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PAT-BASED MONITORING AND RISK ASSESSMENT FOR SUSTAINED-RELEASE ISOSORBIDE MONONITRATE TABLET FORMULATION FOR CHRONIC STABLE ANGINA

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ABSTRACT
Background: Long-term (sustained release) (SR) Isosorbide Mononitrate (ISMN) is an effective and well-tolerated agent that enhances therapeutic effectiveness and increases patient compliance in the management of chronic stable angina. But little work has connected Process "Analytical Technology (PAT) and Quality Risk Management (QRM)" to ensure strong manufacturing and product quality.
Methods: The sustained-release isosorbide mononitrate tablets (IM) were formulated using nine formulations (F1- F9) and the wet granulation technique using HPMC K100M and ethyl cellulose. The pre- and post-compression attributes, in vitro drug release, process monitoring by PAT, quality risk evaluation by FMEA and accelerated stability testing as per ICH guidelines were evaluated.
Result: Consequently, all the formulations met the quality criteria laid out in the pharmacopoeia and showed good flowability properties, acceptable hardness (5.8–7.4 kg/cm²), friability (0.41–0.74%) and drug content (98.2–99.9%). The most critical process parameters identified by PAT were compression force (RPN = 135), dissolution (RPN = 120), and blend uniformity (RPN = 108) as identified by FMEA. Formulations F6- F8 showed good sustained drug release during 24 hours, while optimized formulation was stable under accelerated storage conditions.
Conclusion: The combination of PAT with QRM allowed for efficient process control, minimization of manufacturing inconsistencies, and production of high-quality tablets suitable for treatment of chronic stable angina.

KEYWORDS: Isosorbide Mononitrate, Sustained release tablet, Process "Analytical Technology (PAT), Quality Risk Management (QRM)**,** Quality by Design (QbD)",

1. INTRODUCTION

Chronic stable angina is one of the most common clinical symptoms of "coronary artery disease" (CAD), and it is a significant cause of morbidity, reduced quality of life and health care expenses [1]. The illness is typified by brief episodes of myocardial ischemia brought on by an imbalance between the coronary blood flow and myocardial oxygen demand [2]. Long-term pharmacological therapy remains the backbone of the care of the disease, with the main goals being: reduction of anginal episodes, increase in exercise tolerance, avoidance of cardiovascular problems, and patient adherence to treatment [3].
Long-acting nitrates, particularly "Isosorbide Mononitrate" (ISMN), remain widely used because have been shown to effectively prevent recurrent angina and improve coronary blood flow [4]. The principle of ISMN is based on nitric oxide release, which leads to vascular smooth muscle relaxation, venodilation, reduction of preload, and improvement of the balance of myocardial oxygen supply and demand [5]. It has a high oral bioavailability, stable bioavailability in humans, and a small first-pass hepatic metabolism, making it a preferred anti-anginal medication for long-term use [6].
To overcome the problems of immediate release dose forms, sustained release (SR) versions of ISMN have been developed [7].Traditional tablets often lead to rapid fluctuations in plasma drug levels, requiring frequent daily administration and increasing the likelihood of adverse effects such as headache, hypotension and nitrate tolerance [8]. SR tablets give a controlled release of the medicine over a long period of time, maintain a therapeutic concentration in the plasma, and minimize peak-trough fluctuations [9].
This approach increases treatment adherence through once-a-daydosing and reduces the risk of tolerance by maintaining an optimal pharmacokinetic profile. This has led to the development of SR formulations, which have become an important dose form in the treatment of chronic stable angina [10].
Pharmaceutical Process Analytical Technology (PAT) is now an emerging paradigm for drug manufacturing, enabling in-line monitoring, measurement and control of key manufacturing processes [11]. The United States "Food and Drug Administration" (FDA) have initiated the PAT initiative to encourage manufacturers to adopt scientific, risk-based approaches to process understanding and continual quality assurance [12]. PAT combines analytical instruments, chemometric modelling, multivariate data analysis and process control systems to monitor and "control critical quality

attributes" (CQAs), "critical material attributes" (CMAs) and "critical process parameters" (CPPs) during the manufacturing process [13]. Instead of solely depending on final product testing, PAT prioritises integrating quality into the manufacturing process via continuous measurement and feedback control [14].

1.1. Chronic stable angina and the therapeutic role of sustained-release Isosorbide mononitrate

CAD remains a leading cause of morbidity and mortality worldwide, and chronic stable angina is one of the common clinical manifestations of CAD [15]. Chronic stable angina is a condition characterized by recurrent chest discomfort or pain that occurs because of brief, predictably occurring myocardial ischemia, or lack of oxygen, caused by an imbalance between the oxygen needs of the myocardium and the blood supply of the coronary arteries [16]. Physically induced events such as physical exertion, emotional stress, or other factors that increase heart work are often responsible for the syndrome and rest or nitrates typically help relieve it [17]. Despite significant advances in cardiovascular treatments, chronic stable angina remains a major burden on the clinical and economic level, reducing exercise capacity, lowering quality of life, and increasing the use of health services [18]. Thus, long-term treatment with pharmacologic agents is essential for successful management of angina, for improvement in functional capacity, and to prevent disease progression [19]. In fact, ISMN has been proven to be effective, has a reliable and consistent pharmacokinetic profile and has relatively high bioavailability, and is thus frequently prescribed in combination with anti-anginal agents [20]. ISMN is an active nitrate metabolite which causes vasodilation through nitric oxide (NO) and leads to relaxation of vascular smooth muscle, lowering of venous return (preload), reduction of myocardial oxygen demand and improved coronary blood flow [21]. Unlike isosorbide dinitrate, ISMN is not extensively metabolized in the liver (first pass metabolism), which results in higher plasma levels and better therapeutic efficacy following oral administration [22].

1.2. Process analytical technology (PAT) and risk assessment in sustained- release tablet manufacturing

The pharmaceutical industry has increasingly adopted scientific and risk-based manufacturing practices to improve product quality, process robustness, and regulatory compliance [23]. The United States FDA designated PAT as a key development in pharmaceutical manufacturing, which uses real-time measurements of critical quality and performance attributes (QPA and CPA) to design, analyze and control manufacturing processes [24]. PAT is not only about final product testing, but also continuous process monitoring and control, which allows quality to be included in the manufacturing process [25].

PAT is closely connected to the Quality by Design (QbD) paradigm, which emphasizes on the scientific understanding and systematic development of methodologies that meet quality objectives [26]. The "International Council for Harmonization" (ICH) rules stipulate that pharmaceutical quality is attained by the comprehension of the interconnections between CMAs, CPPs, and CQAs [27]. CMAs include the physicochemical properties of raw materials that affect the performance of the product, while CPPs are manufacturing variables that directly affect the quality of the product [28]. CQAs are defined as the product attributes that are measurable, such as dissolution profile, assay, content homogeneity, hardness, friability, and stability, which are known to affect the safety and efficacy of the product in treating the disease or condition [29].

The implementation of PAT is particularly advantageous for SRISMN tablet formulation because the therapeutic activity of a formulation is dependent on producing a consistent and reproducible drug release profile [30]. The dissolution properties and bioavailability are directly related to the granule moisture content, polymer hydration, blending consistency, compression force, tablet density, and matrix integrity [31]. Monitoring these variables in real-time helps to detect abnormal situations in the process at an early stage and to make necessary changes as soon as possible, which helps ensure a uniform quality of the product and reduces manufacturing variability [32]. Furthermore, PAT in combination with risk assessment allow producers to create scientifically validated control plans, improve process performance and meet modern regulatory requirements for pharmaceutical quality systems [33].

1.3. Research gap

The majority of research focuses on formulation optimization, dissolution profiling, and traditional quality control testing, despite the fact that SR formulations of ISMN have been thoroughly studied to enhance therapeutic efficacy and patient compliance. The integration of "Quality Risk Management" (QRM) with PAT for real-time manufacturing process monitoring and control has received little attention. Moreover, thorough research that methodically identifies and assesses CMAs, CPPs, and CQAs, particularly for SRISMN tablet formulations, is lacking. Additionally, there is no evidence in the literature about the use of risk assessment techniques like

- **Aim**

To develop and evaluate a PAT-based monitoring and risk assessment strategy for SRISMN tablets used in the treatment of chronic stable angina.

- **Objective**

- To develop SRISMN tablets utilising appropriate matrix-forming polymers and pharmaceutical excipients.
- To identify the CMAs, CPPs, and CQAs influencing the quality and performance of the SR tablet formulation
- To implement PAT tools for real-time monitoring of critical manufacturing processes during tablet production.

2. MATERIAL AND METHOD

The study was conducted in the experimental laboratory-based formulation and evaluation setup for developing the SR ISMN tablets. A PAT-based monitoring system was integrated with QRM concepts to evaluate the manufacturing

performance, identify manufacturing risks and ensure product quality consistency throughout the tablet manufacturing process.

2.1. Materials

ISMN was used as the active pharmaceutical ingredient (API) for formulation of SR tablets in the present study. In order to obtain controlled drug release, the main hydrophilic matrix-forming polymer selected is Hydroxypropyl Methylcellulose (HPMC K100M), and the selected release-retarding polymer is ethyl cellulose. Microcrystalline cellulose (MCC PH-102) and lactose monohydrate were used as diluents for improving compressibility and uniformity of tablets. The wet granulation process binder was polyvinylpyrrolidone (PVP K30), which gave adequate granule strength. Magnesium stearate was used as a lubricant to decrease friction during compression of tablets, and talc was used as a glidant to affect powder flow properties. To achieve uniform die filling and high granule flow ability, a flow-enhancing agent, colloidal silicon dioxide, was added. All the chemicals, polymers and excipients used in the study were of pharmaceutical grade and met the standards of "Indian Pharmacopoeia" (IP), "United States Pharmacopoeia" (USP) and "British Pharmacopoeia" (BP). During the granulation process, purified water was used, and all materials were stored under optimum conditions before formulation for quality and stability.

- **Method:**

Formulation of SRtablets was prepared by the wet granulation method

- **Procedure**

1. Weigh all ingredients accurately (F1 to F9)
2. Sieve the materials through a # 40 mesh
3. Mix ISMN with polymers and excipients
4. Prepare binder solution using PVP K 30
5. Granulate the powder blend
6. Dry granulate at 50-60° C until the moisture content is below 2%
7. Pass dried granulate through # 20 mesh
8. Lubricate with talc and magnesium stearate
9. Compress tablet using a rotary tablet compression machine

2.2. PAT Based Process Monitoring

Table 1: Process analytical technology was employed to monitor critical manufacturing stages in real time

Manufacturing Stage	PAT Parameter	Monitoring Tool
Powder blending	Blend uniformity	NIR Spectroscopy
Granulation	Moisture content	NIR Moisture Analyzer
Drying	Residual moisture	Moisture Sensor
Compression	Compression force, tablet weight	Compression Force Sensor
Final tablets	Tablet thickness and hardness	Automatic Tablet Tester

2.3. Quality Risk Assessment

"Failure Mode and Effects Analysis" (FMEA) was used to identify and assess potential risks that could affect the quality of SRISMN tablets, and a "Quality Risk Assessment" (QRA) was conducted following ICH Q9 principles. CMAs, CPPs and CQAs were identified and scored for "Severity (S), Occurrence (O) and Detectability (D)". The "Risk Priority Number (RPN = S × O × D)" was calculated for each failure mode for each part. PATwas considered as an effective tool for monitoring and controlling the high-risk parameters in order to minimize process variations and ensure product consistency.

"The risk priority Number (RPN) was calculated as":

RPN = Severity × Occurrence × Detectability

Parameters with high RPN values were considered critical, and appropriate control strategies were established

2.4. Evaluation of sustained release tablets

The SRISMN tablets were evaluated as per IP and USP. Pre-compression analyses included bulk density, tapped density, angle of repose, Carr's index and Hausner ratio for the evaluation of the flow properties of granules. Post-compression parameters were evaluated such as weight variation, tablet thickness, hardness, friability, drug content uniformity and in-vitro dissolution using USP Type II (paddle) dissolution apparatus. The dissolution data were also analyzed using different models of drug release: zero-order, first-order, Higuchi and Korsmeyer–Peppas models, which were used to determine the mechanism of drug release. All tests were performed in triplicate, the result of which was represented by the mean ± standard deviation to ensure the quality, consistency and prolonged release ability of the formulated product.

2.5. Stability study

The stability study of the manufactured SRISMN tablets was conducted based on the ICH Q1A(R2) guidelines at 40 ± 2°C and 75 ± 5%RH for 3 months under accelerated conditions. Tablets were placed in suitable containers and evaluated at certain time intervals (0, 1, 2 and 3 months) for physical appearance, hardness, friability, and drug content and in vitro

dissolution profile. The results were compared with the initial values to check the durability of the formulation and its ability to maintain the quality, efficacy, and SR properties of the tablets over the course of the storage period.

2.6. Good Manufacturing Practice (GMP) Compliance

Formulation and assessment were all performed under Good Manufacturing Practice (GMP) guidelines. Before use, equipment was calibrated and environmental conditions controlled, and all manufacturing processes were documented to ensure repeatability and compliance with regulations.

3. RESULT

3.1. Formulation Composition

To maximize the sustained-release profile of isosorbide mononitrate tablets, nine formulations (F1–F9) were created by adjusting the concentrations of HPMC K100M and ethyl cellulose.

Table 1: Formulation development of SR Isosorbide Mononitrate tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Isosorbide Mononitrate	60	60	60	60	60	60	60	60	60
HPMC K100M	30	40	50	60	70	80	90	100	110
Ethyl Cellulose	10	15	20	25	30	35	40	45	50
MCC PH102	165	150	135	120	105	90	75	60	45
Lactose	20	20	20	20	20	20	20	20	20
PVP K30	8	8	8	8	8	8	8	8	8
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total Weight (mg)	300	300	300	300	300	300	300	300	300

Interpretation: in table 1 reported that thenine formulations (F1–F9) of isosorbide mononitrate sustained release tablets containing 60 mg of the active ingredient (ISMN) but different compositions are shown in the table. The amounts of MCC PH102 were proportionately reduced to maintain the tablet weight, but the concentrations of ethyl cellulose (10–50 mg) and HPMC K100M (30–110 mg) were increased to study their effect on the release of the drug. All formulations had the same amounts of lactose, PVP K30, talc, and magnesium stearate. This formulation design facilitates optimization of the polymer concentration without altering the tablet composition to obtain the desired sustained release profile.

3.2. Pre-compression Evaluation

The pre-compression characteristics of the granules, like bulk density, tapped density, Carr's index, Hausner ratio and angle of repose, were evaluated to determine the flowability and compressibility. These factors are crucial during compression to ensure uniform tablet quality, minimize weight variation, and ensure uniform die filling.

Table 2: Pre-Compression parameters

Formulation	Bulk Density	Tapped Density	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)
F1	0.46	0.54	14.8	1.17	28.4
F2	0.47	0.55	14.5	1.17	28.1
F3	0.48	0.56	14.2	1.16	27.8
F4	0.49	0.57	14.0	1.16	27.5
F5	0.49	0.57	13.9	1.16	27.3
F6	0.50	0.58	13.8	1.16	27.0
F7	0.50	0.58	13.7	1.15	26.8
F8	0.51	0.59	13.6	1.15	26.6
F9	0.51	0.59	13.5	1.15	26.5

Interpretation: Table 2 defines thatall formulations (F1–F9) had acceptable flow and compressibility properties during pre-compression. All the bulk density (0.46 – 0.51 g/cm³), tapped density (0.54 – 0.59 g/cm³), Carr's Index (13.5 – 14.8 %), Hausner ratio (1.15 – 1.17) and angle of repose (26.5 – 28.4) were within the acceptable limits, indicating good powder flow and appropriateness for direct compression. All the sustained release tablet formulations exhibited good pre-compression properties.

3.3. Post–Compression Evaluation

The compressed SRL tablets were evaluated for post-compression properties like weight variation, thickness, hardness, friability, drug content and in vitro dissolution according to IP/USP criteria. The assessments were conducted to ensure the overall quality, mechanical strength, content uniformity and sustained release of the prepared tablets.

Table 3: Post–Compression parameters

"Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)"
F1	299.8	4.78	5.8	0.74	98.2
F2	300.4	4.80	6.0	0.69	98.5
F3	300.2	4.82	6.2	0.64	98.9
F4	300.1	4.83	6.4	0.58	99.1
F5	300.3	4.84	6.6	0.54	99.3
F6	300.5	4.85	6.8	0.49	99.4
F7	300.6	4.86	7.0	0.46	99.6
F8	300.5	4.87	7.2	0.43	99.8
F9	300.4	4.88	7.4	0.41	99.9

Interpretation: Table 3 reported thatthe formulations F1–F9 were subjected to a post-compression study, and all the tablets were found to satisfy the pharmacopoeia quality criteria. Good weight homogeneity was demonstrated by the average pill weight remaining about 300 mg. The thickness of the tablets was determined as 4.78–4.88 mm, which ensured their good mechanical strength; the hardness of the tablets was in the range of 5.8–7.4 kg/cm², which also confirmed the mechanical strength of the tablets; the friability of the tablets was in the range of 0.41–0.74%, which is under 1%. The content homogeneity of the drug was good, with the range between 98.2% and 99.9%. All formulations possessed good post-compression characteristics and were suitable for the evaluation of a sustained-release tablet.

3.4. PAT Monitoring observation

Important manufacturing parameters were monitored in real time during the manufacture of sustained-release isosorbide mononitrate tablets using PAT. Blend uniformity, moisture and residual moisture after drying, compression force, tablet weight, and tablet hardness were monitored regularly to ensure process uniformity and product quality. Real-time monitoring minimized manufacturing variability, ensured all key manufacturing parameters remained within specified acceptance limits, and provided early detection of manufacturing process deviations, helping to guarantee tablet quality and regulatory compliance.

Table 4: PAT monitoring observation

Manufacturing Step	Critical Parameter	Target	Observed
Blending	Blend Uniformity	≥98%	99.3%
Granulation	Moisture (%)	3–5	3.4
Drying	Residual Moisture (%)	<2	1.6
Compression	Compression Force (kN)	12–15	13.7
Compression	Tablet Weight (mg)	300±5	300.4
Finished Tablet	Hardness (kg/cm²)	6–8	6.9

Interpretation: Table 4 reports that**the** production process met all predetermined important quality parameters. The moisture after granulation and after drying was acceptable (3.4%, 1.6%), and the homogeneity of the blend was 99.3%, which means a uniform distribution of the drugs. The average compression weight of the tablets was 300.4mg and the hardness was 6.9kg/cm² produced between the target force of 13.7kg. These findings confirm that the production process was well controlled and regularly gave rise to tablets that met the quality requirements.

- ❖ PAT confirmed stable process performance

3.5. Quality Risk Assessment

In order to identify potential manufacturing risks associated with sustained-release isosorbide mononitrate tablets, ICH Q9 recommendations were followed with a systematic Quality Risk Assessment (QRA), which was performed using a Failure Mode and Effects Analysis (FMEA) approach. "The Critical Material Attributes (CMAs), Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs)" were evaluated for severity (S), occurrence (O) and detectability (D). The process variables that had to be monitored more were then prioritized in descending order of importance using the Risk Priority Number (RPN).

Table 5: Failure mode and effects analysis

Process Parameter	Severity	Occurrence	Detection	RPN	Risk
API Assay	8	2	2	32	Low
Blend Uniformity	9	4	3	108	High
Granule Moisture	8	4	3	96	Medium
Drying Temperature	7	3	3	63	Medium
Compression Force	9	5	3	135	High
Lubrication Time	6	3	3	54	Low

Tablet Hardness	8	2	2	32	Low
Dissolution	10	4	3	120	High

Interpretation: Table 5 defines that the Quality Risk Assessment identified compression force (RPN = 135), dissolution (RPN = 120) and blend homogeneity (RPN = 108) as process characteristics that were most likely to compromise the quality of the product. The other risk factors, such as API test, lubrication time, and tablet hardness, were classified as low-risk. Granule moisture (RPN = 96) and drying temperature (RPN = 63) were found to be medium-risk factors. The assessment demonstrates the importance of controlling the key process parameters to ensure product quality and long-term drug release

3.6. In vitro dissolution study

The USP Type II (paddle) dissolution equipment was used in the in vitro drug dissolution investigation to assess the manufactured isosorbide mononitrate tablets' sustained-release behaviour. Samples were collected at predetermined time points for drug release testing, and dissolution testing was performed in a controlled environment in phosphate buffer (pH 6.8). In order to elucidate the drug release process, the dissolution data were fitted with various kinetic models, namely zero-order, first-order, Higuchi and Korsmeyer-Peppas. The amount of released drug was determined by spectrophotometry and expressed as the cumulative percentage of the released drug. The data were presented as mean ± SD, and duplicate analysis was done to ensure the consistency and reliability of the study.

Table 6: Percentage cumulative drug release

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	18	16	15	14	13	12	11	10	9
2	30	28	26	24	22	21	20	18	17
4	48	45	42	39	37	35	33	31	29
6	63	60	56	53	50	48	46	43	40
8	76	72	68	64	60	58	55	52	49
12	90	87	84	80	77	74	71	68	65
16	98	96	93	90	88	85	82	79	76
20	100	99	98	97	95	93	91	88	85
24	100	100	100	100	99	99	98	97	95

❖ F6-F8 exhibited a desirable sustained release profile extending drug release up to 24 h

Interpretation: Table 6 reported that the in vitro dissolution study revealed that all formulations (F1–F9) gave a sustained release profile of the drug for 24 hours. The drug release decreased as the concentration of HPMC K100M and ethyl cellulose increased, indicating that the polymer matrix system was effective in controlling the drug release rate. F1–F4 revealed 100% drug release in 24 hours, while F5–F9 revealed delayed release, with F9 showing 95% drug release in 24 hours. The results indicate that a sustained-release profile of drug release has been achieved by increasing the polymer concentration, and that the sustained-release profile of F5–F7 was the best.All formulations (F1–F9) demonstrated sustained drug release over 24 hours, according to the in vitro dissolution analysis. As HPMC K100M and ethyl cellulose concentrations increased, drug release reduced, demonstrating the polymer matrix's effective control.

Table 7: Drug release kinetics model

Model	R^2
Zero-order	0.989
First-order	0.945
Higuchi	0.982
Korsmeyer–Peppas	0.996

Interpretation: Table 7 indicates thatthe Korsmeyer–Peppas model had the highest correlation coefficient (R^2 = 0.996), indicating the best fit for the dissolution data, according to the drug release kinetic study. The Zero-order model (R^2 = 0.989) and the Higuchi model (R^2 = 0.982) came next, and the first-order model (R^2 = 0.945) displayed the lowest correlation.

3.7. Stability study

The optimized sustained release tablets were subjected to accelerated stability testing for a period of three months at 40 ± 2°C and 75 ± 5%RH, as per the ICH Q1A (R2) criteria. The hardness, friability, drug content, dissolving property and physical appearance of the formulation were periodically evaluated.

Table 8: Stability study (40±2°C/75 ± 5% RH)

Storage Period	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)	Drug Release at 24 h (%)

Initial	6.90	0.49	99.40	99.0
1 Month	6.85	0.50	99.10	98.9
2 Months	6.78	0.52	98.80	98.6
3 Months	6.70	0.54	98.50	98.3

Interpretation: Table 8 reported thatthe optimized sustained-release tablets were found to be stable after 3 months of storage during the stability testing. Friability increased slightly from 0.49% to 0.54%, although hardness (6.90 to 6.70 kg/cm²), drug content (99.40% to 98.50%), and 24-hour drug release (99.0% to 98.3%) only slightly decreased. During the research period, the formulation kept its physical integrity and drug content within acceptable limits of the pharmacopeial specification, and the sustained release functionality remained the same.

3.8. Good Manufacturing Practice (GMP) Compliance

Good Manufacturing Practice (GMP) conditions were used during the manufacturing process to guarantee regulatory compliance and batch-to-batch consistency. Environmental conditions were kept within acceptable bounds during processing, manufacturing equipment was calibrated, and raw materials were confirmed before production.

Table 9: GMP Compliance assessment

GMP Parameter	Observation	Compliance Status
Raw material verification	Pharmaceutical-grade materials approved	Complied
Equipment calibration	Completed before production	Complied
Environmental monitoring	Within specified limits	Complied
Personnel hygiene	SOPs followed	Complied
In-process quality control	All parameters within limits	Complied
Batch documentation	Complete and traceable	Complied
Finished product testing	IP/USP specifications achieved	Complied

Interpretation: Table 9 reported thatthe GMP compliance evaluation indicated that all the manufacturing process phases met the criteria of Good Manufacturing Practice. The batch documentation, equipment calibration, environmental monitoring, human hygiene, in-process quality control, raw material verification and finished product testing were all found to comply. From these findings, it is clear that the assembly process was well managed, well documented and produced tablets that met all quality and legal specifications.All phases of the manufacturing process complied with Good Manufacturing Practice (GMP) regulations, according to the GMP compliance evaluation. Before production, pharmaceutical-grade raw materials were confirmed, equipment was appropriately calibrated, and environmental conditions were kept within predetermined bounds during the manufacturing process.

4. DISCUSSION

The study found that nine isosorbide mononitrate tablet formulations with sustained release properties were successfully developed by altering the amount of ethyl cellulose and HPMC K100M in the tablets without changing the amount of the drug and tablet weight. This formulation design enabled a qualitative assessment of the effect of polymer concentration on the long-term drug release. Adnan et al., (2016) reported that the flow and tablet quality of sustained release ISMN tablets prepared by wet granulation technique were excellent and satisfactory. Most formulations showed controlled drug release as per the Higuchi model, while few formulations showed zero-order release. For all formulations, the release behaviour of the F1 formulation was similar to the reference sustained release drug (Monis XR)[30].

The analysis of the tablet showed that all the designed sustained release tablets conform to the standard parameters of the pharmacopoeia such as weight variation, thickness, hardness, friability and drug content. The mechanical integrity, uniformity of assay and content uniformity of the tablets exceeded the required standard, indicating good formulation and reliable tablet quality for the sustained release drug delivery.The minimum requirement for sustained release tablets was fulfilled with good mechanical integrity, uniformity of assay and content uniformity of the tablets achieved in the formulation process. Sridevi and Chinnadevi reported that the study of the tablets revealed that all the Isosorbide Mononitrate sustained-release tablets met the specifications for weight variation, thickness, hardness, friability and drug content of the pharmacopoeia. The tablets showed excellent mechanical strength, uniformity, content uniformity, and low friability, which suggested good formulation and tablet uniformity suitable for sustained-release drug delivery [34].

The analysis affirmed that PAT successfully monitored and regulated all crucial manufacturing parameters within designated limits, assuring process consistency, lowered variability, and the creation of sustained-release Isosorbide Mononitrate tablets with the necessary quality features. Zhao et al., (2025) reported that Today, controlled-release (CR) tablets have been a part of modern pharmaceutical formulations,helping to improve therapeutic efficiency, reduce dosage frequency, and improve patient compliance. However, the quality and regulatory approval of these formulations is a complex challenge due to different manufacturing techniques, quality controls, and regulatory requirements across the globe. In this critique, the formulation of CR pills is explored in detail, highlighting critical principles of formulation, quality assurance, and regulatory requirements in the region. It covers key aspects such as dissolution testing, in vitro – in vivo correlation (IVIVC) and stability evaluation, while highlighting how the use of artificial intelligence (AI) and new formulation techniques are increasingly improving drug release properties. In addition, the analysis compares the regulatory requirements in various key regions, such as the United States, the European Union, China and Japan, and

emphasises the need for harmonized international standards. Addressing these challenges requires cross-disciplinary collaboration to align regulatory requirements, enhance quality control precision and facilitate innovation in controlled release pharmaceuticals [35].

5. CONCLUSION

In the present study sustained release Isosorbide Mononitrate tablets were successfully prepared with the help of the wet granulation method using the matrix-forming polymers HPMC K100M and Ethyl cellulose. The formulated tablets showed good pre- and post-compression parameters and met the pharmacopeial requirements for the tablets. Through PAT-based monitoring, the critical parameters in the process were effectively kept within the desired limits, whereas the FMEA-based quality risk assessment identified compression force, blend uniformity and dissolution as the most critical parameters, for which continuous monitoring was desired. The optimized formulation exhibited a controlled 24-hour release profile, acceptable stability in accelerated storage conditions and showed good mechanical strength. In addition, Good Manufacturing Practice (GMP) standards were ensured, providing a strong and repeatable manufacturing process. In conclusion, the PAT integration with quality risk management offers a promising approach to enhance process control, reduce manufacturing variability and guarantee the production of a high-quality sustained-release Isosorbide Mononitrate tablet in the treatment of chronic stable angina.

Standard pre-compression and post-compression parameters like flowability, hardness, friability, weight uniformity, and drug content were found appropriate for all the formulations as per pharmacopoeial standards. PAT integration helped to monitor critical manufacturing parameters in real time, enabling efficient monitoring and reducing manufacturing variability and ensuring consistent process performance. Furthermore, the following process parameters were demonstrated as being of the highest priority for continuous monitoring and control to guarantee the product's quality, using Failure Mode and Effects Analysis (FMEA)–based Quality Risk Management (QRM): compression force (RPN = 135), dissolution (RPN = 120), and blend homogeneity (RPN = 108).

REFERENCE

1. Camm AJ, Manolis A, Ambrosio G, Daly C, Komajda M, de Sa EL, Lopez-Sendon JL, Mugelli A, Muggli F, Tamargo J. Unresolved issues in the management of chronic stable angina. International Journal of Cardiology. 2015 Dec 15;201:200-7.
2. Heusch G. Myocardial ischemia: lack of coronary blood flow or myocardial oxygen supply/demand imbalance?. Circulation research. 2016 Jul 8;119(2):194-6.
3. Ciuca-Pană MA, Boulmpou A, Ileri C, Manzi G, Golino M, Ostojic M, Galimzhanov A, Busnatu S, Mega S, Perone F. Chronic heart failure and coronary artery disease: pharmacological treatment and cardiac rehabilitation. Medicina. 2025 Jan 24;61(2):211.
4. Padala SK, Lavelle MP, Sidhu MS, Cabral KP, Morrone D, Boden WE, Toth PP. Antianginal therapy for stable ischemic heart disease: a contemporary review. Journal of Cardiovascular Pharmacology and Therapeutics. 2017 Nov;22(6):499-510.
5. Daiber A, Münzel T. Organic nitrate therapy, nitrate tolerance, and nitrate-induced endothelial dysfunction: emphasis on redox biology and oxidative stress. Antioxidants & redox signaling. 2015 Oct;23(11):899-942.
6. Sharma K, Sathe S, Desai B, Manchanda S, Mohan J, Bansal M, UM N, Oomman A, Pande A, Shah J, Christopher J. Optimizing cardiovascular outcomes with bisoprolol: an evidence-based perspective. Cureus. 2025 Aug 7;17(8).
7. Zhang H, Luo D, Zhou X, Zeng X, Xiong R, Xu Y. Cost-effectiveness of sustained-release isosorbide mononitrate capsules for coronary heart disease: A network meta-analysis. Journal of Chinese Pharmaceutical Sciences. 2025 Apr 1;34(4).
8. Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. Nature Reviews Neurology. 2016 Oct;12(10):575-83.
9. Patne AY, Akramuddaula K, Patel D, Suryawanshi M, Vinchurkar K. Applications of natural polymers in controlled-release systems. InInnovative Pharmaceutical Excipients: Natural Sources 2025 Jul 29 (pp. 249-298). Singapore: Springer Nature Singapore.
10. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once-vs. twice-daily regimens and their potential impact on medication adherence. EP Europace. 2015 Apr 1;17(4):514-23.
11. Wasalathanthri DP, Rehmann MS, Song Y, Gu Y, Mi L, Shao C, Chemmalil L, Lee J, Ghose S, Borys MC, Ding J. Technology outlook for real-time quality attribute and process parameter monitoring in biopharmaceutical development—A review. Biotechnology and Bioengineering. 2020 Oct;117(10):3182-98.
12. O'Connor TF, Lawrence XY, Lee SL. Emerging technology: A key enabler for modernizing pharmaceutical manufacturing and advancing product quality. International journal of pharmaceutics. 2016 Jul 25;509(1-2):492-8.
13. Yang S, Hu X, Zhu J, Zheng B, Bi W, Wang X, Wu J, Mi Z, Wu Y. Aspects and implementation of pharmaceutical quality by design from conceptual frameworks to industrial applications. Pharmaceutics. 2025 May 8;17(5):623.
14. Fisher AC, Kamga MH, Agarabi C, Brorson K, Lee SL, Yoon S. The current scientific and regulatory landscape in advancing integrated continuous biopharmaceutical manufacturing. Trends in biotechnology. 2019 Mar 1;37(3):253-67.
15. Pokharel B, Dhakal B. Coronary artery disease (CAD) Demystified-Causes, symptoms & treatment. The American Journal of Patient Health Info. 2024 Jul 20;1(1).
16. Nossam S, Sowjanya M, Penabaka V, Patan A. A review on prevalence of angina pectoris in association with ccf (congestive cardiac failure) in gender and age-based population. UPI Journal of Pharmaceutical, Medical and Health Sciences. 2025 Oct 23:18-25.

17. Franklin BA, Rusia A, Haskin-Popp C, Tawney A. Chronic stress, exercise and cardiovascular disease: placing the benefits and risks of physical activity into perspective. International journal of environmental research and public health. 2021 Sep 21;18(18):9922.
18. Joshi PH, De Lemos JA. Diagnosis and management of stable angina: a review. Jama. 2021 May 4;325(17):1765-78.
19. Raghavan L, Brown M, Michniak-Kohn B, Ng S, Sammeta S. In vitro release tests as a critical quality attribute in topical product development. InThe role of microstructure in topical drug product development 2019 Aug 8 (pp. 47-87). Cham: Springer International Publishing.
20. Nanjappa SH, Somasekhar V, Kamath M, Prakash SS, Kumar A, Pai R, Shinde R. Formulation and evaluation of isosorbide dinitrate-loaded flash-release dispersible sublingual wafers. RSC Pharmaceutics. 2026.
21. Khan M. Long-term oral treatment with nitrates what is important?. 120 Years of Nitrate Therapy-Prepared for the Next Millenium. 2020 Oct 12:43.
22. Soman B, Vijayaraghavan G. The role of organic nitrates in the optimal medical management of angina. E-Journal of Cardiology Practice. 2017 Apr;15(2).
23. Duarte JG, Duarte MG, Piedade AP, Mascarenhas-Melo F. Rethinking pharmaceutical industry with quality by design: application in research, development, manufacturing, and quality assurance. The AAPS journal. 2025 May 20;27(4):96.
24. Wu H, Dong Z, Li H, Khan M. An integrated process analytical technology (PAT) approach for pharmaceutical crystallization process understanding to ensure product quality and safety: FDA scientist's perspective. Organic Process Research & Development. 2015 Jan 16;19(1):89-101.
25. Chanda A, Daly AM, Foley DA, LaPack MA, Mukherjee S, Orr JD, Reid III GL, Thompson DR, Ward HW. Industry perspectives on process analytical technology: tools and applications in API development. Organic Process Research & Development. 2015 Jan 16;19(1):63-83.
26. Singh BN. Product development, manufacturing, and packaging of solid dosage forms under QbD and PAT paradigm: DOE case studies for industrial applications. AAPS PharmSciTech. 2019 Sep 16;20(8):313.
27. de Oliveira Nascimento L, da Silva FV, Stephano MA. Pharmaceutical Quality System for Biotechnology Products. InPharmaceutical Biotechnology 2021 Jul 15 (pp. 325-353). CRC Press.
28. Namjoshi S, Dabbaghi M, Roberts MS, Grice JE, Mohammed Y. Quality by design: Development of the quality target product profile (QTPP) for semisolid topical products. Pharmaceutics. 2020 Mar 23;12(3):287.
29. Al-Qubati AA. In Vitro Comparative Quality Evaluation of Locally Manufactured and Imported Diclofenac Dispersible Tablets in Sana'a, Yemen.
30. Adnan S, Shehzadi K, Farooq M, Ranjha NM, Hanif M, Masood Z, Zaman M. Application of Box-Behnken Design for the Development of Isosorbide Mononitrate Sustained Release Matrix Tablets. Latin American Journal of Pharmacy. 2016 Jan 1;35(5):1018-25.
31. Sacchetti M, Teerakapibal R, Kim K, Elder Jr EJ. Role of water sorption in tablet crushing strength, disintegration, and dissolution. AAPS PharmSciTech. 2017 Aug;18(6):2214-26.
32. Shadman Nashif MR, Islam MR, Imam MH. Heart disease detection by using machine learning algorithms and a real-time cardiovascular health monitoring system. World Journal of Engineering and Technology. 2018 Nov;6(4).
33. Mkpa BO, Ahmed FA. Data-Driven Detection of Out-of-Specification Trends in Pharmaceutical Production: A Public Health Imperative. American Journal of Scholarly Research and Innovation. 2026 Mar 16;5(01):198-238.
34. Sridevi D, Chinnadevi G. Formulation and In Vitro Evaluation of Isosorbide Mononitrate Sustained Release Tablets.
35. Zhao L, Chen N, Wang L. Quality Control and Regulatory Standards for Controlled-Release Tablets: A Global Perspective. Journal of Medicine and Life Sciences. 2025 Apr 11;1(2):84-92.