Research Article

Evaluation of Critical Quality Attributes of Sustained-Release Isosorbide Mononitrate Tablets: An Experimental Study

Anmol Gautam[1]*, Mohammad Shahnaz[2], Varsha Bali[3], Dr Jagdeep Singh Dua[4], Anju Goyal[5]

[1]Assistant Professor Shivalik College of Pharmacy Nangal, Punjab Email: anmol.gautam13@gmail.com
[2]Assistant Professor Shivalik College of Pharmacy, Nangal, Punjab Email: mohd.shahnaz2983@gmail.com
[3]Assitant Professor Shivalik College of Pharmacy, Nangal, Punjab Email: varshabali18@gmail.com
[4]Principal Shivalik College of Pharmacy, Nangal, Punjab Email: jsdua2002@yahoo.com
[5]Professor cum Dean University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali-140104 Email: anju_goyal2003@rediffmail.com

Abstract

Background: Isosorbide Mononitrate tablets are taken as sustained-release medication and are widely used for the long-term treatment of chronic stable angina, maintaining the benefits of the medicine and reducing the need for frequent doses. Methods: Three brands of sustained-release Isosorbide Mononitrate tablets were evaluated in compliance with USP and IP requirements. The organoleptic properties, weight variations, tablet dimensions, friability, active ingredient content, in vitro dissolution and drug-release kinetics were investigated using common analytical methods. The dissolution data were analyzed using the zero-order and first-order kinetic models, Higuchi model and Korsmeyer–Peppas model. One-way ANOVA was used for statistical evaluation. Result: All formulations met the physical characteristics, weight discrepancy, friability and concentration of the active ingredient standards outlined in the Pharmacopoeia. The tablets had outstanding dimensional stability and strength. In vitro dissolution test showed the dissolution of the drug was regulated in the range of 95.87 – 98.43% after 24 hours. The Higuchi model was the best fit for the drug-release kinetics (R^2 = 0.991–0.995), and the "Korsmeyer–Peppas model indicated that anomalous (non-Fickian)" diffusion was present (n = 0.50–0.61). For most physical quality characteristics, no significant differences ($p > 0.05$) were found across the brands. Conclusion: Analysed sustained-release Isosorbide Mononitrate tablets were found to be of pharmaceutical quality and exhibited consistent pharmaceutical quality, drug release and reliable sustained-release properties, demonstrating their pharmaceutical equivalence and therapeutic reliability.

Keywords: Isosorbide Mononitrate, Sustained Release Tablet, Critical Quality Attributes (CQAs), Quality by Design.

1. Introduction

Isosorbide mononitrate (ISMN) is a type of nitrate that is frequently used for treating chronic stable angina for prevention and long-term [1]. In contrast to isosorbide dinitrate, ISMN has almost total oral bioavailability due to less first-pass hepatic metabolism [2]. The medicine works primarily by generating nitric oxide (NO), which activates soluble guanylate cyclase in vascular smooth muscle cells, resulting in increased cyclic guanosine monophosphate (cGMP) synthesis. [3]. A biochemical sequence that causes vessels to become relaxed and dilates veins and arteries [4]. When venous return decreases, preload of ventricles decreases, and when arterial dilatation decreases, afterload decreases, which reduces the requirement of oxygen by the myocardial cells [5]. In addition, coronary vasodilators improve myocardial perfusion and thus help to prevent ischemic events. ISMN's pharmacodynamics properties make it one of the most widely recommended long-acting nitrates for chronic cardiovascular therapy [6].

Immediate-release nitrates must be taken several times a day because they have a very short duration of action [7]. Frequent delivery reduces patient adherence, results in a fluctuation of plasma drug levels, and can result in nitrate tolerance [8]. Therapeutic plasma levels have been developed for a sustained release (SR) formulation to ensure therapeutic levels remain stable for a prolonged period of time, decrease the frequency of doses, improve patient compliance, and minimize side effects of high plasma levels [9]. Sustained-release tablets are prepared using a special polymer matrix or multiparticulate systems that are coated with polymer to give a delayed release of the drug in the gastrointestinal tract [10]. Formulation and manufacturing quality are of paramount importance for therapeutic efficacy [11].

Pharmaceutical quality sustained-release tablets are often much more complex than immediate-release tablets because, in addition to the amount of drug in the system, the sustained-release [12]. tablet's ability to release drug over

a certain period at a controlled rate must be sufficient to make the tablet effective [13]. The dissolution profile can vary widely depending on minor variations in manufacturing processes, polymer used, compression pressure, granule size and coating thickness, which in turn can affect the bioavailability of the drug [14]. Thus, it is necessary to perform rigorous quality evaluation to ensure batch-to-batch uniformity, product reliability and therapeutic equivalence during the product lifecycle [15].

The regulatory authorities such as the International Council for Harmonisation (ICH), the United States Food and Drug Administration (USFDA), the European Medicines Agency (EMA) [16] and the World Health Organization (WHO) have all emphasized a science- and risk-based approach to pharmaceutical development through the implementation of Quality by Design (QbD) approaches in recent years [17]. QbD promotes a structured Product Development process starting with clear product objectives and a structured attention to the understanding of the product and the process, along with a strong emphasis on sound scientific principles and Quality Risk Management [18]. QbD paradigm focuses on pharmaceutical quality in the product during its development rather than solely relying on final product evaluations [19].

Critical Quality Attributes (CQAs) detection and monitoring are an integral part of Quality by Design (QbD) [20]. ”Critical Quality Attributes (CQAs)” are physical, chemical, biological, or microbiological attributes [21] which must be controlled within specified limits to ensure that the product meets the desired quality, safety and performance attributes as intended, based on ICH Q8 (R2) [22]. The appearance, weight variation, content uniformity, dissolution, impurity profile, moisture content, stability and hardness/friability of the tablet are typical critical quality attributes of sustained release tablets [23]. The efficacy of these dose forms is directly affected by these features, and ultimately by therapeutic outcomes [24].

The in vitro performance and therapeutic effect can be affected by variation of the important quality attributes of commercially available products, due to variations like raw materials, the manufacturing method used, the storage conditions, and the formulation technology employed [25]. Therefore, the comparison of marketed sustained-release formulations is required to guarantee compliance with the pharmacopoeia, to ensure batch consistency and for the generic product interchangeability [26]. These investigations can offer scientific information to support quality assurance requirements for regulated products as well as opportunities for manufacturers to continually improve the process to enhance the confidence of healthcare professionals and patients in the quality and reliability of sustained-release products [27].

1.1. Isosorbide Mononitrate and Critical Quality Attributes of sustained-release tablets

Isosorbide Mononitrate is a metabolite of isosorbide dinitrate that acts as a nitric oxide (NO) releasing agent that causes relaxation of vascular smooth muscle, resulting in artery and vein dilatation [28]. ISMN has an exceptionally high oral bioavailability, stable pharmacokinetic properties and a long duration of action, which has led to extensive development for its use as a sustained-release tablet taken once daily [29]. These formulations are effective only with strict quality control of the production process and formulation parameters that control the rate of medication release [30]. The release profile can be altered and the resulting effectiveness of the medicine compromised by variations in tablet formulation, compaction pressure, polymer properties or production parameters [31]. Therefore, it is essential to regularly evaluate the CQAs to ensure that commercial products continue to meet quality standards [32].

The CQAs are important for evaluating the pharmacological equivalency and reliability of the sustained-release products [33]. Weight change, thickness, hardness, friability and drug concentration are used for measuring the physical and chemical integrity of tablets, while dissolving assays and release kinetics are used for measuring functional efficacy [34]. Mathematical models like zero-order, first-order, and “Higuchi and Korsmeyer–Peppas” models are valuable tools for understanding the underlying mechanisms of release and predicting performance in vivo when analysing the pharmacological release data [35]. A comprehensive assessment of these quality features enables compliance with regulations, ensures consistency between batches and helps healthcare providers and producers maintain high-quality products and therapeutic activity [36].

1.2. Pharmaceutical quality Assessment of sustained-release dosage forms and role of critical quality attributes in product performance

Sustained-release (SR) formulations are used to deliver drugs over an extended period of time at a controlled rate, which

helps to maintain therapeutic plasma levels with less frequent dosing and improves patient compliance [37]. Sustained release tablets provide prolonged action and reduce fluctuations in plasma drug levels compared to immediate release tablets and reduce the risk of dose-related adverse effects [38]. However, the therapeutic effectiveness of the sustained release versions depends on the homogeneity of the therapeutic quality of the tablets [39]. The formulation composition, method of manufacturing, compression pressure, or polymer properties could significantly influence drug release and the overall product performance [40]. Therefore, the evaluation of pharmaceutical quality should be comprehensive and vital to ensure that sustained release tablets meet the quality standard continually [41]. Common quality tests include checks on physical factors like appearance, weight differences, thickness, hardness, and friability, as well as medication content consistency and dissolving ability [42]. These evaluations help ensure batch-to-batch consistency and reliability in production, and meet pharmacopoeial standards, ensuring safe, effective and quality sustained-release pharmaceutical products [43].

Aim

To analyse the pivotal quality attributes (CQAs) of market-available sustained-release Isosorbide Mononitrate tablets in alignment with USP and IP criteria.

Objective

1. To analyse the physicochemical attributes of marketed sustained-release Isosorbide Mononitrate tablets.
2. To evaluate the pharmaceutical composition and in vitro dissolving properties of the tablet formulations
3. To evaluate the drug-release kinetics and overall medicinal efficacy of several commercial brands

2. Materials and Method

2.1. Study design

The critical quality attributes (CQAs) of commercial sustained-release (SR) isosorbide mononitrate tablets were assessed through an experimental study carried out in a laboratory. Every test was conducted in accordance with the protocols outlined in the Indian Pharmacopoeia (IP) and United States Pharmacopoeia (USP) for extended-release tablets.

2.2. Materials and Instruments

Sustained-release Isosorbide Mononitrate tablets (60 mg) of different commercial brands were purchased from authorized retail pharmacies for evaluation. All the chemicals used in the research were analytical grade potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, methanol, phosphate buffer (pH 6.8) and distilled water. All of the reagents and solvents used were of analytical grade or HPLC grade. The experimental evaluation was carried out using a digital analytical balance (Shimadzu, Japan), UV-Visible spectrophotometer (Shimadzu UV-1800, Japan), USP Dissolution Apparatus II (Paddle type; Electrolab, India), Roche friabilator, Monsanto tablet hardness tester, digital Vernier calliper (Mitutoyo, Japan), pH meter, ultrasonic bath, filtration apparatus, and standard laboratory glassware. All devices were calibrated before use to ensure the accuracy and reliability of the results of the trial.

2.3. Methods

The research was designed as a laboratory-based experimental evaluation of the essential quality characteristics (CQAs) of the commercial sustained-release Isosorbide Mononitrate (ISMN) tablets. Three brands of Isosorbide Mononitrate, each 60 mg, were evaluated according to the methodology described in the United States Pharmacopoeia (USP) and the Indian Pharmacopoeia (IP). The visual appearance, weight variations, thickness, diameter, hardness, friability and amount of active ingredient were assessed for the tablets. In vitro dissolution studies were carried out using USP Dissolution Apparatus II (paddle method) using 900 mL of phosphate buffer at 37 ± 0.5°C with 50 rpm agitation.

Samples were collected at regular intervals, filtered, and analyzed using a UV-Visible spectrophotometer at the λmax of isosorbide mononitrate. To keep sink conditions consistent, an equal volume of fresh dissolving medium was replaced after each sampling. The total percentage of drug release was computed, and the dissolution data were analysed using the zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models to determine the drug release process.

2.4. Evaluation of critical quality attributes

- **Visual inspection**

Tablets underwent a visual assessment for hue, form, surface texture, coating consistency, and any apparent

imperfections like fissures, fragments, or discolouration.

- **Weight variation**
  Each brand's twenty tablets were meticulously weighed with a calibrated analytical balance. The average weight of the tablets and the percentage of departure of each tablet from the mean weight were determined in accordance with USP/IP standards.
- **Tablet thickness and Diameter**
  The dimensions and diameter of ten tablets from each batch were assessed with a digital Vernier calliper, and the average ± standard deviation was determined.
- **Hardness test**
  The compressive strength of ten tablets from each brand was assessed utilising a Monsanto hardness tester. Outcomes were articulated in kilograms per square centimetre (kg/cm^2).
- **Friability test**
  Twenty pre-measured tablets were subjected to rotation in a Roche friabilator at 25 revolutions per minute for a duration of 4 minutes (totalling 100 revolutions). The tablets were cleaned of dust and subsequently reweighed. The percentage of friability was determined, with results under 1% being acceptable.

2.5. Drug Content

All 10 tablets were completely powdered, and an equivalent of 60 mg of Isosorbide Mononitrate was added to a volumetric flask filled with phosphate buffer. This solution was then sonicated and filtered, and then the solution was appropriately diluted and measured by UV-Visible spectrophotometry at the desired wavelength. The amount of the drug was determined by a calibration curve that was prepared beforehand. Content should be within USP guidelines of 90% to 110% of the claimed content.

2.6. In vitro dissolution study

The dissolution investigation was conducted utilising USP Dissolution Apparatus II (Paddle technique) with 900 mL of dissolving medium kept at 37 ± 0.5°C and a paddle rotation speed of 50 rpm. Samples were taken after various time intervals “(1, 2, 4, 6, 8, 12 and 24 hours)”, filtered and analyzed by UV spectrophotometry. The new dissolving media were replaced with an equal volume for each sample to maintain sink conditions, while the media were stored at the same temperature. The total percentage of release of the medication was calculated.

- **Drug Release Kinetics**
  The dissolution data were analysed using “Zero-order, First-order, Higuchi, and Korsmeyer–Peppas kinetic models”. The model exhibiting the greatest coefficient of determination (R^2) was deemed the most suitable for elucidating the drug-release process.

3. Result

Three marketed sustained-release Isosorbide Mononitrate (60 mg) tablet products were carefully evaluated for a set of key product characteristics, referred to as quality attributes (CQAs), per the USP and IP guidelines. The organoleptic properties, weight changes, tablet thickness, tablet diameter, organoleptic friability, drug content, in vitro dissolution and achievement of kinetics of drug release and statistical assessment were analyzed. The data obtained were found to meet the quality criteria specified in the Pharmacopoeia, and these formulations possessed good physical, mechanical and functional properties. A few differences were identified for the marketed brands; however, these were not shown to affect the overall therapeutic quality or extended release mechanism of the formulations. The detailed results for each evaluative parameter are explained in the following text

3.1. Visual and Organoleptic Evaluation

Three brands of sustained release (SR) isosorbide mononitrate tablets (Brand A, Brand B, and Brand C) were evaluated for their important quality attributes. Visual inspection of all the formulations found no capping, chipping, cracking, discolouration or irregular surface, and all the pills were white and spherical with no obvious defects. The appearance and smooth surfaces of the tablets indicated good manufacturing quality. It was determined that during the investigation, there was no evidence of coating damage or physical deterioration.

Table 1: Organoleptic Characteristics of Marketed SR Isosorbide Mononitrate Tablets

Parameter	Brand A	Brand B	Brand C
Color	White	White	White
Shape	Round	Round	Round
Surface Texture	Smooth	Smooth	Smooth
Coating	Film-coated	Film-coated	Film-coated
Cracks/Chipping	None	None	None
Overall Appearance	Acceptable	Acceptable	Acceptable

Interpretation: Table 1 reported that the physical properties of the three brands of sustained release (SR) Isosorbide Monohydrate (ISMN) tablets were similar by organoleptic analysis. All the tablets were white in colour, round and had a film coat with a smooth surface texture, signifying that there were manufactured uniformly and finished properly. All formulations appeared structurally sound with no cracks, chipping or container or formulation defects of the coating such as capping, indicating satisfactory physical integrity and mechanical damage as a result of handling and storage. Moreover, the impression of the overall presentation of the three brands was judged satisfactory; fulfilled the pharmaceutical quality criteria.

3.2. Evaluation parameter

The critical quality attributes (CQAs) of three commercially available sustained-release Isosorbide Mononitrate tablet formulations were assessed for pharmaceutical quality and pharmacopoeial compliance. Several criteria were evaluated, including weight variation, tablet thickness and diameter, friability, drug content, in vitro dissolution, and drug release kinetics. Results indicated that all the formulations had the desired physical properties, the dosage unit homogeneity, mechanical strength was adequate and drug content was satisfactory. Moreover, dissolution studies showed consistent and controlled drug release for 24 hours, and kinetic modelling provided insights into the release process. The results for each quality metric are detailed in the paragraphs below.

3.3. Weight Variation

All three brands' average pill weights were within pharmacopoeia norms. With a percentage deviation well within the USP/IP approval standards, the mean weight varied from 299.82 ± 2.41 mg to 301.56 ± 2.73 mg. Excellent weight homogeneity among pills was evidenced by the low standard deviation.

Table 2: Weight Variation of Marketed Sustained- release Isosorbide Mononitrate Tablets

Brand	Average Weight (mg)	Standard Deviation (SD)	Percentage Deviation (%)	Pharmacopoeial Compliance
Brand A	300.84	2.56	0.85	Pass
Brand B	299.82	2.41	0.81	Pass
Brand C	301.56	2.73	0.91	Pass

Interpretation: Table 2 reported that weight variation findings demonstrated that each of the three marketed sustained-release Isosorbide Mononitrate tablet brands conformed to pharmacopoeial criteria. The typical pill mass fluctuated between 299.82 ± 2.41 mg and 301.56 ± 2.73 mg, with percentage variations ranging from 0.81% to 0.91%. The reduced standard deviation and deviation metrics demonstrate outstanding weight uniformity and dependable production quality across every brand.

- **Thickness and Diameter**

Every tablet brand has remarkably similar dimensions. While the diameter varied between 9.93 and 10.01 mm, the average thickness varied between 4.73 and 4.86 mm. Uniform compression during tablet manufacturing was indicated by minimal variation.

Table 3: Thickness and Dimension of Marketed Sustained- Release Isosorbide Mononitrate Tablets

Brand	Thickness (mm)	Diameter (mm)
Brand A	4.82 ± 0.04	9.98 ± 0.05
Brand B	4.73 ± 0.05	9.93 ± 0.04
Brand C	4.86 ± 0.06	10.01 ± 0.03

Interpretation: Table 3 reported that commercially available sustained-release Isosorbide Mononitrate tablets did not vary significantly in thickness and width between the three tablets. The thickness of the tablet varied from 4.73 ± 0.05 mm to 4.86 ± 0.06 mm, and the width varied from 9.93 ± 0.04 mm to 10.01 ± 0.03 mm. These results showed a very satisfactory degree of dimensional consistency and homogeneous compression of the tablets, thus establishing that all the formulations were produced with good quality.

- **Friability Test**

Every brand that was assessed had friability values less than 1%, meeting the USP/IP acceptance threshold. The minimal proportion of weight loss indicated sufficient abrasion resistance.

Tablet 4: Friability test of Marketed Sustained Release Isosorbide Mononitrate tablet

"Brand	Initial Weight (g)	Final Weight (g)	Friability (%)"	Pharmacopoeia Compliance
Brand A	6.515	6.489	0.40	Pass
Brand B	6.488	6.458	0.46	Pass
Brand C	6.532	6.507	0.38	Pass

Interpretation: Table 4 reported that friability percentages of the commercially available sustained-release Isosorbide Mononitrate tablets ranged from 0.38 to 0.46%, well below the 1.0 to 20.0% recorded limit for friability in the

Pharmacopoeia. The friability test was conducted for all three brands, and all the brands finished the test, were mechanically durable, and were resistant to handling, packing and transport

3.4. Drug Content Assay

Excellent content homogeneity across all commercially available sustained-release formulations was shown by the laboratory findings. The drug content met the pharmacopoeia criteria of 90–110% of the labelled claim, ranging from 98.74% to 101.24%.

Tablet 5: Drug Content of Isosorbide Mononitrate tablets

Brand	Drug Content (% of Label Claim)
Brand A	99.42 ± 0.62
Brand B	98.74 ± 0.81
Brand C	101.24 ± 0.55

Interpretation: Table 5 reported that the assay of medication content revealed compliance of all three brands of sustained-release Isosorbide Mononitrate tablets with the required standard for content uniformity specified by the pharmacopoeia. Its concentration range was between 98.74 ± 0.81 % and 101.24 ± 0.55 % of the specified label, with a precision of the loaded pharmacological active compound that was precise across all of the formulations.

3.5. In vitro dissolution study

The dissolution profiles exhibited a prolonged and regulated release of Isosorbide Mononitrate during a 24-hour timeframe. The release of the drug escalated gradually over time across all brands. Brand C demonstrated the greatest total drug release at 24 hours (98.43%), while Brand B exhibited the least release (95.87%). Nonetheless, all formulations adhered to the anticipated sustained-release properties.

Table 6: In vitro dissolution profile of marketed sustained-release isosorbide mononitrate tablet

Time (h)	Brand A (% Drug Release)	Brand B (% Drug Release)	Brand C (% Drug Release)
1	18.56 ± 0.71	17.24 ± 0.82	19.44 ± 0.66
2	30.22 ± 0.92	28.81 ± 0.90	31.65 ± 0.84
4	46.73 ± 1.03	44.62 ± 1.14	48.12 ± 1.06
6	59.81 ± 1.15	57.38 ± 1.21	61.54 ± 1.11
8	70.94 ± 1.08	68.75 ± 1.18	72.66 ± 1.05
12	85.18 ± 1.13	83.45 ± 1.20	87.22 ± 1.16
16	91.62 ± 1.04	89.68 ± 1.12	93.18 ± 1.01
20	95.24 ± 0.98	93.14 ± 1.06	96.42 ± 0.94
24	97.36 ± 0.91	95.87 ± 0.95	98.43 ± 0.88

Interpretation: Table 6 states that in vitro dissolving analysis showed that all three brands of sustained-release Isosorbide Mononitrate tablets exhibited a controlled, mid-life release of the drug. The total drug release progressively escalated over time, achieving 97.36 ± 0.91% for Brand A, 95.87 ± 0.95% for Brand B, and 98.43 ± 0.88% for Brand C after 24 hours. The drug release profiles of all formulations met the criterion of >95% drug released, indicating good sustained-release performance and consistent with the desired release profile.

- **Drug release kinetics analysis**

The dissolution data were analyzed using various kinetic models to determine the mechanism of drug release. The maximum correlation coefficient (R^2) was achieved with the Higuchi model for each of the three brands, indicating a diffusion-controlled release from the matrix system. The "Korsmeyer–Peppas" model produced release exponent (n) values ranging from 0.50 to 0.61, signifying anomalous (non-Fickian) diffusion that encompasses both diffusion and polymer relaxation processes.

Table 7: Drug release kinetics analysis of marketed sustained–release Isosorbide mononitrate tablets

Kinetic Model	"Brand A (R^2)	Brand B (R^2)	Brand C (R^2)"
Zero-order	0.973	0.969	0.976
First-order	0.942	0.939	0.946
Higuchi	0.994	0.991	0.995
Korsmeyer–Peppas	0.987	0.985	0.989
Release Exponent (n)	0.56	0.50	0.61

Interpretation: Table 7 reported that the kinetic analysis of drug release revealed that the Higuchi model had the strongest association, with a correlation coefficient (R2 = 0.991-0.994) across all three brands, suggesting that the release mechanism is predominantly governed by diffusion. The Korsmeyer–Peppas model was employed and demonstrated an excellent fit (R^2 = 0.985–0.989), with the release exponent (n) varying from 0.50 to 0.61, signifying anomalous (non-Fickian) transport, where both diffusion and polymer relaxation influence drug release. The findings concur that all three formulations exhibit effective sustained release properties

4. Discussion

The study confirms that all assessed sustained-release Isosorbide Mononitrate tablet brands demonstrated similar and satisfactory sensory attributes. The lack of observable flaws and the consistent look of the tablets signify compliance with good manufacturing principles (GMP) and reflect reliable product quality, which is crucial for guaranteeing patient acceptance and preserving dosage form integrity. Sabbatini and Beatrice (2024) reported that Oral solid dosage (OSD) forms exist in the most stable and economical forms, can be easily manufactured, are easy to administer, and are the best accepted by patients, making them the most popular pharmaceutical dosage form. Sustained release tablets are designed to release the therapeutic agent over time, to ease the frequency of administration, and to enhance therapeutic effects. It depends on the formulation design, excipient selection and conformance to pharmaceutical quality requirements, and quality evaluation is essential for ensuring product safety, efficacy and consistency in the quality of pharmaceutical products. [44]

The study confirms that all three brands satisfied pharmacopoeia weight variation thresholds, showing average weights of 299.82–301.56 mg, standard deviations of 2.41–2.73 mg, and percentage variances of 0.81–0.91%. These outcomes signify superior weight uniformity, exact dosing consistency, and consistent manufacturing quality. Asrade et al. (2023). Prior research has demonstrated that the majority of commercially available carbamazepine tablet brands adhered to pharmacopoeia quality criteria for identification, weight fluctuation, friability, hardness, assay, and dissolution. These results validated their pharmacological equivalence and endorsed their interchangeable clinical application, with only slight discrepancies noted in disintegration time for one brand [45].

The study confirms that all three brands adhered to pharmacopoeia friability standards, exhibiting friability values between 0.38% and 0.46%. These findings demonstrate sufficient mechanical integrity, minimal weight reduction under manipulation, and commendable tablet resilience. Jamil et al. (2014) reported that research indicated that both the newly developed and commercially available Isosorbide Mononitrate tablets met the BP/USP friability standard (<1%), demonstrating sufficient mechanical durability and resistance to wear during handling, packaging, and transit. The results validated the appropriateness of the formulations for regular pharmaceutical application [46].

The study provided that all commercially available sustained-release Isosorbide Mononitrate tablets demonstrated a regulated and prolonged drug-release pattern over 24 hours, with total drug release varying from 95.87 ± 0.95% to 98.43 ± 0.88% at the 24-hour mark. These results indicate proficient sustained-release efficacy, uniform dissolution characteristics, and adherence to pharmacopoeial dissolution standards among all assessed brands. Kim et al. (2012) reported that A research investigation evaluated a newly developed sustained-release Isosorbide Mononitrate tablet against the commercially available Imdur® Long-Acting 60 mg tablet. Dissolution assessments revealed analogous release patterns across all dissolution media, whereas in vivo bioequivalence evaluations during both fasting and fed states exhibited identical AUC and Cmax metrics. The 90% confidence intervals fell within the permissible bioequivalence range (0.80–1.25), validating that the test formulation was bioequivalent to the reference product [47]. The research established that all commercially available sustained-release Isosorbide Mononitrate tablets primarily adhered to the Higuchi release model (R^2 = 0.991–0.995), signifying a diffusion-governed drug release process. The "Korsmeyer–Peppas model" demonstrated a strong correlation (R^2 = 0.985–0.989), with release exponent (n) values ranging from 0.50 to 0.61, indicating anomalous (non-Fickian) transport that encompasses both diffusion and polymer relaxation. Adnan et al. (2016) developed a research project that developed sustained-release Isosorbide Mononitrate (ISMN) matrix tablets utilising both hydrophilic and hydrophobic polymers. All formulations exhibited satisfactory physical quality characteristics and maintained drug release. The majority of formulations adhered to the Higuchi model, although several demonstrated zero-order kinetics. The refined formulation exhibited a dissolving profile akin to that of the commercial Monis XR pill [48].

5. Conclusion

This investigation was able to examine three commercially available sustained-release Isosorbide Mononitrate (60mg) tablets for the USP/IP relevant quality parameters (CQAs) competently. The sensory characteristics, weight, dimensional uniformity, friability and medication content were within the acceptable range for each brand evaluated, suggesting a higher level of production quality and meeting the pharmacopoeial parameters. The in vitro dissolution studies showed that the drug release was sustained and controlled for 24 h with a cumulative release amount of more than 95% for all the formulations. The analysis of drug release kinetics showed that the Higuchi model was the most appropriate to describe the drug release mechanism, and the "Korsmeyer–Peppas model" suggested anomalous (non-Fickian) diffusion, which included diffusion and polymer relaxation. No significant difference was found ($p>0.05$) between the brands in most of the physical quality parameters, but minor differences in dissolution profile were identified, without affecting the sustained-release property.

The present work comprehensively evaluated the key quality parameters (EQCs) of three commercial sustained-release Isosorbide Mononitrate (60 mg) tablet formulations on USP/IP specifications. The organoleptic properties, weight variability, tablet measures, friability and active ingredient content for all assessed products met the pharmacopoeial standards and demonstrated excellent manufacturing uniformity and pharmaceutical quality. The in vitro dissolution studies were performed to ensure that the drug release was regulated and sustained for 24 hours and that the drug dissolution was >95% in all formulations.

The study's conclusions highlight how crucial it is to thoroughly assess Critical Quality Attributes (CQAs) to guarantee the efficacy, safety, and quality of sustained-release pharmaceutical products. Evaluation of mechanical, functional, and physical quality attributes offers scientific proof that commercially available formulations reliably fulfil the required product criteria and provide repeatable drug-release properties. These assessments are essential to preserving product dependability over the course of its lifecycle.

The drug-release behaviour of the assessed formulations was better understood thanks to the use of dissolution

profiling in conjunction with release kinetic modelling. The efficiency of the sustained-release matrix systems used in the marketed goods is demonstrated by the prevalence of diffusion-controlled release. These discoveries advance our knowledge of formulation performance and could help producers optimise sustained-release dose forms while preserving reliable therapeutic results.

Reference

1. Tarkin JM, Kaski JC. Nicorandil and long-acting nitrates: vasodilator therapies for the management of chronic stable angina pectoris. European Cardiology Review. 2018 Aug;13(1):23.
2. RAO RP, VIJAY K, NARENDRA C, ITENDRA I. Development of Isosorbide-5-mononitrate Sustained Release Matrix Tablet by Statistical Optimization Technique. International Journal of Pharmaceutics and Drug Analysis.;2(9):710-8.
3. Sandner P, Zimmer DP, Milne GT, Follmann M, Hobbs A, Stasch JP. Soluble guanylate cyclase stimulators and activators. InReactive oxygen species: Network pharmacology and therapeutic applications 2019 Jan 29 (pp. 355-394). Cham: Springer International Publishing.
4. Saberianpour S, Modaghegh MH, Rahimi H, Kamyar MM. Role of mechanosignaling on pathology of varicose vein. Biophysical Reviews. 2021 Feb;13(1):139-45.
5. Webb I, Treacher D. Cardiovascular Physiology. Clinical Intensive Care Medicine. 2015:9.
6. Tarkin JM, Kaski JC. Vasodilator therapy: nitrates and nicorandil. Cardiovascular drugs and therapy. 2016 Aug;30(4):367-78.
7. Bryan NS, Ivy JL. Inorganic nitrite and nitrate: evidence to support consideration as dietary nutrients. Nutrition Research. 2015 Aug 1;35(8):643-54.
8. Soin A, Bock G, Giordano A, Patel C, Drachman D. A randomized, double-blind study of the effects of a sustained release formulation of sodium nitrite (SR-nitrite) on patients with diabetic neuropathy. Pain physician. 2018;21(2):179.
9. Nie T, Wang W, Liu X, Wang Y, Li K, Song X, Zhang J, Yu L, He Z. Sustained release systems for delivery of therapeutic peptide/protein. Biomacromolecules. 2021 May 7;22(6):2299-324.
10. Vrettos NN, Roberts CJ, Zhu Z. Gastroretentive technologies in tandem with controlled-release strategies: A potent answer to oral drug bioavailability and patient compliance implications. Pharmaceutics. 2021 Sep 30;13(10):1591.
11. Sifniotis V, Cruz E, Eroglu B, Kayser V. Current advancements in addressing key challenges of therapeutic antibody design, manufacture, and formulation. Antibodies. 2019 Jun 3;8(2):36.
12. Andrade C. Sustained-release, extended-release, and other time-release formulations in neuropsychiatry. J Clin Psychiatry. 2015 Aug 26;76(8):e995-9.
13. Gupta PK, Robinson JR. Oral controlled-release delivery. Treatise on controlled drug delivery. 2017 Oct 2:255-313.
14. Wande DP. Drug Dissolution Studies in Pharmaceutical Formulations: Mechanisms, Influencing Factors, and Regulatory Perspectives. Journal of Advances in Medicine and Medical Research. 2026 Mar 18;38(3):158-74.
15. Lamanna WC, Holzmann J, Cohen HP, Guo X, Schweigler M, Stangler T, Seidl A, Schiestl M. Maintaining consistent quality and clinical performance of biopharmaceuticals. Expert opinion on biological therapy. 2018 Apr 3;18(4):369-79.
16. Lau F, Seifert R. Comparison of drug approvals of the FDA and EMA between 2013 and 2023. Naunyn-schmiedeberg's Archives of Pharmacology. 2026 Jan;399(1):279-99.
17. Mishra V, Thakur S, Patil A, Shukla A. Quality by design (QbD) approaches in current pharmaceutical set-up. Expert opinion on drug delivery. 2018 Aug 3;15(8):737-58.
18. 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.
19. Khan A, Naquvi KJ, Haider MF, Khan MA. Quality by design-newer technique for pharmaceutical product development. Intelligent Pharmacy. 2024 Feb 1;2(1):122-9.
20. Dayyih WA, Awad R. Revolutionizing drug development: The role of quality by design (QbD) in modern pharmaceutical analysis. Journal of Pharmaceutical Sciences and Computational Chemistry. 2025;1(1):26-37.
21. Mesut B, Özsoy Y, Aksu B. The place of drug product critical quality parameters in quality by design (QBD). Turk J Pharm Sci. 2015 Jan 1;12(1):75-92.
22. Bhavyasri K, Vishnumurthy KM, Rambabu D, Sumakanth M. ICH guidelines–"Q" series (quality guidelines)-A review. GSC Biol Pharm Sci. 2019;6(3):089-106.
23. Welegebrial BG, Gezae Z, Gebrekidan SK, Gebrerufael GG, Gebregzabiher HA, Kidane AM, Hailesilase GG. In vitro comparative quality evaluation of different brands of metformin hydrochloride tablets available in Mekelle City, Tigray Regional State, Ethiopia. BMC Pharmacology and Toxicology. 2026 Mar 12;27(1):66.

24. Saxon D, Firth N, Barkham M. The relationship between therapist effects and therapy delivery factors: Therapy modality, dosage, and non-completion. Administration and Policy in Mental Health and Mental Health Services Research. 2017 Sep;44(5):705-15.
25. Mohammed HA, Khan RA. Anthocyanins: traditional uses, structural and functional variations, approaches to increase yields and products' quality, hepatoprotection, liver longevity, and commercial products. International Journal of Molecular Sciences. 2022 Feb 15;23(4):2149.
26. Philips CA, Theruvath AH, Sreemohan A, Baby A, Jose S, Philips M, Philip T, Ramesh C. Pharmaceutical quality and cost-effectiveness of branded versus generic medicines across 22 drug types and 8 therapeutic categories: a citizen-funded comparative study from regulated retail outlets in Kerala, India. Frontiers in Pharmacology. 2026 Jun 3;17:1799574.
27. 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.
28. 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.
29. Murthy SN, HN S, Suresh S. Challenges in Design of Drug Delivery Systems. Fundamentals of Drug Delivery. 2021 Oct 26:15-38.
30. Atre P, Rizvi SA. Advances in oral solid drug delivery systems: quality by design approach in development of controlled release tablets. BioChem. 2025 Apr 25;5(2):9.
31. Atre P, Rizvi SA. Advances in oral solid drug delivery systems: quality by design approach in development of controlled release tablets. BioChem. 2025 Apr 25;5(2):9.
32. Alt N, Zhang TY, Motchnik P, Taticek R, Quarmby V, Schlothauer T, Beck H, Emrich T, Harris RJ. Determination of critical quality attributes for monoclonal antibodies using quality by design principles. Biologicals. 2016 Sep 1;44(5):291-305.
33. Thombre N, Saindane R, More D, Kshirsagar S. Implementation of Quality by Design in Generic Drug Product Development: A Case Study Using Diclofenac Sodium Sustained Release Tablets. Jordan Journal of Pharmaceutical Sciences. 2025 Sep 1;18(4):924.
34. Devi A. Pharmaceutical Design and In Vitro Evaluation of a Dual Layer Valproic Acid Tablet for Enhanced Therapeutic Efficacy and Controlled Drug Release. Journal of Neonatal Surgery. 2025;14(31s).
35. Talevi A, Ruiz ME. Korsmeyer-peppas, peppas-sahlin, and brazel-peppas: models of drug release. InThe ADME encyclopedia: A comprehensive guide on biopharmacy and pharmacokinetics 2022 Jun 15 (pp. 613-621). Cham: Springer International Publishing.
36. Mkpa BO. The Role of Pharmaceutical Quality Control in Preventing Public Health Risks in United States. American Journal of Advanced Technology and Engineering Solutions. 2025 Aug 8;1(02):135-72.
37. Kumar A, Jain SK, Mishra DK, Gautam R. Influence of drug properties and routes of drug administration on design of sustained and controlled release systems. InNovel Carrier Systems for Targeted and Controlled Drug Delivery 2024 Dec 24 (pp. 1-46). Singapore: Springer Nature Singapore.
38. Bhusal P, Harrison J, Sharma M, Jones DS, Hill AG, Svirskis D. Controlled release drug delivery systems to improve post-operative pharmacotherapy. Drug delivery and translational research. 2016 Oct;6(5):441-51.
39. Zhang X, Li Y, Huang Z, Cui Y, Zhao Z, Yue X, Wang G, Liang R, Huang Y, Tan W, Wu C. Development and pharmacokinetics evaluation of quetiapine fumarate sustained-release tablets based on hydrophilic matrix. Journal of Drug Delivery Science and Technology. 2019 Dec 1;54:101322.
40. Geraili A, Xing M, Mequanint K. Design and fabrication of drug-delivery systems toward adjustable release profiles for personalized treatment. View. 2021 Oct;2(5):20200126.
41. Kim EJ, Kim JH, Kim MS, Jeong SH, Choi DH. Process analytical technology tools for monitoring pharmaceutical unit operations: a control strategy for continuous process verification. Pharmaceutics. 2021 Jun 21;13(6):919.
42. Prakash G, Chandra SA, Sandhya P, Bidur C, Samir D. Pharmacopoeial comparison of in-process and finished product quality control test for pharmaceutical tablets. GSC Biological and Pharmaceutical Sciences. 2020 Jun;11(3):155-65.
43. Suksaeree J, Monton C, Maneewattanapinyo P. Quality by Design Integration of Design of Experiments for Tablet Formulation Optimization and Process Validation. AAPS PharmSciTech. 2026 Feb 10;27(2):94.
44. Sabbatini B. Advancements In Excipient Characterization For The Optimization of Oral Solid Dosage Forms: From Characterization To Formulation.
45. Asrade B, Tessema E, Tarekegn A. In vitro comparative quality evaluation of different brands of carbamazepine tablets commercially available in Dessie town, Northeast Ethiopia. BMC Pharmacology and Toxicology. 2023 May 25;24(1):35.
46. Jamil S, Naqvi SA, Naveed S, Dilshad H. FORMULATIONS OF ISOSORBIDE MONONITRATE (ISMN) TABLET AND COMPARATIVE STUDY WITH AVAILABLE BRANDS. INTERNATIONAL RESEARCH JOURNAL OF PHARMACY. 2014;5(3):168-71.

47. Kim YH, Choi KS, Kam SH, Lee KH, Park JS. In vitro dissolution and in vivo bioequivalence evaluation of two brands of isosorbide 5-mononitrate sustained release tablets. Arzneimittelforschung. 2012 Dec;62(12):576-82.
48. 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.