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QUALITY ASSESSMENT AND STABILITY STUDIES OF METRONIDAZOLE TABLETS FORMULATIONS OBTAINED VIA CRYSTALLO CO-AGGLOMERATION TECHNIQUE

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ABSTRACT

Stability studies are essential for assessing the quality, safety, and efficacy of pharmaceutical products, ensuring they maintain their properties over time. This study aimed to assess the stability of metronidazole tablets stored in a desiccator with charged silica gel following the International council for harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines. Metronidazole tablets were formulated from metronidazole co-agglomerates using different excipients by direct compression method and stored for 6 and 12 months at 25±2°C/60±5% relative humidity. Quality parameters such as weight variation, diameter, thickness, hardness, friability, content uniformity, and dissolution rate were evaluated at intervals using the United States Pharmacopeia – National Formulary and British Pharmacopeia specifications. The tablets maintained uniformity in weight, diameter, thickness and content over 12 months, meeting pharmacopeial standards. They exhibited high crushing strength, low friability, and consistent disintegration times (<5 min), across formulations and storage durations with no significant changes after storage, indicating stable performance. The sustained high crushing strength, friability ratio (CSFR) and crushing strength, friability, disintegration time (CSFR/Dt) ratios suggested high tablet strength and quality. *In-vitro* dissolution studies showed release rates of 87.31 – 100.81 %, with a significant decrease at 6 months within pharmacopeial standards but no change at 12 months. Content uniformity was maintained throughout storage. Metronidazole tablets formulated from crystallo co-agglomerates demonstrated good stability and mechanical strength over 12 months of storage. Storage in air-tight containers with desiccants at controlled room temperature (25±2°C) or below their relative humidities is recommended for maintaining tablet quality.

Keywords: Stability studies, Crystallo-co-agglomeration, Metronidazole tablets, Quality assessment, Storage

INTRODUCTION

Stability studies are crucial for ensuring the quality, safety, and efficacy of pharmaceutical products throughout their shelf life. These studies are conducted according to predefined protocols established by organizations like the International Council *for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* **(**ICH**)** and the World Health Organization (WHO)**.** They assess a product's ability to maintain its properties and characteristics over time (Rencber *et al.*, 2019).

A pharmaceutical product is considered stable if it maintains its physical, chemical, microbiological, toxicological, protective, and informational specifications within a specific container/closure system (Panda *et al.*, 2013; Noman *et al.*, 2024). The United States Pharmacopeia (USP) defines stability as the extent to which a product retains its specified characteristics throughout its storage and usage period. Stability testing is conducted throughout various stages of product development to ensure that the product's characteristics remain unchanged from production until patient use**,** making it a critical quality indicator (Punam *et al.*, 2014; Rencber *et al.*, 2019).

Stability testing involves assessing the impact of environmental factors such as light, heat, and moisture on the quality of the drug substance or formulated product during storage and use. It helps predict shelf life**,** determine storage conditions, and guide labeling instructions. Factors influencing pharmaceutical stability are numerous and complex. They include the stability of active ingredients, interactions between ingredients and excipients, manufacturing processes, type of dosage forms, packaging materials, and environmental conditions during handling and storage (Maclean *et al.*, 2022). Chemical reactions like oxidations, reduction, hydrolysis, and degradation reactions can significantly impact stability of a pharmaceutical product, as can physical changes such as alterations in appearance, consistency, and particle size (Narayan and Manupriya, 2019). A pharmaceutical product may experience alterations in its appearance, consistency, content uniformity, clarity (in the case of solutions), moisture content, particle size and shape, pH, and package integrity, all of which can impact its stability.

These changes can result from factors such as impact, vibration, abrasion, and temperature fluctuations, including freezing, thawing, or shearing. Chemical reactions such as solvolysis, oxidation, reduction, and racemization can also occur in pharmaceutical products, leading to the formation of degradation products and a loss of potency in the active pharmaceutical ingredient (API) as well as a reduction in excipient activity, such as antimicrobial preservative action and antioxidant properties (Alfred-Ugbenbo *et al.*, 2017). Additionally, microbiological changes, such as the growth of microorganisms in non-sterile products and alterations in preservative efficacy, can impact the stability of pharmaceutical products (Syukri *et al.*, 2019).

Stability testing primarily focuses on evaluating chemical degradation to ensure the safety of the product throughout its shelf life. Accelerated stability studies are commonly used to study chemical degradation, with the data extrapolated for long-term storage predictions (Faisal *et al.*, 2013). Additionally, physical stability must be evaluated to ensure product performance remains unaffected during storage.

The stability of a pharmaceutical dosage form refers to its ability to maintain its properties and characteristics over time. It is a critical quality indicator, expressed as shelf life or expiry period, essential for patient safety, drug efficacy, and

overall product quality (Costa *et al.*, 2021). Stability studies involve exposing samples to environmental factors like temperature, humidity, and light, with evaluations conducted at various time intervals (Faisal *et al.*, 2013; Syukri *et al.*, 2019).

Stable tablets are expected to maintain their original properties, including size, shape, weight, color, and texture, under normal handling and storage conditions throughout their shelf life (Alderborn and Frenning, 2017, Salim *et al.*, 2023). Dosage forms must be evaluated under storage conditions that assess their thermal stability and sensitivity to moisture, encompassing storage, shipment, and subsequent use (Qiu, 2018).

This study aims to assess the stability of directly compressible metronidazole tablets formulated from crystallo co-agglomerates of metronidazole. Stability parameters such as weight variation, dimensions, hardness, friability, content uniformity, and dissolution were evaluated at 0, 6, and 12 months under controlled temperature and relative humidity conditions**.**

MATERIALS AND METHODS

Materials

All excipients and chemicals were of pharmaceutical grade and directly obtained from the manufacturers. The tablet excipients included Ludipress® (BASF, Germany), Combilac® (Meggle Group, Megglestrasse, Wasserburg, Germany), Sodium starch glycolate (ATOZ Pharmaceuticals Ltd, Ambaltur, India), Microcrystalline cellulose PH 200 (Avicel®) (Dupont Nutrition Ltd, Ireland), Starlac® (Meggle Group, Megglestrasse, Wasserburg, Germany), Prosolv® (JSR Pharm, GmbH and Co. KG, Rosenberg, Deustchland, Germany), Talc powder (BDH Chemicals Ltd Poole, England), Magnesium stearate (BDH Chemicals Ltd Poole, England), Maize starch (BDH Chemicals Ltd, England). All other solvents and reagents were of analytical grade.

Methods

Tablets Preparation

The tablets were prepared following the method described in Abdullahi et al.'s study (Abdullahi *et al.*, 2023). The active pharmaceutical ingredient (metronidazole) was prepared using the crystallo co-agglomeration technique. The tablets were formulated according to Table 1. Tablets containing 200 mg metronidazole were directly compressed with five different direct compression excipients vis: Ludipress®, Avicel®, Prosolv®, StarLac® and Combilac®. They were mixed along with magnesium stearate (0.5% w/w) and talc (1.5% w/w) for 5 min in a glass jar. The powder blend (500 ± 2 mg) was directly compressed into tablets on a single stroke tablet press equipped with 12 mm punch at a compression pressure of 5.5 to 8.0 kN.

Table 1: Batch Formular for Metronidazole 500 mg tablet prepared using direct compression method

Ingredients	F1	F2	F3	F4	F5
Metronidazole Co-agglomerates (mg)	200	200	200	200	200
Ludipress® (mg)	290	—	—	—	—
Avicel® (mg)	—	290	—	—	—
Prosolv® (mg)	—	—	290	—	—
Starlac® (mg)	—	—	—	290	—
Combilac® (mg)	—	—	—	—	290
Magnesium stearate (mg)	2.5	2.5	2.5	2.5	2.5
Talc (mg)	7.5	7.5	7.5	7.5	7.5
Total (mg)	500	500	500	500	500

Key: F=formulation

Stability studies

The metronidazole tablet batches underwent a stability test and were stored in a desiccator charged with silica gel, following ICH guidelines, at 25±2 °C / 60 ±5 % relative humidity for 6 and 12 months (WHO, 2009; SADC, 2004). The physical characteristics of the tablets, including appearance, weight uniformity, diameter, thickness, hardness, friability, content uniformity, and *in-vitro* drug release profiles, were assessed over the 12-month period.

Uniformity of weight

Ten (10) tablets were randomly chosen from each batch and weighed individually using an analytical balance. The mean weight of the ten tablets was calculated, and the standard deviation for each batch was determined.

Diameter and thickness studies

The diameter and thickness of ten (10) tablets were randomly measured using a digital caliper, and the results were presented as the mean and standard deviation.

Tablet hardness

Ten (10) tablets were randomly chosen and placed individually between the platen of the hardness tester. The adjustable knob was then tightened to ensure contact with the tablet, and sufficient pressure was applied to cause the tablet to break. The result represents the average of 10 determinations in kg/f.

Tensile strength (Ts)

A Monsanto tablet hardness tester was used to measure a load across the diameter of each tablet to find the hardness F when crushing. The following equation was then used to calculate the tensile strength (Ts) (Olowosulu *et al.*, 2015).

$$Ts = \frac{6.24F}{Dt} \quad (1)$$

Here F is the crushing force (Kg/f), D is the diameter of the tablet in mm, and t is the thickness of the tablet in mm.

Friability test

Ten (10) tablets from each batch were weighed and subjected to combined abrasion and shock in a plastic chamber. The friabilator was operated at a rate of 25 revolutions per minute for 4 minutes. During each revolution, tablets were dropped from a height of 6 inches. Afterward, the tablets were dusted using a brush, and their final weight was measured. The percentage of friability was calculated using equation 2.

$$Friability = \frac{Wo-W}{Wo} \times 100 \quad (2)$$

Where Wo is the initial weight of tablets, W is the final weight of the tablet after subjecting it through the friabilator.

Tablet Disintegration Test

The disintegration test apparatus, containing 0.1 N HCl and maintained at 37±1 °C, was used for the test. Six tablets from a batch, one per tube, were tested simultaneously. The time taken for each of the six tablets to disintegrate and pass through the mesh was recorded, and the mean disintegration time of each batch was calculated.

In-vitro drug release study

The *in-vitro* dissolution studies for the prepared tablets were conducted using USP Apparatus I (Basket type), with a rotation speed of 100 rpm in 900 mL of dissolution medium (0.1 N HCl) maintained at 37 ± 1 ℃. Samples were withdrawn at various time intervals (10 sec, 30 sec, 1, 2, 5, 10, and 15 min), and the percentage of metronidazole released from the tablet was estimated spectrophotometrically at 277.0 nm using 0.1 N HCl as the blank. The amount of metronidazole released at each time point was analyzed, and the percentage drug release was calculated.

Content uniformity

Twenty (20) tablets from each batch were randomly selected, weighed on the analytical balance and then pulverized in a ceramic mortar. A 0.50 g aliquot of the powder was transferred into a volumetric flask, dissolved in 200 ml 0.1 N HCl and then filtered. This was diluted with 100 ml of the medium, obtaining a concentration of 0.025 mg/ml. samples were analyzed by UV-spectrophotometer at 277.0 nm.

Statistical Analysis and Data Presentation

All experiments were conducted in replicates to ensure validity of statistical analysis. Analysis of variance (ANOVA) was employed to compare the properties across various categories of data sets using SPSS software, version 25. Differences were deemed significant for *P values < 0.05*. The results were presented as mean, standard error of the mean (SEM), and percentages (%) in tables and figures.

RESULTS AND DISCUSSION

Metronidazole tablets were successfully prepared from crystallo co-agglomerates of metronidazole. Upon examination, the surface revealed a remarkable uniformity, characterized by its smoothness and shiny surface.

The results as presented in Table 2, presents various tablet parameters of the five (5) different direct compression excipients utilized in the formulation of tablets containing metronidazole CCA. Notably, fluidity and compression properties exhibit variations depending on the specific co-agglomerate-direct compression excipient combination. The mean weight of the tablets demonstrates consistency, with repeatable tablet weight fluctuation falling within the permissible deviation of 5 % of the total tablet weight as specified by the B. P. (2010). In terms of tablet thickness, this too has demonstrated repeatability and consistency throughout the time under investigation.

Evaluating the friability of the formulations, the friability of tablets formulations F2, F3 and F4 demonstrated less than 1 % friability, thereby passing the test. While that of formulation F1 and F5 show a failure of the friability test.

Table 2: Summary of stability studies of metronidazole tablet (n=3, means±SD)

Formu-lation	Time (month)	Appearance	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/f)	Friability (%)	Content uniformity	Drug released (%)
F1	t=0	Acceptable	498±4.47	12.03±0.24	3.10±0.02	7.40±1.12	2.00	101.11	98.19
	t=6	Acceptable	502±0.00	12.03±0.02	3.09±0.04	7.50±0.45	2.15	98.34	94.65
	t=12	Acceptable	492±10.00	12.03±0.01	3.07±0.51	7.53±0.18	2.00	98.66	92..89
F2	t=0	Acceptable	504±5.48	12.02±0.40	3.03±0.30	8.20±1.14	0.82	100.37	98.58
	t=6	Acceptable	499±0.00	12.02±0.03	3.03±0.03	7.90±0.74	0.81	100.48	95.21
	t=12	Acceptable	492±0.51	12.02±0.02	3.07±0.81	7.90±0.45	0.80	93.36	87.31
F3	t=0	Acceptable	504±5.48	12.03±0.13	3.05±0.02	8.50±0.84	0.80	99.12	99.27
	t=6	Acceptable	498±8.37	12.03±0.02	3.04±0.03	8.60±0.58	0.84	107.75	100.01
	t=12	Acceptable	498±13.04	12.02±0.01	3.08±0.22	8.63±0.84	0.84	97.61	89.52
F4	t=0	Acceptable	494±5.48	12.03±0.26	3.06±0.03	7.90±0.55	0.94	97.74	95.66
	t=6	Acceptable	502±4.47	12.03±0.04	3.09±0.05	7.70±0.27	1.16	97.93	94.32
	t=12	Acceptable	504±8.94	12.02±0.01	3.02±0.64	7.60±0.33	1.20	89.33	93.70
F5	t=0	Acceptable	496±5.48	12.03±0.34	3.01±0.03	11.10±0.67	1.18	99.64	102.53
	t=6	Acceptable	502±4.47	12.02±0.02	3.05±0.04	10.30±0.74	1.19	100.12	91.25
	t=12	Acceptable	505±12.25	12.02±0.02	3.07±0.43	10.80±1.89	1.23	99.57	89.73

Key: F=formulation, n=replicant

Stability testing was conducted to assess potential changes in the quality of manufactured tablets over time due to environmental factors like temperature, humidity, and storage conditions. These tests are crucial for monitoring drug degradation through the process of time. Following the guidelines set forth by WHO (2009) and SADC (2004), the study employed a climatic chamber set at 25 °C ± 2 °C and 60 % ± 5 % relative humidity for periods of 0, 6 and 12 months. The stability evaluation of metronidazole tablets produced via direct compression (DC) encompassed weight variation, diameter, thickness, hardness, friability, content uniformity, and tablet dissolution rate.

Uniformity of tablet weight

In this study, at the beginning the average weight of batch formulation F1 – F5 were found to be 497.33±0.00 g, 498.33±0.00 g, 500.00±0.00 g, 500.00±0.00 g, and 501.00±0.00 g, respectively. Ensuring that each tablets formulation batch are within an appropriate size range is of prime importance, as slight variations in tablet weight can indicate differences in the content of the active ingredient.

The British Pharmacopoeia (BP 2010) specifies that for tablets exceeding 250 mg mean weight, no more than two tablets per batch can deviate from the average by more than ±5 %, and none by more than ±10 % (British Pharmacopoeia, 2010). Poor granule flow, improper die filling, or air entrapment in the powder bed can all contribute to excessive weight variation (Rencber *et al.,* 2019). Following stability testing, none of the formulations exhibited visual changes, and all maintained an average weight within the pharmacopeial limits (mean ± 5 %) established by both USP and BP. Consequently, all formulations passed the official weight uniformity test (Table 3).

Diameter and thickness studies

The diameter and thickness of all tablets are reported in Table 3. Notably, no statistically significant changes in these values were observed after storing the tablets in a desiccator with silica gel for 12 months (data in Table 3). For uncoated tablets, the USP-NF recommends a thickness between 2.0 and 8.0 mm, and a diameter between 2.0 and 25.0 mm, depending on the tablet shape and size (USP-NF, 2020).

Across all formulations (F1 to F5) and storage time points (0, 6, and 12 months), the diameter remained relatively consistent. Minor fluctuations within each formulation, typically within the range of ±0.01 to ±0.05 mm, were observed. For example, the diameters ranged from 12.01 mm to 12.03 mm at the initial measurement (t=0), with similar variations observed at 6 (t=6) and 12 months (t=12). Overall, there was generally no significant change in tablet diameter for most formulations over time, indicating consistent manufacturing processes and minimal impact from storage duration.

The thickness of the tablets showed slightly more variability compared to the diameter, with fluctuations observed across different formulations and storage durations. However, these changes were not statistically significant. In formulation F1, the thickness ranged from 3.07 mm to 3.10 mm at the initial measurement (t=0), with similar variations at 6 (t=6) and 12 months (t=12). Similarly, in formulation F5, the thickness ranged from 3.01 mm to 3.07 mm at the initial measurement, with similar variations observed at subsequent time points. Despite these fluctuations, the tablets maintained acceptable thickness levels throughout the storage duration.

These variations in tablet diameter and thickness are minimal and generally fall within acceptable ranges for pharmaceutical tablets, as outlined by Lachman and Lieberman (2013). These minor fluctuations are typical in manufacturing processes and do not significantly impact the overall quality and performance of the tablets.

Tablet hardness

Tablets require sufficient strength (hardness) and resistance to crumbling (friability) to endure the mechanical stresses encountered during manufacturing, packaging, and shipping (Punam *et al.,* 2014). The force needed to break a tablet in half is termed its hardness or crushing strength (CS). CS of a tablet is an important parameter, reflecting the ease of tablet handling as well as its compressional behaviour. Crushing strength of 4 – 15 Kg/f (40 – 150 N) is recommended satisfactory for oral tablets (British Pharmacopoeia, 2010).

All formulations initially exhibited high crushing strength values, ranging from 7.40 to 11.10 Kg/f, as detailed in Table 4. While storing the tablets in a controlled temperature and humidity chamber for 12 months resulted in changes to their crushing strength values. However, the changes observed in the tablets after storage was not statistically significant (Table 4). As crushing strength alone doesn't definitively assess a tablet's resistance to damage, friability studies were conducted to further evaluate their resilience to fracture and breakage.

Friability

Friability, as described by Oliveira et al. (2013), measures a tablet's resistance to chipping, abrasion, and breakage during handling and use. It ensures minimal weight loss and maintains the tablet's form for accurate dosing. A maximum friability limit of 1 % is generally considered acceptable for maintaining tablet quality. Factors like insufficient binder concentration or inadequate compression pressure can contribute to exceeding this limit and compromise tablet integrity.

In this study, only formulation F1 exhibited friability exceeding 2 %, while others remained below 1 % (Table 3). This indicates that all formulations, except F1, met the friability specifications ($p \geq 0.05$). It's important to note that friability is inversely proportional to crushing strength (Lachman and Lieberman, 2013; Maclean *et al.,* 2022). A lower friability value signifies a harder tablet with better resistance to mechanical stresses. Both crushing strength and friability are essential properties for patient acceptance as they guarantee a well-formed and robust tablet throughout its lifespan.

Tensile strength (TS)

The formulations exhibited higher tensile strength values (Table 3), indicating improved resistance to mechanical stresses during handling. This enhanced strength is attributed to the strong inter-particulate bonding within the crystallo-co-agglomerated metronidazole (Abdullahi *et al.,* 2023). This technique, employing polymers, facilitates the formation of these strong bonds between the agglomerated crystals.

Furthermore, Table 4 reveals a positive correlation between drug loading and tensile strength. This suggests that higher drug content leads to the formation of more crystal bridges due to increased interaction between drug molecules. These additional bridges contribute to a stronger and more robust compact.

Table 3 provides a comparison between the mechanical properties of the formulated tablet batches vis-a-vis their stability over time. In all the mechanical properties assessed; Crushing strength, Friability, Tensile strength and their relationship with disintegration time showed that all the tablet batches formulated had a higher index of mechanical quality and a good balance of CSFR/Dt. All the tablets were observed to disintegrate in less than 3 min.

There appears to be an inverse relationship between disintegration time and friability. Tablets that disintegrate faster tend to have lower friability, indicating greater mechanical resilience. However, crushing strength values do not consistently follow this trend, suggesting that other factors may influence tablet strength.

Despite the strong crushing strength of formulation F5 tablets, high friability values diminished the CSFR indices. Hence, it can be inferred that a combination of high crushing strength and low friability values are conducive to yield higher CSFR indices, and consequently, superior mechanical strength. This superior balance between mechanical strength and disintegration time was observed in F2, F3 and F4 tablets.

The tensile strength gives a measure of the bonding strength and is used in assessing the mechanical strength of the tablets formed with the various direct compression excipients. This indicated that all the tablet formulations have tablets that possess sufficient mechanical strength.

Table 3: Relationship between the mechanical properties of metronidazole tablet

Formulation	Time (month)	Crushing strength (Kg/f)	Friability (%)	Disintegration time (min)	CSFR	CSFR/Dt	Tensile strength
F1	t=0	7.40±1.12	2.00	1.48±0.44	3.70	2.50	1.24
	t=6	7.50±0.45	2.15	1.48±0.56	3.06	2.07	1.26
	t=12	7.53±0.18	2.00	1.47±1.53	3.77	2.56	1.27
F2	t=0	8.20±1.14	0.83	3.51±0.65	9.75	2.78	1.40
	t=6	7.90±0.74	0.81	3.53±0.64	9.88	2.80	1.35
	t=12	7.90±0.45	0.80	3.57±2.52	9.88	2.77	1.34
F3	t=0	8.50±0.84	0.80	2.33±0.54	10.24	4.39	1.45
	t=6	8.60±0.58	0.84	2.34±3.06	10.27	4.39	1.47
	t=12	8.63±0.84	0.84	2.34±0.46	10.63	4.54	1.45
F4	t=0	7.90±0.55	0.94	1.59±0.11	9.40	5.91	1.34
	t=6	7.70±0.27	1.16	2.57±0.11	6.64	2.58	1.29
	t=12	7.60±0.33	1.20	2.59±2.52	6.33	2.44	1.31
F5	t=0	11.10±0.67	1.18	2.51±0.10	9.41	3.75	1.91
	t=6	10.30±0.74	1.19	2.51±1.53	8.78	3.50	1.75
	t=12	10.80±1.89	1.23	2.49±0.11	8.66	3.48	1.83

Key: F=formulation

Disintegration time (Dt)

Tablet disintegration**,** the breakdown of a tablet into smaller particles in an aqueous environment, plays a crucial role in both formulation stability and drug delivery (Berardi *et al.,* 2021). Disintegration time is a critical parameter that can influence drug dissolution and subsequent absorption, potentially even becoming the rate-limiting step in the process (Quodbach and Kleinebudde, 2015).

Maintaining consistent disintegration time throughout a tablet's shelf life is a crucial aspect of stability. Changes in disintegration time could indicate potential degradation of the tablet matrix or alteration in excipient properties, impacting drug release. For uncoated tablets, the British Pharmacopoeia sets a maximum disintegration time limit of 15 minutes (British Pharmacopoeia, 2010). While not a direct measure of stability, crushing strength may provide some indication of disintegration behavior (Clancy *et al.,* 2018).

The present study found that all formulated tablet batches displayed rapid disintegration (< 5 minutes)**,** which is a desired characteristic for tablets produced by direct compression. This rapid disintegration not only ensures efficient drug delivery but also conforms to the BP specifications for uncoated tablets (British Pharmacopoeia, 2010).

Disintegration time values vary among formulations and storage durations, indicating differences in tablet composition and formulations processes. Formulation F1 shows relatively consistent disintegration times range from 1.47 to 1.48 minutes at different storage durations, showing consistency. Formulation F4 exhibits a significant increase in disintegration time from 1.59 min at t=0 to t=6, followed by 2.59 min at t=12, indicating a potential change in the tablets properties over time. Formulation F5 demonstrates relatively stable disintegration times around 2.5 minutes across all the different storage durations.

Disintegration time can be influenced by factors such as crushing strength, friability, and tensile strength. Tablets with higher crushing strength may have longer disintegration times (Lachman and Lieberman, 2013; Clancy *et al.,* 2018), as seen in formulation F4, where an increase in crushing strength corresponds to an increase in disintegration time. Formulation F5 consistently demonstrates the longest disintegration time among all formulations, indicating slower tablet breakdown. In contrast, formulations like F1 and F2 exhibit shorter disintegration times, suggesting faster tablet breakdown and potentially quicker drug release. In some cases, storage duration may impact disintegration time, as seen in the variations between t=0, t=6, and t=12 for certain formulations. However, for most formulations, disintegration times remain relatively stable over the storage duration, indicating consistent performance and stability of the tablets.

Crushing strength friability (CSFR) ratio

The CSFR combines two vital aspects of tablet quality: strength and friability (Alebiowu et al., 2009). This ratio offers a comprehensive assessment by considering both a tablet's resistance to breaking (crushing strength) and its resistance to chipping and abrasion (friability). Bamiro et al. (2014) established that a higher CSFR value signifies a stronger tablet. This is because a strong tablet will have a high crushing strength to withstand pressure and a low friability to minimize chipping and breakage.

Therefore, the CSFR provides valuable insights into a tablet's ability to withstand various physical stresses encountered throughout its manufacturing, packaging, transportation, and use. This combined measure plays a crucial role in ensuring tablet integrity and patient acceptance.

Higher CSFR values indicate greater tablet strength relative to friability, suggesting improved stability and resistance to mechanical stress. Across the formulations and storage durations, the CSFR values vary, reflecting differences in tablet hardness and compactness. Formulation F5 consistently demonstrates the highest CSFR values among all formulations, indicating superior stability and mechanical strength. Other formulations exhibit relatively lower but still acceptable CSFR values, suggesting overall stability under the tested conditions. Despite minor fluctuations, CSFR values generally remain within acceptable ranges across formulations and storage durations, indicating consistent tablet stability.

CSFR/Disintegration time (Dt) ratio

While the crushing strength-friability ratio (CSFR) offers valuable insights into tablet quality, a more comprehensive approach can be achieved by considering the CSFR/disintegration time (DT) ratio**.** As suggested by Alebiowu et al. (2009), this ratio provides a superior measure by incorporating both strength and weakness aspects of a tablet.

Strength is reflected by crushing strength and friability, indicating the tablet's ability to resist breaking and chipping, respectively. These parameters are linked to bond strength within the tablet matrix. However, a strong tablet may not necessarily disintegrate well, potentially hindering drug release. Weakness, on the other hand, is represented by disintegration time. This parameter indicates how quickly the tablet breaks down in an aqueous environment, facilitating drug release.

The CSFR/DT ratio takes both aspects into account, simultaneously evaluating the positive impacts of high crushing strength and low friability on bond strength while also assessing their potential negative impact on disintegration time. A higher CSFR/DT ratio signifies a better balance between these opposing forces, indicating a robust tablet that disintegrates appropriately (Ayorinde, 2012).

Formulation F1 exhibits relatively high CSFR/Dt values, indicating good stability per unit of disintegration time across all storage durations. Other formulations also demonstrate acceptable CSFR/Dt values, suggesting stable performance relative to their disintegration times. Despite minor variations, CSFR/Dt values generally remain consistent or improve slightly over the storage durations, indicating maintained or enhanced tablet stability with time.

Figure 1 – 5 depicts the *in-vitro* drug release profiles of metronidazole tablets formulated as F1, F2, F3, F4 and F5 at different storage time durations. The graphs illustrate how the release of metronidazole from the tablets changes over time under specified storage conditions. These profiles are crucial for assessing the stability and performance of the formulation over its shelf life.

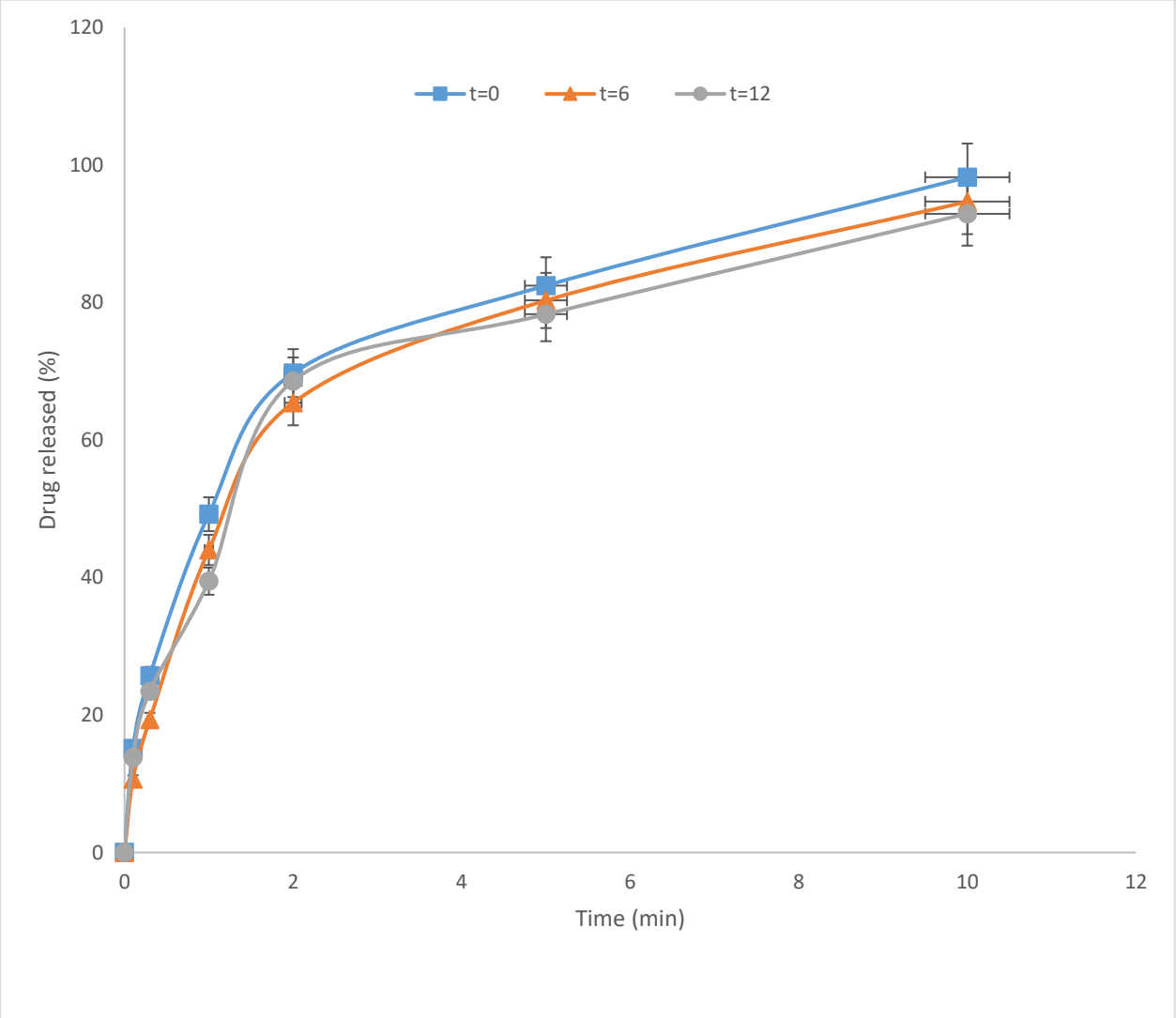

Figure 1: The *in-vitro* release profiles of metronidazole tablets (formulation F1) at various storage durations

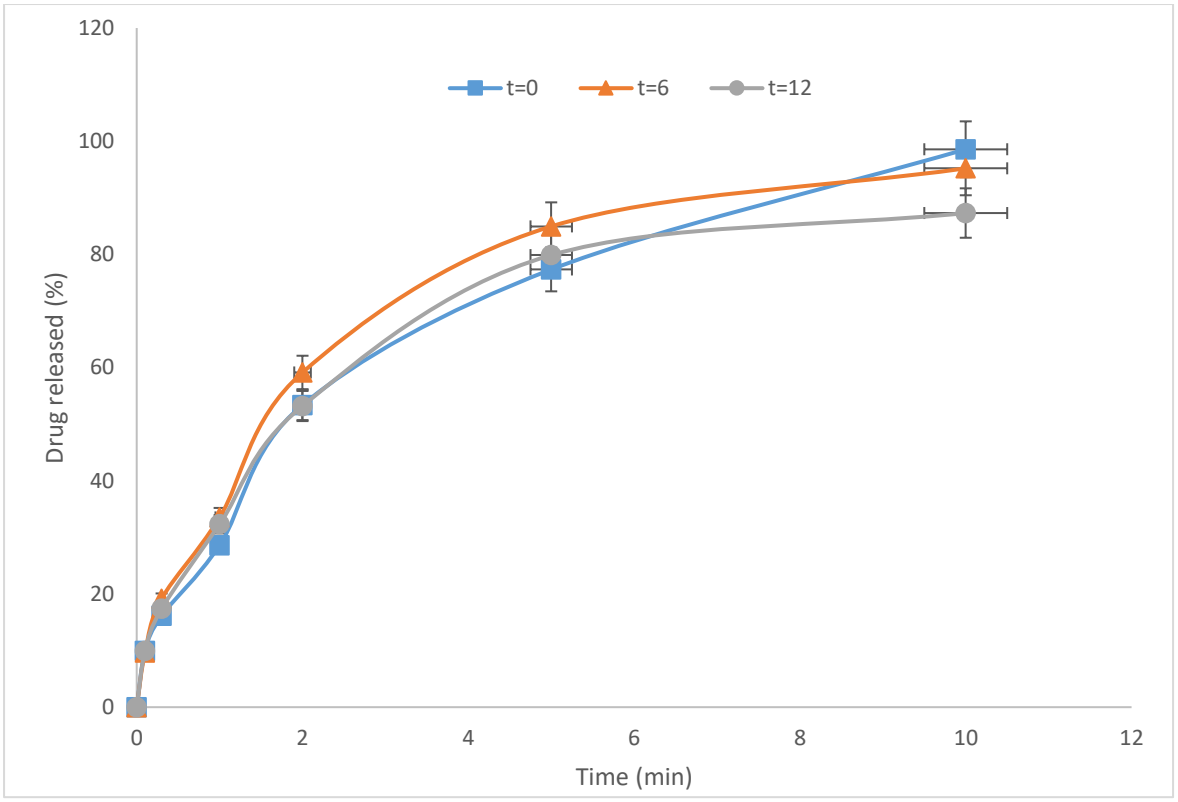

Figure 2: The *in-vitro* release profiles of metronidazole tablets (formulation F2) at various storage durations

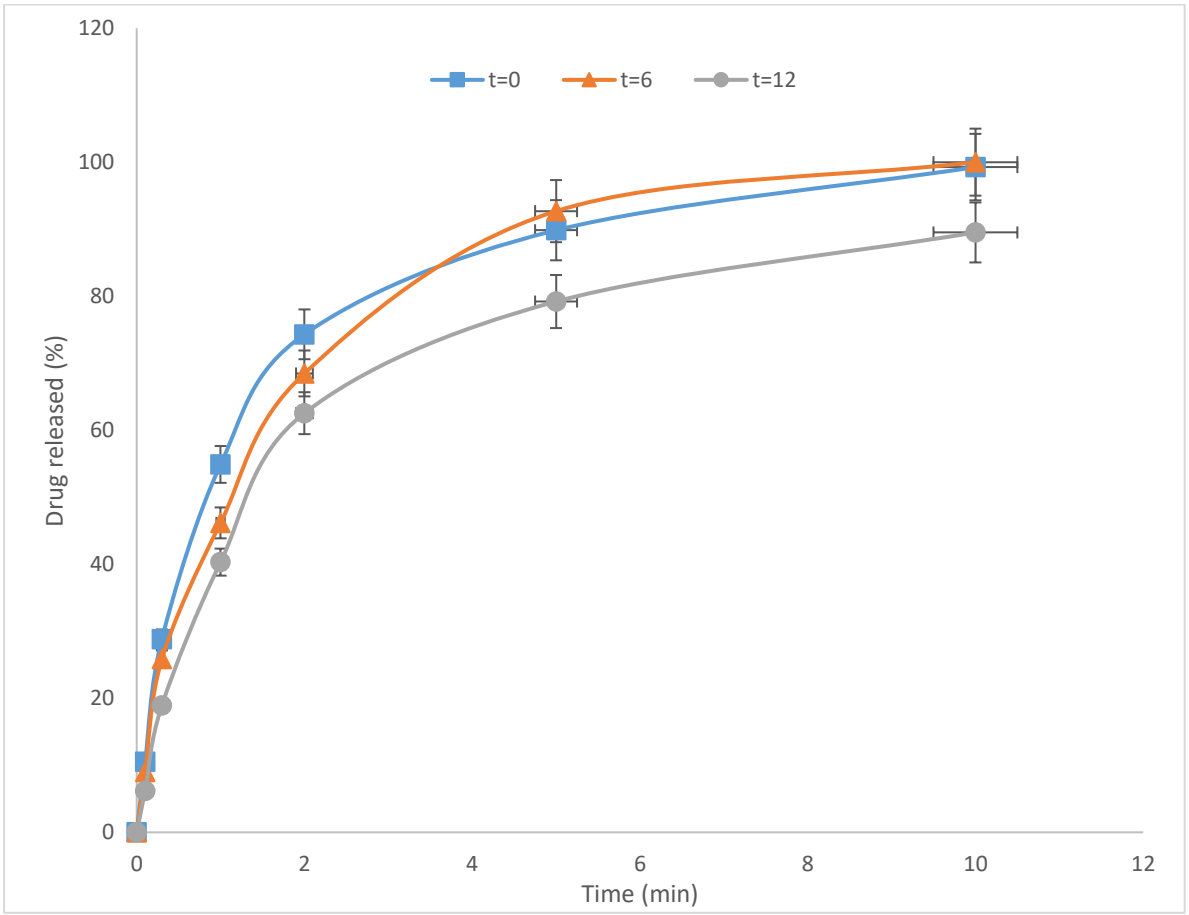

Figure 3: The *in-vitro* release profiles of metronidazole tablets (formulation F3) at various storage durations

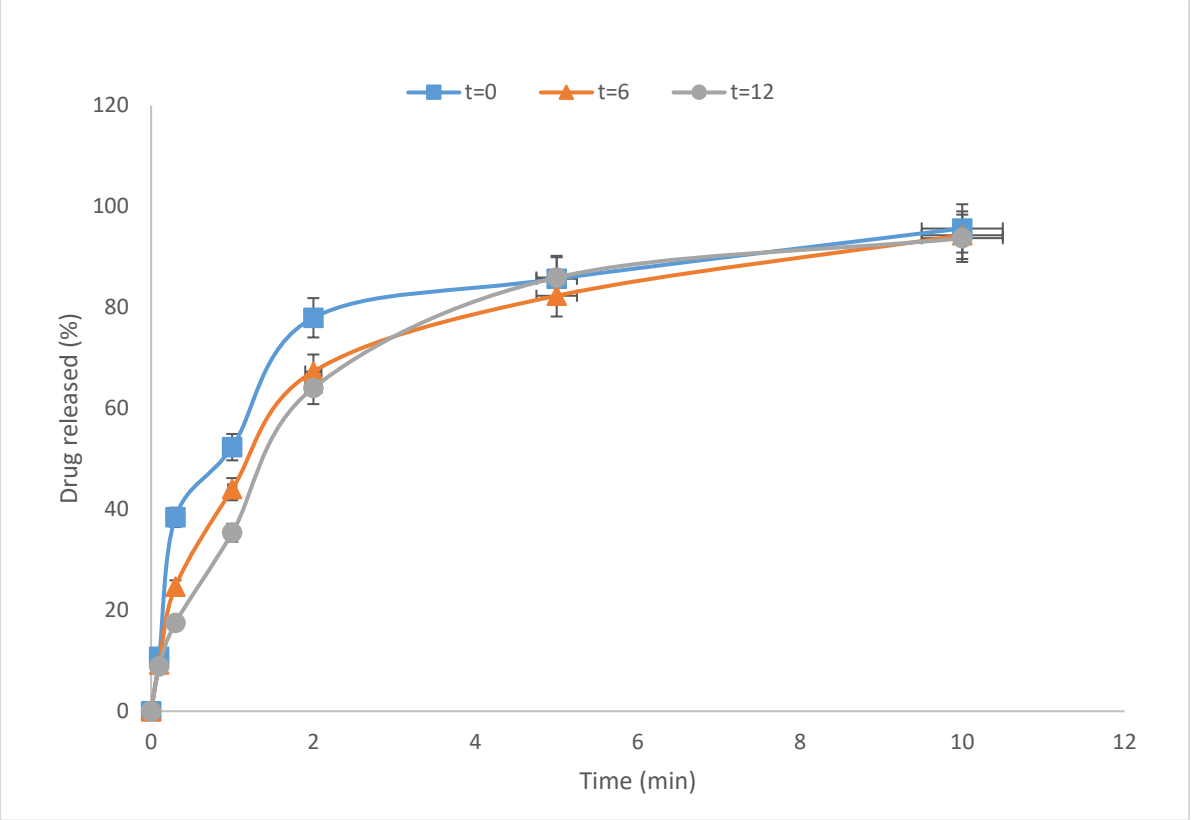

Figure 4: The *in-vitro* release profiles of metronidazole tablets (formulation F4) at various storage durations

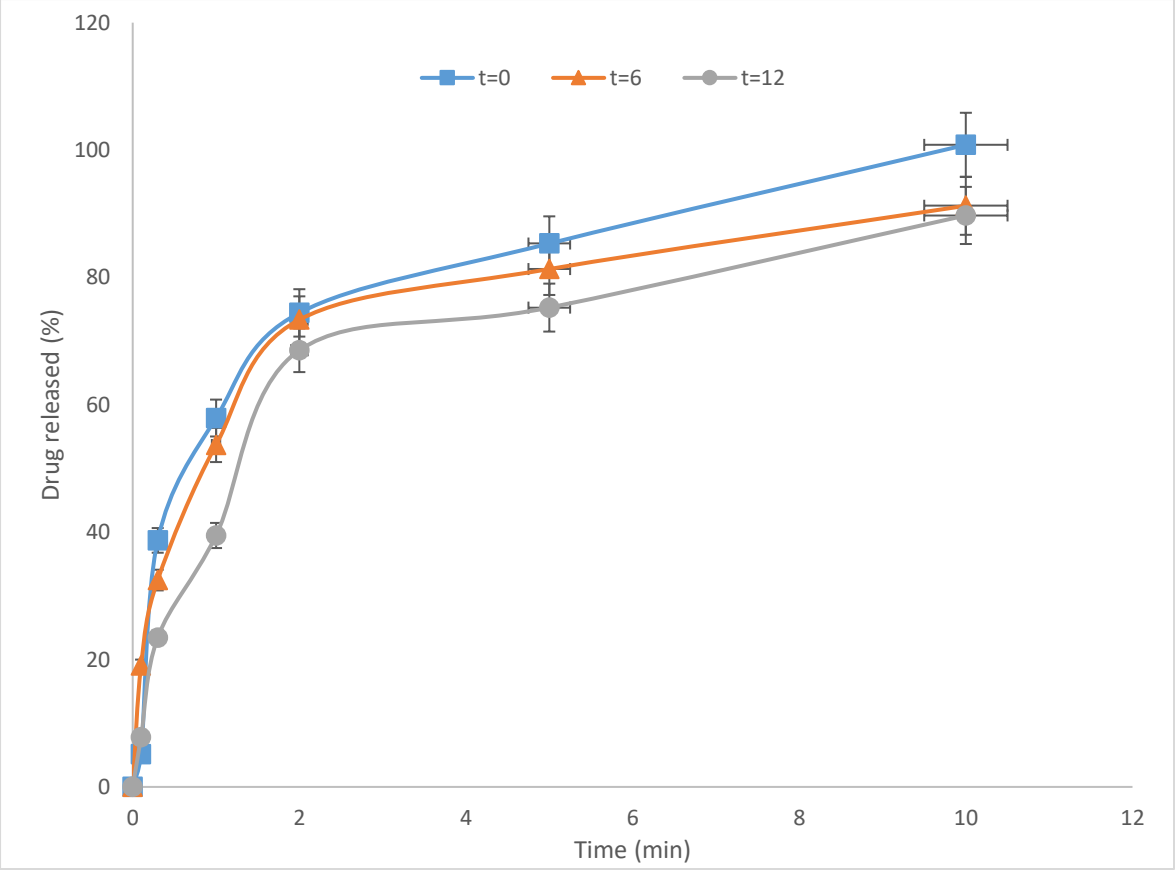

Figure 5: The *in-vitro* release profiles of metronidazole tablets (formulation F5) at various storage durations

In-vitro drug release study

In-vitro dissolution testing is crucial for assessing drug release from tablets, subsequently impacting *in-vivo* bioavailability (Skieneh & Rohani, 2017). Initial results showed promising release rates (89-96 %, Table 3). However, a decrease was observed at 6 months under both storage conditions (Table 3). This warrants further investigation. Encouragingly, drug release profiles (Figures 1-5) remained consistent after 12 months, indicating stability.

Content uniformity

An initial assessment of content uniformity revealed that the tablets contained 94-97 % of the target amount, demonstrating consistent drug distribution throughout the dosage form (Tables 2). This falls within the acceptable range for content uniformity.

Following 12 months of storage in desiccator containing silica gel, the drug content of the tablets remained statistically unchanged ($p \geq 0.05$, Table 2). This indicates that the presence of silica gel effectively mitigated potential changes in content uniformity over the storage period. This observation suggests that silica gel inclusion can be advantageous in preserving content uniformity during long-term storage.

CONCLUSION

In this study, stability studies were performed on metronidazole tablets produced from metronidazole crystallo co-agglomerates that were stored in a desiccator charged with silica gel under 25±2 °C/60±5 % relative humidity.

A comprehensive stability evaluation was conducted over a 12-month period, encompassing various physicochemical properties of the tablets, including weight, diameter, thickness, hardness, friability, content uniformity, and dissolution rate. Gratifyingly, no statistically significant changes were observed in any of these parameters throughout the study. These findings provide robust evidence for the remarkable stability of metronidazole tablets formulated using the crystallo co-agglomeration technique.

To ensure optimal product performance and maintain quality throughout their designated shelf life, we strongly recommend storing these tablets in airtight containers equipped with a desiccant. Ideally, the storage environment should be maintained at a controlled room temperature (25 °C or below) with controlled relative humidity. These recommendations will contribute to preserving the integrity and efficacy of the tablets throughout their intended storage period.

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