Journal of Research in Pharmacy

Research Article

www.jrespharm.com

Improved flowability, mechanical and dissolution properties of metronidazole obtained from crystallo co-agglomeration technique for direct tableting

Abba Khalid ABDULLAHI[1], Adeniji Kehinde OLOWOSULU[1], Teryila Suzanne ALLAGH[1]

[1]Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University Zaria, Nigeria.

*Corresponding author:Abba Khalid Abdullahi (A.K.A.); Email: khalidabba90@yahoo.com;
Tel: +234 8030790928

Received: 30 April 2023 / Revised: 24 September 2023 / Accepted: 25 September 2023

ABSTRACT:There has recently been growing interest in exploring the potential of direct compression (DC) method of tableting as an alternative to the conventional granulation technique. This approach involves straightforward powder mixing and compression, resulting in time and cost savings, and has successfully been applied to various drugs. However, drugs require good micromeritic qualities, such as flowability, good reproducible compression behaviour to be directly compressed because it affects its *in-vitro* and *in-vivo* performance. Since many active pharmaceutical ingredients lack these qualities, the crystallo co-agglomeration technique hasemergedas a potential area of research for particle design,utilised in the development of active ingredients best suited for direct compression of tablet dosage forms. Pure metronidazole exhibited significantly higher Carr's index, Hausner's ratio, and angle of repose of 41.93°±1.05, indicating cohesiveness and irregular shape of the crystals.Whereas the crystallo-co-agglomerates were found to have an angle of repose of 29.33°±0.96, denoting an improvement in the flowability of the agglomerated crystals. Improvements in mechanical handling parameters was revealed in metronidazole co-agglomerate tablets produced with DC excipients (F1, F2). These tablets were found to be more robust and of higher quality compared to those formulated using pure metronidazole (F4, F5, F6), which were of no significant difference with metronidazole formulated via wet granulation method (F7, F8, F10, F11).*In-vitro* dissolution studies of metronidazole co-agglomerates tablets showed no significant difference in the percentage drug release profilebetween tablets produced via direct compression and wet granulation method. Thus, the crystallo co-agglomeration technique can be effectively used in the formulation of metronidazole tablets by direct compression using Avicel® and Prosolv®, presenting an efficient and streamlined approach to tablet manufacturing.

KEYWORDS: Crystallo co-agglomeration; Metronidazole co-agglomerates; Direct compression; Wet granulation; Pure metronidazole

1. INTRODUCTION

Today's pharmaceutical industry is focused on developing improved drug delivery concepts while still making simple standard formulations as cost-effective as feasible. Finding directly compressible formulations is one of the most economical alternatives, and this is crucial for products with high volume. They are more capable of maintaining the stability of an active pharmaceutical ingredient (API) over its shelf life when compared to liquid or semi-solid dosage forms [1].The most prevalent and commonly utilized dose form is the conventional tablet. The durability and simplicity of administration of tablets are the primary reasons for their unrivaled appeal among producers and customers alike [2]. Compression is used to create common uncoated tablets by common techniques such as wet granulation (WG), dry granulation (DG) and direct compression (DC). These particular tablets have both systemic and local effects. But certain issues still make the multi-step process of making tablets more difficult [3]. Before an active ingredient is prepared to be manufactured as tablets,a protracted series of events must occur [4].

There has recently been a lot of interest in exploring the potential of direct compression method of tableting as an alternative to conventional granulation technique. Straightforward powder mixing and compression are used in the making of these tablets, which saves time and money [5]. Thus, the direct tableting technique has been successfully applied to various drugs. However, drugs require good micromeritic qualities, such as

How to cite this article: Abdullahi AK, Olowosulu AK, Allagh TS. Improved Flowability, Mechanical and Dissolution Properties of Metronidazole Obtained From Crystallo Co-Agglomeration Technique For Direct Tableting. J Res Pharm. 2024; 28(3): 844-859.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.744

flowability, good reproducible compression behaviour to be directly compressed because it affects its *in-vitro* and *in-vivo* performance [5], however, the quality of the crystals used is a determining factor.
To impart these micromeritic and dissolution properties, APIs are subjected to particle design techniques such as the crystallo co-agglomeration technique (CCA) [6]. This technique achieves a high degree of particle functionality thereby improving manufacturing processes.During the compaction process, the deformation mechanism of pharmaceutical powders used in formulating directly compressed tablets affects the physico-mechanical characteristics of the tablets formed. The properties of the resulting compact can be influenced by the presence of a lubricant and binder since pharmaceutical materials normally consolidate by more than one mechanism [7].
The tensile strength (TS), Crushing strength (CS), friability (FR), disintegration time (DT) and dissolution rate of the tablet dosage form made from co-agglomerated crystals were superior than those made from granules [5]. Thus, this method of drug particle design has become one of the areas of active research in pharmaceutical manufacturing. It is straightforward, less expensive, and advantageous for developing it on a commercial scale for the manufacture of tablets, and it has attracted a lot of interest and importance due to the fact that crystal habit can be changed during the crystallization process [8].
The DC method has been considered the simplest and most economical method of manufacturing tablets. It is thus, widely used because it requires fewer processing steps [9]. Despite its advantages, there are very few excipients suitable for use in DC because of the requirements for high standards for stability, compatibility, and safety. This study aims to evaluate and compare the improved flowability, mechanical and dissolution properties of metronidazole co-agglomerates tablets produced using direct compression and wet granulation technique.

2. RESULTS

The results showed a significant improvement in the drug's micromeritic characteristics when subjected to crystallo co-agglomeration technique inpresence of hydrophilic polymers (PEG 6000 and PVP K30). The co-agglomerates showed improvement in flow properties when compared with pure metronidazole as indicated by increase flow rate and smaller angle of repose. The mean particle diameter of the co-agglomerates shows a 3-fold increase in size over the pure drug particle with generation of low percentage fines. The Carr's index and Hausner's ratio of metronidazole co-agglomerates was 10.00±0.10 and 1.11±0.01 respectively compared to that of pure metronidazole (29.85±0.27% and 1.43±1.22).

Table 1: Micromeritics of Metronidazole co-agglomerates and Pure Metronidazole powder

Parameters	Metronidazole co-agglomerates	Pure Metronidazole powder
Bulk density (g/ml)	0.36±0.01	0.47±0.08
Tapped density (g/ml)	0.40±0.01	0.67±0.13
Flow rate (g/sec)	3.75±0.13	2.93±0.18
Angle of repose (θ)	29.33±0.96	41.93±1.05
Carr's index	10.00±0.10	29.85±0.27
Hausner's ratio	1.11±0.01	1.43±1.22
Mean particle size (μm)	303.53±0.00	99.75±0.00
Fines (%)	2.35±0.00	22.75±0.00

2.1. Tabletability

The ability of a powdered substance to be converted to tablet of a specific strength when subjected to compaction pressure is known as tabletability. An illustration of tabletability is presented as a plot of tablet tensile strength vs compaction pressure. Figure 1 below depicts the tabletability profile of pure metronidazole and metronidazole co-agglomerates. This symbolises formation of inter particle bonds which is more and stronger in metronidazole co-agglomerates.

Journal of Research in Pharmacy
Research Article

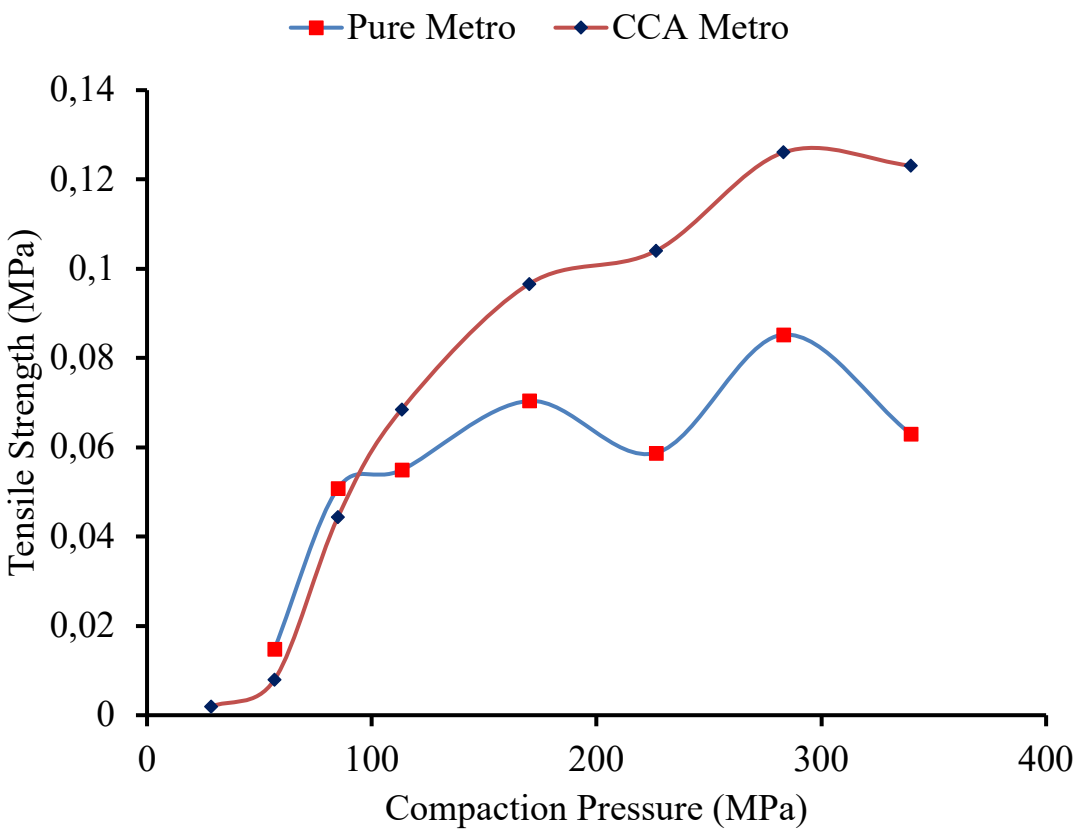


Figure 1. Tabletability plot of pure metronidazole and metronidazole co-agglomerates

2.2. Direct Compression (DC) Method

The result presented in Table 2 outline various tablet parameters for three (3) different direct compression excipients used in the formulation of metronidazole tablet from co-agglomerates of metronidazole. An examination of the friability property reveals that only tablets produced using metronidazole co-agglomerates in batches F1 (Avicel®) and F2 (Prosolv®) passed the friability test, with values <1%. While none of the tablet batches produced using pure metronidazole met the requirements for the friability test. The tensile strength (TS) and crushing strength (CS) of the tablets produced from metronidazole co-agglomerates can be ranked in the order of F1> F2> F3. Notably, the TS of these tablets were higher than those containing puremetronidazole,with maximum TS observed with tablet produced with Combilac® which correlates with the result of the CS. The tablet's *in-vitro* disintegration time was observed to be less than 3 min for batches F1, F2, F3 and less than 1 min for batches F4, F5, F6.

Table 2: Tablet Parameters for metronidazole 500 mg produced using metronidazole co-agglomerates (F1 – F3) and pure metronidazole (F4 – F6) via Direct Compression Method

Parameters	F1 (Avicel®)	F2 (Prosolv®)	F3 (Combilac®)	F4 (Avicel®)	F5 (Prosolv®)	F6 (Combilac®)
Crushing Strength (Kgf)	8.20±1.14	8.50±0.84	10.30±0.67	7.50±1.12	7.90±0.55	7.40±1.14
Friability (%)	0.82*	0.80*	1.63	2.00	2.83	2.25
Disintegration time (min)	2.13±0.64	1.18±0.46	0.51±0.10	0.48±0.44	0.59±0.11	0.55±0.10
Tensile Strength (MN/m^2)	1.32	1.58	1.85	1.24	1.33	1.29

***Key: F=**Formulation

http://dx.doi.org/10.29228/jrp.744
J Res Pharm 2024; 28(3): 844-859

This analysis underscores the significance of the choice of excipients and the method used in tablet formulation. The successful passing of the friability test and the enhanced tensile and crushing strength in batches F1 and F2 demonstrate the efficiency of using co-agglomerates of metronidazole in the DC method.

2.3. Wet Granulation (WG) method

Table 3, presented below, outlines the physicochemical properties of metronidazole formulated using wet granulation method. The granules, prepared from three (3) distinctbinders,exhibitrelatively low bulk and tapped densities, which were indicative of their high quality. Furthermore, the angle of repose indicates that the flow rate of the various granules was of good quality. Specifically, the angle of repose for the granules produced using different binders ranged from 25.34° to 30.39°. This range is considered favourable, demonstrating that the granules have good flowability.

Table 3. Micromeritic properties of metronidazole granules produced using various Wet granulation binders

Parameters	F7 (Acacia)	F8 (Gelatine)	F9 (Maize Starch)	F10 (Acacia)	F11 (Gelatine)	F12 (Maize Starch)
Bulk Density (g/ml)	0.40±0.01	0.38±0.01	0.43±0.01	0.40±0.01	0.39±0.01	0.37±0.01
Tapped Density (g/ml)	0.45±0.01	0.42±0.01	0.46±0.01	0.46±0.01	0.43±0.00	0.44±0.01
Flow Rate (g/sec)	3.89±0.05	3.43±0.03	3.53±0.06	2.87±0.01	3.09±0.29	3.21±0.13
Angle of Repose (θ)	25.57±0.66	25.72±0.26	25.34±1.35	28.29±0.64	28.58±1.32	30.39±1.43
Carr's Index	11.24±0.18	9.64±0.17	6.60±0.11	13.16±2.91	11.94±0.43	15.90±0.57
Hausner's Ratio	1.13±0.00	1.11±0.00	1.07±0.00	1.16±0.04	1.14±0.08	1.19±0.01

***Key: F=**Formulation

The data presented in Table 3 above provides valuable insights into the formulation process, highlighting the importance of selecting appropriate binders and methods to achieve desired granule characteristics. The positive attributes such as low densities and favourable angle of repose contributed to the granules' high quality, paving the way for successful tablet production

The results displayed in Table 4 below providedan analysis of various tablet parameters of the three (3) different wet granulation binders used in the formulation of metronidazole tablets produced from metronidazole co-agglomerates and pure metronidazole. The consistency in the mean weight of the tablets is notable and falls within the permissible deviation of 5% of the total tablet weight as stipulated by the B. P. Standards. The friability property reveals that only tablets produced with maize starch binder show friability values > 1%, while acacia, and gelatine have an acceptable friability value of < 1%. Examining the tensile strength, a parameter reflecting bond strength, and crushing strength, which gauges a tablet's resistanceto mechanical shock during handling, variations were observed among the different formulations. For tablets produced from metronidazole co-agglomerates, the strength tends to increase from F7 < F9 < F8. In contrast, for tablets containing pure metronidazole, crushing strength and friability tends to increase from F10<F12<F11. *In-vitro* disintegration time of the tablet's was found to be less than 15 min for all the batches.

Journal of Research in Pharmacy
Research Article

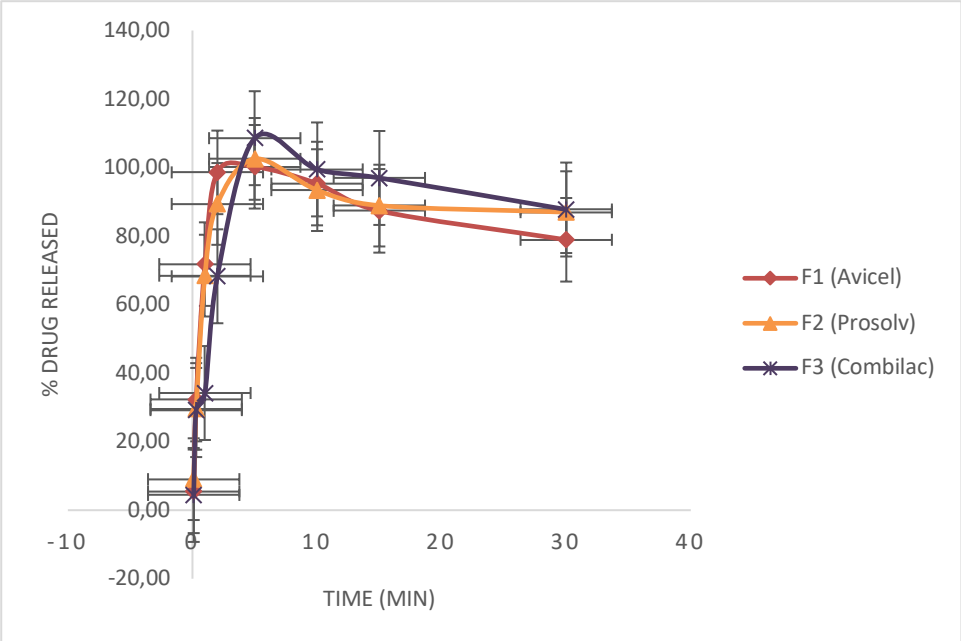
Table 4. Tablet Parameters for metronidazole 500 mg produced using metronidazole co-agglomerates (F7 – F9) and pure metronidazole (F10 – F12) via wet granulation method

Parameters	F7 (Acacia)	F8 (Gelatine)	F9 (Maize Starch)	F10 (Acacia)	F11 (Gelatine)	F12 (Maize Starch)
Crushing Strength (Kgf)	5.50±0.87	9.80±1.10	6.60±1.14	6.70±0.76	10.15±1.16	9.35±1.11
Friability (%)	0.80	0.40	1.19	0.90	0.76	1.52
Disintegration time (min)	9.22±1.81	11.05±3.42	2.52±1.23	6.20±2.01	9.35±1.75	4.20±1.21
Tensile Strength (MN/m²)	0.91	1.32	1.06	0.77	0.93	0.89

***Key: F=**Formulation

2.4. Dissolution Studies

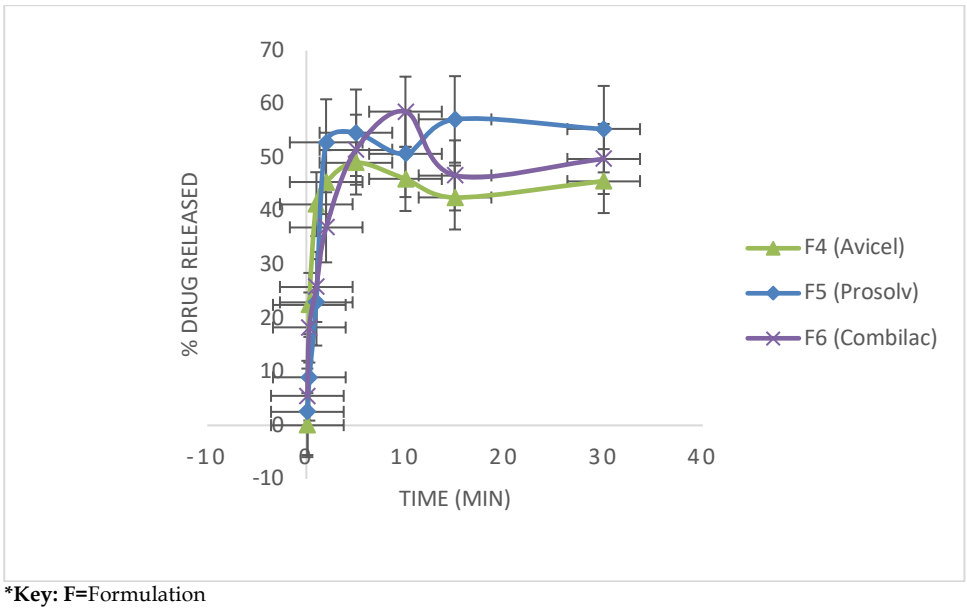
The dissolution profiles of co-agglomerates of metronidazole formulated using direct compression excipients exhibited improved metronidazole dissolution behaviour. The drug release profile of metronidazole co-agglomerates demonstrates noticeably faster drug release when compared with tablet batches of pure metronidazole formulated both via direct compression and wet granulation methods.



***Key: F=**Formulation

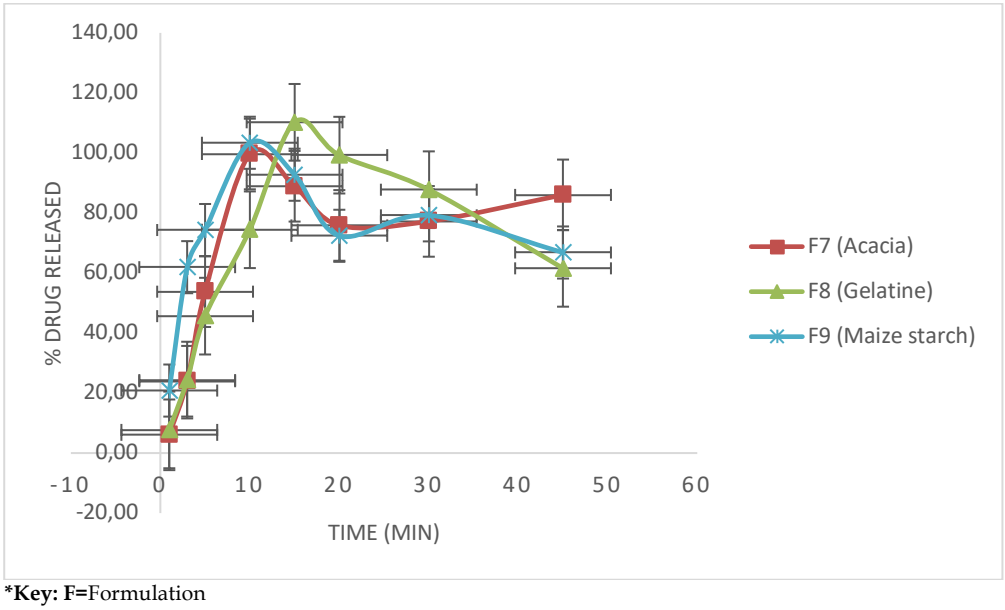
Figure 2. The drug release profile of metronidazole tablet formulations produced using metronidazole co-agglomerates with three (3) direct compression excipients via DC method

http://dx.doi.org/10.29228/jrp.744
J Res Pharm 2024; 28(3): 844-859



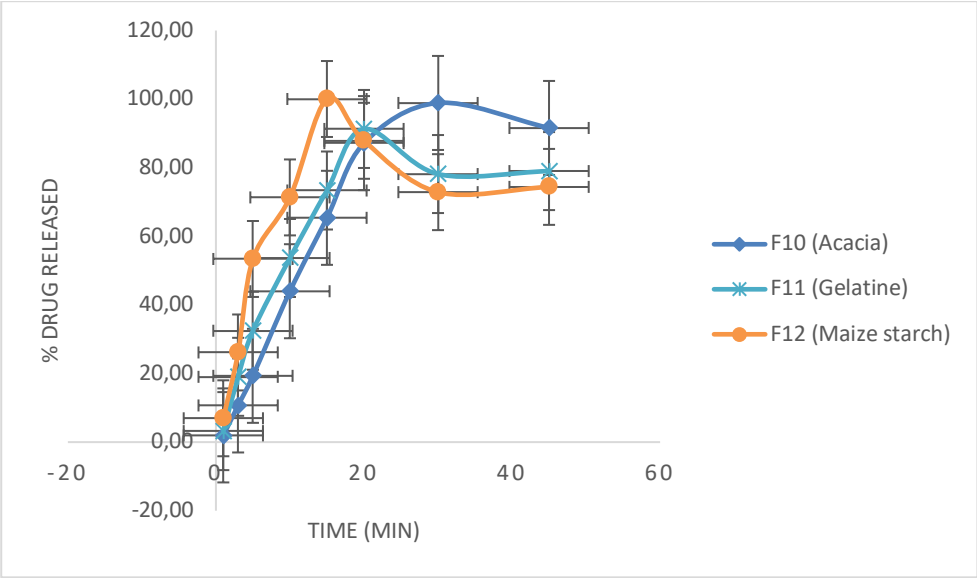
***Key: F=**Formulation

Figure 3. The drug release profile of metronidazole tablet produced using pure metronidazole with various direct compression excipients via DC method



***Key: F=**Formulation

Figure 4. Cumulative percentage release profile of metronidazole tablets formulated using metronidazole co-agglomerates with various binder by WG method.



***Key: F=**Formulation

Figure 5. Cumulative percentage release profile of metronidazole tablets formulated using pure metronidazole with various binder by WG method.

Table 5. Disintegration time and drug release indices of metronidazole tablet formulated using metronidazole co-agglomerates (F1 – F3) and pure metronidazole (F4 – F6) via DC method

Parameters	F1 (Avicel®)	F2 (Prosolv®)	F3 (Combilac®)	F4 (Avicel®)	F5 (Prosolv®)	F6 (Combilac®)
t_d (min)	2.13±0.64	1.18±0.46	0.51±0.10	0.48±0.44	0.59±0.11	0.55±0.10
$t_{50\%}$ (min)	0.35	0.37	1.25	__	1.42	4.30
$t_{80\%}$ (min)	1.15	1.23	2.41	__	__	__

Table 6. Disintegration time and drug release indicators of metronidazole tablet formulated using metronidazole co-agglomerates (F7 – F9) and pure metronidazole (F10 – F12) via WG method

Parameters	F7 (Acacia)	F8 (Gelatine)	F9 (Maize starch)	F10 (Acacia)	F11 (Gelatine)	F12 (Maize starch)
t_d (min)	9.22±1.81	11.05±3.42	2.52±1.23	6.20±2.01	9.35±1.75	4.20±1.21
$t_{50\%}$ (min)	4.41	5.30	4.50	11.30	8.30	2.27
$t_{80\%}$ (min)	7.26	10.55	11.28	17.41	16.23	6.00

3. DISCUSSION

The different micromeritic properties of pure metronidazole and metronidazole co-agglomerate crystals, which reveal distinctly different crystal habits are presented in Table 4. These differences in crystal habits result in variation in contact points, frictional forces, and cohesive forces between the crystals. Such variations may be the cause of the differences in the bulk densities [10]. When considering the use of pharmaceutical blend in direct compression (DC), bulk density requires a significant attention [11]. Analysis of particle size and bulk density data reveals that co-agglomerate crystals with low bulk density demonstrate improved flow qualities. These qualities are consistent with the flow rates and corroborate earlier research findings [12,13].

In contrast, metronidazole co-agglomerates exhibit lower values of both bulk and tapped densities compared to pure metronidazole powder, implying a higher die fill volume [14].Moreover,the Carr's index and Hausner's ratio of the metronidazole agglomerates reveal that they are more flowable than pure metronidazole. Generally, an increase in these indices (Carr's index and Hausner's ratio) leads to decreased powder flow, which can result in formulation problems such as weight and content variation [14]. Furthermore, the high intrinsic cohesiveness of pure metronidazole powder, hindering its flowability, can becorrelatedwith the values of Carr's index and Hausner's ratio.

A comparison between the flow rates and bulk densitydatashows that CCA crystals with reduced bulk density have better flow characteristics. This improvement in flow is also correlated with the angle of repose. While the angle of repose for crystallo-co-agglomerates is 29.33°±0.96, Pure metronidazole has a significantly

higher value of 41.93°±1.05, indicating that the pure crystals are cohesive and irregular in shape. Small angles of repose (≤ 30º) correspond to a faster flow rate of the material, an index of flowability of a powdered or granular substance [15].

A statistically significant difference was observed in the mean particle size (*P value* < *0.05*). The mean particle diameter of agglomerates was found to be 3-times greater than that of pure drug crystals, suggesting particle growth by simultaneous agglomeration following crystallization. This may be due to enhanced bonding and bridging in the presence of polymers, a finding that aligns with research of Shah and Sorathia on the evaluation of spherical agglomerates of Fluvastatin [16].

Examining the physicochemical properties of metronidazole co-agglomerates formulated with various WG binders like acacia, gelatine, and maize starch reveals that the granules are of high quality with good flowability, and compressibility, as expressed in Table 6.To ensure the final dose form has the minimum tablet weight possible, a directly compressible excipient mustpossess a high dilution potential. This is influenced by the compressibility of the pharmaceutical active ingredient [17]. High dilution potential is an important requirement of directly compressible diluents [18].By subjecting metronidazole co-agglomerates to dilutions with a direct compressible excipient (Ludipress), an optimal percentage concentration was found to yield tablets with the desired mechanical properties. The obtained results indicates that Ludipres can accommodate 40% metronidazole co-agglomerates,a concentration used to formulate tablet batches with various excipients via both DC and WG method.

The various tablet parameters of the metronidazole batches formulated using DC excipients show that fluidity and compression properties vary depending on the pure metronidazole / co-agglomerate-direct excipient combination. The mean weight of the tablets shows consistency and repeatable tablet weight fluctuation within the permissible 5% deviation from the total tablet weight as specified in the British Pharmacopoeia [19].

The mechanical characteristics of the tablets are a gauge of their resilience to the challenges encountered during production, shipping, dispensing, and consumption. Factors such as CS, FR and TS are vital in quantifying these characteristics. Comparatively, metronidazole co-agglomerates tablets produced with DC excipients (depicted in table 5) were found to be more robust and of better quality than pure metronidazole tablet batches produced via WG method (as depicted in Table 7).

Crushing Strength (CS) of a tablet is a significant metric reflecting its ease of handling and compressional behaviour. A CS value ranging from 4 – 15 Kgf (40 – 150 N) is deemed satisfactory for tablets [20]. This metric gauges the tablets' resistance to mechanical shock during handling, manufacture, packaging and transportation [20]. Both the tablet batches produced via DC technique, 7.50 – 10.30 Kgf (table 5), and WG, 4.70 – 9.80 Kgf (table 7), passed the crushing strength test. The robust crushing strength obtained reveals the effectiveness of the binding agent,optimal binder concentration, good binder incorporation method, adequately dried granules, and optimal compression force. This strength might result from enhanced bridging, bonding during metronidazole crystallo co-agglomeration with polymers, and the increased cohesivene interaction between the DC excipients and agglomerated crystals [21].

The tensile strength (TS) of the tablets, which was determined using equation 8, exhibited significant enhancement in metronidazole co-agglomerates compared to pure metronidazole tablets. This was particularly evident in formulation F1 - F 3 and F7 - F9, showing stronger interparticulate bonds and increased mechanical handling characteristics as expressed in table 5 and 7 [22].The increase in compact's TS resulted from more crystal bridges created by drug-drug molecles during the drug loading, and favourable interactions between various components, such as polymer-polymer, polymer-drug, drug-drug, and drug-talc [23].

Friability (FR) serves as a disruptive force employed to assess the tablets'resilience to resist mechanical wear and tear, chipping,andbreakage while in use, and is generally held inversely proportional to CS [24]. For compressed tablets, a maximum loss in weight of ≤1% usually signifies quality [25]. It was observed that only DC excipients; Avicel® (0.82%) and Prosolv® (0.80%) showed acceptable friability values, while batches F7, F8, F10 and F11 produced via WG show acceptable friability values. Exceptions were found in batches F9 and F12, failing to pass the friability assessment due to weak binding capacity of maize starch [17].On the whole, decreasing FR values suggest an enhancement in the tablets' ability to withstand mechanical manipulation, and characteristics like CS and FR are neccessary for patient acceptance[23].

Disintegration time is frequently a crucial phase for dissolution and may be the factor that determines the rate of drug absorption. According to B.P [19], uncoated tablets must disintegrate within a maximum time of 15 min Whileresearchers have sought to correlate disintegration time with CS, it is essential to recognise that although tablet CS represents a useful guage of strength, some tablet formulations may laminate or cap under high pressure, yielding exceptionally hard tablets [26].

Tablet disintegration is defined as the combined effect of adhesive and disintegrating forces that are triggered when the tablet is introduced to an aqueous environment [27]. Generally, tablets produced by direct compression method exhibit shorter disintegration time because they are composed of primary particles. Conversely, in wet granulation, the disintegration of agglomerated particles may depend on the efficiency of the disintegrant used [17].

The disintegration times for metronidazole tablets made from crystallo co-agglomerates using direct compression method in formulation F1, F2 and F3 are as follows: 2.13±0.64, 1.18±0.46 and 0.51±0.10 min respectively. All batches formulatedbyDC method displayed a rapid disintegration (< 5 min), in line with B.P (2010) specifications for uncoated tablets, while those made by wet granulation remained within the official limits of< 15 min.The dissolution study serves as a vital tool for assessing drug release from a dosage form and summarizing drug release in the GIT. The disintegration time and dissolution rates showed a positive association. Dissolution studies on the co-agglomerate's batches created from CCA were essential for understanding the pharmacokinetics and thus the bioavailability of the produced product (tablet). The British Pharmacopoeia mandates that a minimum of 70% of uncoated tablets must dissolved in 45 min [19].

The solubility of a drug molecule within a designed tablet influences its *in-vivo* absorption and bioavailability, both of which areaffected by the *in-vitro* dissolution rate [28]. CCA tablet batches (F1 to F3) produced via DC had over 70% drug dissolved at 5 min (figure 2), possibly due to the improvements in drug particles facilitated by the hydrophilic polymers used in the CCA technique. Conversely, tablets produced using wet granulation released more than 75% of metronidazole within 12 min.

The extent of drug dissolved in 5 min appear to be the highest drug release across all batches containing metronidazole co-agglomerates, with Combilac® having the highest drug release of108.58%, followed by Prosolv®at102.53%, and Avicel® 100.23%. None of the batches produced using pure metronidazole with various direct compression excipients reached up to 60% drug release throughout the study duration. This reveals that batches F4, F5, and F6 failed the dissolution studies (Figure 3).

The empirical reflectorst$_{50\%}$ and t$_{80\%}$ signifies the onset of action, with low values indicating fast drug release [24]. *In-vitro* dissolution study of metronidazole tablets produced using pure metronidazole and metronidazole co-agglomerates via WG were further investigated, showing varied drug release profile (Figures 4 and 5). Tablets batch of F1, F2, and F3 achieved t$_{80\%}$ in less than 3 min, meeting the pharmacopeial criteria of 80% drug release from uncoated immediate-release tablets [29]. This quicker dissolution observed in batches formulated via direct compression could be related to increased surface area and wetting [30]. The internal porous structure and inclusion of hydrophilic polymers in metronidazole agglomerates resulted in enhanced wettability and faster dissolution[31]. The tablets produced by DC disintegrate more quickly into API particles instead of granules that immediately come into contact with dissolution fluid [3]. In the evaluation of various batches of tablets formulated from pure metronidazole and metronidazole co-agglomerates through both DC and WG, distinct differences in the percentage of drug dissolved vis-à-vis mechanical properties are observed. Specifically, batch F1, F2, and F3 demonstrate a significant improvement in mechanical strength and dissolution. This improvement is comparable to the tablet batches obtained via wet granulation. Interestingly, tablets manufactured using DC are less likely to experience changes in the dissolution profile during storage compared to those made through WG [3].Moreover, the official requirements for content uniformity of the active ingredient stipulate that the percentage content of tablets with an average weight above 250 mg must fall within 95-105% [19,29]. A thorough analysis of the metronidazole tablets formulated from batches F1, F2, F3, F7, F8, F9, F10, and F12revealed that they meet this standard, with a mean average content to be in the range of 98.31- 103.89%. This consistency in content uniformity underscores the quality and effectiveness of the formulation process.

4. CONCLUSION

Formulation of metronidazole co-agglomerates with hydrophilic polymers such as PEG 6000 and PVP K30 via crystallo co-agglomeration technique has demonstrated improvements in micromeritic and flowability properties when compared to pure metronidazole. All the tablet batches, formulated through DCmethod,exhibited excellent disintegration < 3 min. While, tablets formulated via WG displayed disintegration < 15 min which is in conformity with B. P. 2010 specification for uncoated tablets. There was no significant difference in the percentage of drug released between metronidazole co-agglomerate batches produced throughDC method (F1, F2, and F3) and pure metronidazole tablet batches (F10, F11 and F12) produced through both WG and DC methods (F7, F8 and F9). Consequently, the crystallo co-agglomeration technique can serve for formulation of active pharmaceutical ingredients that are best suited for tablet production by DC using directly compressible tablet excipients instead of the long and costly WGmethod.As ingredients are processed easier and for a shorter period of time, the chance for contamination is low.

5. MATERIALS AND METHODS

5.1. Materials

Metronidazole powder (CDH Chemicals ltd. New Delhi, India), Dichloromethane (Merck ltd. Darmstadt, Germany),Polyethylene Glycol PEG 6000 (Shanghai Yuchuang chemicals tech. co., Ltd, China), Poly vinyl Pyrrolidone PVP K30 (Shanghai Yu Chuang chemicals tech. co., Ltd, China), Ethanol 95% (BDH chemicals Ltd Poole, England), Acacia gum (Hopkins &Williams, England), Ludipress (BASF, Germany), Lactose (BDH chemicals Ltd Poole, England), Prosolv® (JSR Pharm, GmbH and Co. KG, Rosenberg, Deutschland, Germany), Talc powder (BDH Chemicals Ltd Poole, England), Magnesium stearate (BDH Chemicals Ltd Poole, England), Distilled water (Deptattment of Pharmaceutics and Industrial Pharmacy, A.B.U. Zaria),Maize starch (BDH Chemicals Ltd, England), Gelatin (BDH chemicals Ltd Poole, England), Avicel® PH 200 (FMC Corporation, USA).

5.2. Method

5.2.1. Formulation of metronidazole co-agglomerates

The method of Abdullahi *et al.,* was adopted in the preparation of metronidazole co-agglomerates.
Metronidazole was transferred in to a 250 ml beaker and dissolved in adequate amount of Dichloromethane (good solvent) to make saturated solution at 50 °C. In another beaker PEG 6000 and PVP K30 were dissolved in sufficient amount of water (non-solvent). The whole system (two dispersions) was then added immediately together under constant stirring using a magnetic stirrer attached with thermometer at 700 revolution per min (rpm).
The stirring went on for further 20 min and then ethanol (bridging liquid) was incorporated dropwise to generate co-agglomerates which were then filtered and dried for 24 h in a hot dry oven [32].

Table 7. Composition (g) of Metronidazole co-agglomerates [10]

Ingredient	Amount (g)
Metronidazole	3.00
PEG 6000	0.75
PVP K30	0.75

5.3. Evaluatıon of Physical properties of pure metronidazole and metronidazole co-agglomerate powder

Micromeritic studies:
The angle of repose, bulk density, Carr's Index and Hausnar's ratio were used to assess the flow characteristics of pure metronidazole and metronidazole co-agglomerates. The angle of repose was assessed using the fixed funnel method, the size distribution using the sieving method, whereas Carr's Index and Hausnar's ratio using bulk and tapped densities.

5.3.1. Bulk density (Db):

The initial bulk volume was determined by measuring the loose volume occupied by the powder after 20 g of powder that had been precisely weighed was carefully poured into a 100 ml graduated measuring cylinder using a big funnel. Bulk density was expressed in g/ml and the studies were conductedthree timesand is given by,

$$Db = \frac{M}{Vo} \quad (1)$$

Where, Db = Bulk density (g/ml)
M = mass of powder (g)
Vo = bulk volume of powder (ml)

5.3.2. Tapped density (Dt):

Accurately weighed sample of 20 g was introduced into a clean, dry 100 ml measuring cylinder, this was tied to a stand at a predetermined height above a hard surface and the cylinder was then tapped 100 times from the height repeatedly and the final volume after tapping was recorded. Tapped density was expressed in g/ml and the studies were performed three times and is given by,

$$Dt = \frac{M}{Vt} \quad (2)$$

Where, Dt = Tapped density (g/ml)
M = mass of powder (g)
Vt = tapped volume of powder (ml)

5.3.3. Compressibility index (CI):

Compressibility index is the difference between the tapped and bulk density expressed in percentage [33]. The studies were performedthree times and is given by,

$$CI = \frac{(Dt-Db)}{Dt} \times 100 \quad (3)$$

5.3.4. Hausner ratio (Hr):

Hausner ratio is extrapolated as the ratio of tapped density and bulk density [34]. This was calculated and given by,

$$Hr = \frac{Dt}{Db} \quad (4)$$

5.3.5. Angle of repose (θ):

A 20 g powder sample was poured into a dry glass funnel clamped on a retort stand at 90°to the horizontal surface on which a clean paper was placed, such that the surface of the paper is 10 cm from the tip of the funnel. The powder sample was poured through the funnel while a powder heap was formed on the paper. Angle of repose was measured as the angle between the surface of powder pile and the horizontal plane. Studies were conducted three times and is given by,

$$\tan^{-1}\theta = \frac{h}{r} \quad (5)$$

Where,
θ = angle of repose
h = height of pile,
r = radius of the base of the pile.

5.3.6. Flow Rate (Fr):

Powder flow rate was measured using an electronic balance with a recording device and a vibrator attached to facilitate flow from the container. A 20 g powder sample was passed through the Erweka flow rate machine and the time it took each powder to completely pass through the vibrating metal funnel was recorded.

$$FR = \frac{M}{t} \quad (6)$$

M= weight of powder (g)

t= time (sec)

5.3.7. Particle Size Analysis:

This method involves separating a powder into distinct size ranges (500, 250, 150, 90, 75, 45 µm) by sifting it through a stack of wire mesh sieves. An Erweka vibration sieve was used to sieve a 20 g powder sample through a nest of sieves. The vibration rate was set at 200 strokes per min, and the sieving period for 10 min.The recorded amount of powder retained on each sieve was used to calculate the percentage retained. By plotting the cumulative percentage retained against the sieve aperture size, the particle size distribution curve was generated. From this curve, the mean particle diameter was determined.

5.4. *In-vitro* drug release studies:

To determine the effect of co-agglomeration technique and polymers on drug release, produced co-agglomerates were subjected to *in-vitro*dissolution test using USP Apparatus I (Basket type). At 37°±0.5 °C, 1000 ml of 0.1 N HCl was utilized as the dissolution medium and 100 RPM (as per USP). Samples of 10 ml was removed at a pre-determined time interval (1, 3, 5, 10, 15, 20, 30 min) and the same quantity of dissolution medium was added at each occasion to replace the removed samples. Samples were analyzed after suitable dilution with 0.1 N HCl by UV-spectrophotometer at 277.0 nm and the cumulative % drug release was calculated. Each experiment was carried-out three times, and the average (± S.D) reading was recorded.

5.5. Dilution potential of metronidazole co-agglomerates

A Binary mixtures of metronidazole co-agglomerates and the direct compression excipient (Ludipress®) at different concentrations (30, 40, 50, 60 and 70%) were blended in a mixing jar for 5 min. the powder blends were compressed into tablets (500 ± 2mg) at 5.5 to 8 metric ton a single stroke tablet press fitted with 12 mm circular punches lubricated with 2% w/w dispersion of magnesium stearate in acetone. The tablet weight, crushing strength, diameter, thickness, friability and disintegration time were evaluated.

5.6. Formulation of Metronidazole tablets by Direct Compression method

The metronidazole tablets were formulated using metronidazole co-agglomerates and pure metronidazole using three (3) different direct compression excipients vis Avicel®, Prosolv® and Combilac®. The powder blend (500 ± 2mg) was directly compressed into tablets on a single stroke tablet press equipped with 12 mm punch using 500 mg as mean weight of the tablet.

Table 8. Formula for Metronidazole tablet prepared via direct compression method

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Metronidazole Co-agglomerates (mg)	200	200	200	—	—	—
Pure Metronidazole (mg)	—	—	—	200	200	200
Avicel® PH 200 (mg)	290	—	—	290	—	—
Prosolv® (mg)	—	290	—	—	290	—
Combilac® (mg)	—	—	290	—	—	290
Magnesium Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5
Talc (mg)	7.5	7.5	7.5	7.5	7.5	7.5

***Key:** F = Formulation

5.7. Formulation of Metronidazole tablets by Wet granulation method

The metronidazole tablets were formulated using metronidazole co-agglomerates and pure metronidazole using three (3) different wet granulation binders vis Acacia, Gelatine and Maize starch. The powder blend (500 ± 2mg) was compressed directly into tablets on a single stroke tableting press equipped with 12 mm punch using 500 mg as mean weight of the tablet.

Table 9. Formula for Metronidazole tablet prepared using pure metronidazole via wet granulation method

Ingredients	F7	F8	F9	F10	F11	F12
Metronidazole Co-agglomerates (mg)	—	—	—	200	200	200
Pure metronidazole (mg)	200	200	200	—	—	—
Lactose (mg)	255	255	255	255	255	255
Acacia (mg)	15	—	—	15	—	—
Gelatine (mg)	—	15	—	—	15	—
Maize starch (mg)	—	—	15	—	—	15
Sodium Starch Glycolate (mg)	20	20	20	20	20	20
Magnesium Stearate (mg)	10	10	10	10	10	10

***Key:** F = Formulation

5.8. Evaluation of tablet properties

5.8.1. Determination of Tablet Diameter and thickness

The diameters and thickness of 10 randomly chosen tablets were measured using a digital caliper. The allowable deviation was ± 5%. Calculations were made to determine the mean and standard deviation.

5.8.2. Determination of weight uniformity

Ten tablets (10) were randomly chosen from each batch and weighed on a top-loading analytical balance. The average weight of 10 tablets was used to calculate the weight variation of each batch. The allowable deviation was ± 5%. The mean and standard deviation for each batch was calculated.

5.8.3. Friability Test (FR)

Ten (10) tablets from each batch were weighed and put meticulously in a friabilator. The tablets dell through a height of 6 inches at each rotation of the friabilator, which was operated at a rate of 25 rotations per min for 4 min. The tablets were dusted, final weight was recorded, and the percentage weight loss was calculated from the following equation. The limit for this test is typically < 1%. Tablets meeting this standard are considered to have passed the friability test.

$$Friability = \frac{Wo-W}{Wo} \times 100 \qquad (7)$$

Where Wo is initial tablets weight before test, W is the tablets weight after subjecting it through the friabilator.

5.8.4. Crushing strength (CS)

Tablets crushing strength was determined using a monsanto hardness tester. A diametric compression test was used to measure the crushing strength at room temperature. The tablet was positioned between the platen of the tester and the adjustable knob before being screwed in place to make contact with the tablet. Tablet break as a result of sufficient applied pressure to cause tablet breakage.The limit for crushing strength test was set in the range of 7 -11 kgf. The result was the average of 10 determinations.

5.8.5. Tensile strength (TS)

The prepared tablets from both the co-agglomerates containing batches and pure metronidazole were kept in a silica gel desiccator for roughly 24 h, after which a Monsanto hardness tester was used to measure a load across each tablets diameter to determine its F hardness when crushed. The tensile strength Ts was determined using the following equation.

$$Ts = \frac{6.24F}{Dt} \quad (8)$$

Where; F is the crushing force (N), D is the tablet's diameter, and t is the tablet's thickness.

5.8.6. Tablet Disintegration Test

Adisintegration test device with 0.1 N HCl and a thermostat set at 37±1 °C was used. At a time, six (6) tablets from a batch were tested, one in each tube. The time taken for each of the tablets to disintegrate before passing through the mesh was noted, and the mean disintegration time for each batch was computed.The general requirement for the disintegration test limit is that tablets must disintegrate within 15 min as per B.P standards.

5.8.7. Construction of Calibration curve for metronidazole:

The UV spectrophotometer was calibrated by preparing a serial dilution of metronidazole in 0.1 N HCl (medium). A meticulously weighed 200 mg of metronidazole was dissolved in 100 ml of 0.1 N HCl. 5 ml was withdrawn and diluted with another 5 ml of the medium; this was continued until 9 serial dilutions were obtained. The dilutions were analyzed at 277.0 nm using UV-visible spectrophotometer against 0.1 N HCl solution. Calibration curve of absorbance (y) versus concentration (x) was plotted using Microsoft excel 2013.

5.8.8. Dissolution studies:

*In-vitro*dissolution studies for prepared tablets were performed using USP Apparatus I (Basket type) operated with 900 ml of 0.1 N HCl dissolution medium at a rotation speed at 100 rpm and maintained at 37 ± 1 °C. Samples of 10 ml were removed at a pre-determined time interval (10 sec, 30 sec, 1, 2, 5, 10, 15 and 30 min for direct compression batches) and (1, 3, 5, 10, 15, 20, 30, 45 min for wet granulation batches) and the same amount of fresh dissolution medium was added to replace the withdrawn samples each time.
After adequate dilutions with 0.1 N HCl, samples were analyzed with UV-spectrophotometer at 277.0 nm using 0.1 N HCl as blank and the amount of metronidazole released at each time were analysed and percentage drug release was calculated.

5.8.9. Uniformity of content determination

Randomly chosen twenty (20) tablets from each batch were weighed on the analytical balance and crushed into fine powder in a ceramic mortar. A 200 ml of 0.1 N HCl was used to dissolve 0.50 g portion of the powder, which was then filtered. 100 ml of the medium was used to dilute it. Samples were analyzed with UV-spectrophotometer at 277.0 nm.

5.9. Statistical Analysis and Data Presentation

All experiments were conducted in replicates to ensure validity. The One-way Analysis of Variance (ANOVA) was used. Data analysis was carried out using SPSS software version 25. Differences were considered significant for *Pvalues* <0.05. The results obtained was presented as Mean, Standard deviation and Percentages (%) in tables and figures.

Acknowledgements: The authors wish to appreciate the support of all the staff of the Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University Zaria, Nigeria.

Author contributions:AKA**,** AKO, and TSA conceptualized the idea. AKA collected the data; AKA wrote the first draft and analysed the data while AKO and TSA proofread the draft and all the author approved the final draft for publication.

Conflict of interest statement: The authors declared no conflict of interest

REFERENCES

[1] Khalid GM, Musa H, Olowosulu AK, Jatau AI, Ilyasu S. Comparative FTIR, compaction and *in vitro* dissolution studies of *Plectranthus esculentus* modified starches in metronidazole tablet formulations by direct compression. Pharm Anal Acta. 2018;9:577. http://dx.doi.org/10.4172/2153-2435.1000577.

[2] Limzerwala RB. Optimization of the wet agglomeration of talc. Masters thesis. University of Pune; 1996.

[3] Shashank T, Mahapatra SP. Unit dose form tablet: An overview. Int Res J HumEng Pharm Sci. 2018; 9(1): 2320-2955

[4] Bijaya G, Patel J, Bose P, Roy D. Crystallo Co-Agglomeration - A Review. Int J Rec Sci Res. 2018; 9(2): 24226-24230. https://doi.org/10.24327/IJRSR

[5] Kadam AM, Patil SS. Improvement of micromeritic, compressibility and solubility characteristics of linezolid by Crystallo-co-Agglomeration Technique.Int J App Pharm. 2017; *9*(4); 47–53. https://doi.org/10.22159/ijap.2017v9i4.18915

[6] Paradkar A, York P. Crystal engineering and particle design for the powder compaction process. In: Pharm Powder Comp Technol. 2nd ed. London: 2011. pp. 235-252.

[7] El-Bagory I, Barakat N, Ibrahim MA, El-Enazi F. Formulation and in vitro evaluation of theophylline matrix tablets prepared by direct compression: Effect of polymer blends. Saudi Pharm J. 2012; 20: 229-238. https://doi.org/10.1016/j.jsps.2011.11.007

[8] Paradkar A, Pawar A, Jadhav N. Crystallo-co-agglomeration: A novel particle engineering technique. *Asian J Pharma*. 2010;*4*(1), 4–10. https://doi.org/10.4103/0973-8398.63975.

[9] Ofori-Kwakye K, Mfoafo KA, Kipo SL, Kuntworbe N, El Boakye-Gyasi M. Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. Saudi Pharm J. 2016; 24: 82-91. https://doi.org/10.1016/j.jsps.2015.03.005

[10] Krishna EH, Gupta VRM, Samreen NS, and Jyothi S. Modification of drug particle morphology by spherical crystallization technique to obtain directly compressible material. Der Pharmacia Sinica. 2013; *4*(1): 77–87.

[11] Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment—A review. Int J Pharm. 2014; 473: 64-72. https://doi.org/10.1016/j.ijpharm.2014.06.055

[12] M, Huang Z, To D, Aloia M, Muchira C, Davé RN, Yu AB. Prediction of porosity from particle scale interactions: Surface modification of fine cohesive powders. Powd Technol. 2014; 254: 103-113. https://doi.org/10.1016/j.powtec.2014.01.006

[13] Huang Z, Scicolone JV, Han X, Davé RN. Improved blend and tablet properties of fine pharmaceutical powders via dry particle coating. Int J Pharm. 2015; 478(2): 447-455.https://doi.org/10.1016/j.ijpharm.2014.11.068

[14] Wells II, Aulton ME. Powder flow. In Aulton ME, Taylor KM (Eds.), Aulton's pharmaceutics: The Design and Manufacture of medicines.3rd edn. London: Elsevier UK; 2007.

[15] Apeji YE, Oyi A, Musa H, Olowosulu AK. Investigation of the directcompression properties of microcrystalline starch (MCS) as a filler/binder/disintegrant in metronidazole tablet formulation. Int J Pharm Res Inn. 2010; 1: 8-14

[16] Shah D, Sorathia K. Design and evaluation of sustained release spherical agglomerates of Fluvastatin sodium by crystallo-co-agglomeration. J App Pharm Sci, 2017; *7*(9), 99–108. https://doi.org/10.7324/JAPS.2017.70914

[17] Olowosulu A, Oyi A, Isah A, & Ibrahim M. The Use of Multifunctional Starch Based Coprocessed Excipients (Starac) in the Formulation of Metronidazole Tablets by Direct Compression. African J Pharm Res and Devt, 2015; *7*(2), 101–108.

[18] Rojas J, Kumar V. Comparative evaluation of silicified microcrystalline cellulose II as a direct compression vehicle. Int J Pharm. 2013; 416:120-128.https://doi.org/10.1016/j.ijpharm.2011.06.017

[19] British Pharmacopoeia, Vol. 1. The Pharmaceutical Press, Her Majesty Stationery Office, 2010; London.

[20] Pawar A, Paradkar A, Kadam S, Mahadik K. Effect of polymers on crystallo-co-agglomeration of ibuprofen-paracetamol: Factorial design. Indian J Pharm Sci, 2007; *69*(5), 658–664. https://doi.org/10.4103/0250-474X.38471

[21] Ayorinde J, Odeniyi M, Itiola A. Evaluation of pharmaceutical and chemical equivalence of selected brands of diclofenac sodium tablets. East and Central African JPharm Sci. 2012; 15: 3–9.

[22] Maghsoodi M, Taghizadeh O, Martin GP, Nokhodchi A. Particle design of naproxen – disintegrant agglomerates for directly compression by crystallo co-agglomeration technique. Int J pharm; 2008; 351:45-54.*https://doi.org/10.1016/j.ijpharm.2007.09.033*

[23] Jadhav N, Pawar A, & Paradkar A. Design and evaluation of deformable talc agglomerates prepared by crystallo-co- agglomeration technique for generating heterogeneous matrix. *AAPS Pharm Sci Tech*. 2007; *8*(3). https://doi.org/10.1208/pt0803059

[24] Eraga SO, Arhewoh MI, Uhumwangho MU. Release profile of paracetamol from tablets prepared by direct compression. Asian pacific j tropical biomed. 2015; 5(9), 768-772. https://doi:10.1016/j.apjtb.2015.07.008

[25] British Pharmacopoaeia (BP). The Commission Office London. 2009; 111:6578-85.

[26] Adolfson A, Gustafsson C, Nystrom C. Use of tablet tensile strength adjusted for surface area and mean interparticulate distance to evaluate dominating bonding mechanisms. J Drug Dev Ind Pharm. 1999; 25: 753–64.https://doi.org/10.1081/ddc-100102235

[27] Adebayo AS, Itiola OA. Evaluation of breadfruit and cocoyam starches as exodisintegrants in a paracetamol tablet formulation. J Pharm Pharmacol Comms.1998; 4: 385-389. https://doi.org/10.1111/j.2042-7158.1998.tb00716.x

[28] Alshehri S, Shakeel F, Ibrahim M, Elzayat E, Altamimi M. Influence of the microwave technology on solid dispersions of mefenamic acid and flufenamic acid. PloS one. 2017; 12(7): e0182011. https://doi.org/10.1371/journal.pone.0182011
[29] United States Pharmacopoeia (USP) General Chapeters <711> Dissolution. 2011, <701> Disintegration 2008.
[30] Deshkar SS, Borde GR, Kale RN, Waghmare BA, Thomas AB. Formulation of cilostazol spherical agglomerates by crystallo-co- agglomeration technique and optimization using design of experimentation. Int'l J Pharm Invest.2017; 7 (4):164–73. https://doi:10.4103/jphi.JPHI_39_17
[31] Maghsoodi M, Barghi L. Design of Agglomerated Crystals of Ibuprofen During Crystallization: Influence of Surfactant. Iranian J Basic Med Sci. 2011;14(1), 57–66.https://doi.org/10.22038/ijbms.2011.4965
[32] Abdullahi AK, Olowosulu AK, Allagh TS. Crystallo co-agglomeration technique for Improving Physicochemical Properties, Compressibility and Solubility Characteristics of Metronidazole. Brit JPharm. 2023; 8(1) 1039. http://doi.org/10.5920/bjpharm.1039
[33] Carr R. Evaluating flow properties of solids, Chem Eng. 1965; 72, 163-168.
[34] Hausner H. Friction conditions in a mass. Int J Powd Metallurgy.1967; 3, 7-13.