileyew, 2019).

The method of "mixed mode data analysis" has been chosen as the method for this study to gain insights into the application and implications of process validation in the pharmaceutical industry. In this case, there is a need to collect critical data as well as existing empirical studies in conjunction with the previously published literature concerning sustainable practices. Such an approach enables a comprehensive and up-to-date understanding of the issue, as it involves a comparison of different sources.

From a strategic viewpoint, it is a “Mix-Mode of Data Analysis” aiming to identify and analyse information from external sources such as industry reports, academic studies, or cases. This strategy is also cheap and successful, considering there is a wide range of publicly available information on what makes good sustainable practices. The research by looking at current data has a chance to discover that may not require any fresh data.

In summary, the procedure has been planned with a thorough consideration of the determinants, such as positivism, reasoned logic, and exploitation techniques on given information. It appears that the mix mode approach to exploratory data is a strong way to obtain noteworthy findings relating to process validation in pharmaceuticals.

Data collection

For these aspects of “Process validation of Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended release bi-layered tablets” to be insightful, a thorough data collection strategy would have been required. This project uses mainly secondary data collection methods as a way of acquiring data. This entails a search of already existing literature from reliable sources like peer-reviewed journals, government documents, business periodicals, and appropriate databanks containing real-time information.

The selection of secondary data is based on many factors which enhance the study’s efficacy and strength. Therefore, it needs to be noted that greening activities are a dynamic phenomenon which may take various directions depending on certain conditions. A large amount of historical and current data can be obtained from existing articles and books by the researcher. It is essential to employ a longitudinal perspective for tracing the adoption of sustainability pharmaceuticals, to better shed light upon the drivers and outcomes that affect operations within these entities. Besides, research using secondary sources such as experiments is cheaper and less laborious.

However, this research work has used primary data collection to give the latest and actual information. Using already existing data eliminates extended periods of fieldwork and saves on resources such as time, which are very important parameters due to resource and temporal limitations that are common in research work. Efficiency plays an important role especially while dealing with the widely spread network of the pharmaceutical industry. The data collection method chosen must have many advantages. Firstly, it helps to close any gap in the previous theories by conducting a detailed study of the literature and thereby expanding these theories.

In the final instance, it is important to mention the decision to use secondary data in conjunction with primary data collection for this study on "process validation of Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended release bi-layered tablets" because of its efficacy, cost-effectiveness, and ability to give detailed information about the subject matter. This method of analysis should provide meaningful results that have contributed to existing knowledge about what process validation can do when undertaking environmentally friendly activities in the industry.

RESULT

The studies on Metformin hydrochloride tablets and the Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended-release bilayer tablets highlight differing complexities in process validation. The Metformin study, focusing on prospective or concurrent validation for 500 mg tablets, emphasizes straightforward methodologies and adherence to ISO 17025 standards, ensuring quality through controlled critical parameters in smaller batches. In contrast, the bilayer tablet study involves multiple active ingredients, requiring extensive evaluation of drug interactions and release profiles, adding layers of complexity to the validation process. While both prioritize quality assurance, the Metformin validation is more direct, whereas the bilayer approach presents additional challenges related to maintaining efficacy and stability across combined therapies.

DISSCUSSION AND CONCLUSION

The process validation of dapagliflozin, sitagliptin, and metformin hydrochloride, which had not been previously performed, was initiated through a novel approach. This involved combining the three active pharmaceutical ingredients (APIs) in a single validation process. The study of Dapagliflozin, Sitagliptin, and Metformin hydrochloride extended-release bilayer tablets highlights the advanced formulation approach to enhance diabetes management. Compared to other tablet validation studies, the bilayer extended-release tablets present greater formulation complexity and validation requirements. Ensuring that extended-release profiles are effectively managed is critical for the tablet's success, necessitating rigorous validation processes to meet regulatory standards and ensure patient safety and efficacy. Critical process parameters were identified using process capability analysis and then evaluated by challenging them against lower and upper release specifications. Three initial validation batches (I, II, III) were executed using identical methods, equipment, and validation criteria. Critical parameters across various stages, including sifting, mixing, granulation, drying, sizing, compression, and coating, were identified and assessed according to the validation master plan. The study demonstrated that this novel process validation methodology provides a high degree of assurance that the manufacturing process consistently produces products meeting predetermined specifications and quality attributes. While bilayer extended-release tablets offer advantages in therapeutic efficacy and patient compliance, the process validation for such formulations faces challenges related to complexity, consistency, stability, regulatory requirements, and resource demands.

REFERENCES

1. Jabbour SA, Hardy E, Sugg J, Parikh S, Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes care, 2014; 1, 37(3): 740-50.
2. Dapagliflozin | C21H25ClO6 | CID 9887712 - PubChem (nih.gov)
3. Metformin: Uses, Interactions, Mechanism of Action | DrugBank Online
4. Sitagliptin: Uses, Interactions, Mechanism of Action | DrugBank Online
5. Pathuri R, Muthukumaran M, Krishnamoorthy B, Nishat A. A review on analytical method development and validation of pharmaceutical technology. J Curr Pharma Res, 2013; 3(2): 855. https://scholar.google.com
6. Patil R, Deshmukh T, Patil V, Khandelwal K. Review on analytical method development and validation. Res Rev J Pharm Anal, 2014; 3(3): 1-0. https://scholar.google.com
7. Food and Drug Administration. Guide to Inspections of Oral Solid Dosage Forms Pre. Post Approval Issues for Development and Validation, 1994.

8. Kaur H, Singh G, Seth N. Pharmaceutical process validation: a review. Journal of Drug Delivery and Therapeutics, 2013; 14, 3(4): 189-94.
9. Wawre M, Dodke B, Moon A, Javalkar G. Industrial process validation in solid dosage form: a review. World Journal of Pharmacy and Pharmaceutical Sciences, 2017; 6(3): 301-16.
10. Bala G. An integrated approach to process validation. Pharmaceutical Engineering, 1994; 14: 57.
11. Kakad SB, Kolhe MH, Dukre TP. A review on pharmaceutical validation. International Journal of Pharmaceutical Quality Assurance, 2020; 25, 11(3): 338-42.
12. Kumar S, Gupta A, Kumar S. Technology Transfer and Process Validation of Metformin Hydrochloride Immediate Release Tablet. International Journal For Multidisciplinary Research, 2023; 5(4): IJFMR23044638. https://www.ijfmr.com/
13. Mishra G, Thakur A, Kaur S. Process Validation of Metformin Hydrochloride Tablet (500 mg) according to USFDA. Biological Sciences, 2021; 7, 1(1): 7-18.
14. Shewale PS, Jagtap VA, Varade AA, Badgujar VL. Process Validation of Metformin Hydrochloride Extended Release Tablets USP 500mg. World Journal of Pharmaceutical Research, 2014; 3(6): 1631-1638.
15. Sawant N, Akhtar J, Master S. Studies in Con-Current Process Validation of Metformin Hydrochloride Tablet Dosage Form. Research Journal of Pharmacy and Technology, 2013; 6(7): 718-25.