ORIGINAL PAPER

https://dx.doi.org/10.4314/njpr.v20i1.11

Nig. J. Pharm. Res. 2024, 20 (1) pp 99-114
ISSN 0189-8434 e-ISSN 2635-3555

Available online at http://www.nigjpharmres.com

Physico-Mechanical and Tableting Properties of Metronidazole Obtained by Crystallo Co-Agglomeration Technique

A. K. ABDULLAHI [*A-F], **A. K. OLOWOSULU** [AEF], **T. S. ALLAGH** [AEF]

Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University Zaria, Nigeria

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Due to its simplicity and cost-effectiveness, direct compression has become the approach most frequently used to create tablet. Nonetheless, the active pharmaceutical ingredient should have acceptable flow and good compaction qualities in order to use direct compression in tablet manufacture. Crystallo co-agglomeration (CCA) technique has shown to be efficient in improving the earliest stages of tablet manufacture. By combining crystallization (primary particles design) and agglomeration (secondary particles design), it increases the product's added value.

Objectives: This study exploits the CCA approach to boost the physico-mechanical and tableting properties of metronidazole tablet.

Methods: Metronidazole co-agglomerates was formulated with hydrophilic polymers using CCA technique. The dilution potential of the produced agglomerates was assessed to obtain suitable concentration that was used to prepare metronidazole tablet by direct compression method after which the tablet properties were evaluated.

Results: Metronidazole agglomerate powder had a very good flow rate and angle of repose, low bulk and tapped densities as well as improved Carr's compressibility index, 15.00±0.14% and Hausner's ratio 1.18±0.03 compared to pure metronidazole (27.54±0.14% and 1.38±0.04 respectively). The CSFR/Dt ratio for batches F3 and F4 showed higher compactability and functionality. The dissolution profiles of batches F3 and F4 of metronidazole exhibited improved dissolution behaviour than pure drug containing batches (batches F1 and F2).

Conclusion: The CCA technique yielded metronidazole with increased particle size and compactability resulting in excellent flowability and packability due to reduced inter-particulate friction, which exhibited improved compressibility, dilution potential, disintegration and dissolution rate.

Keywords: Metronidazole tablet, Crystallo co-agglomeration technique, Flowability, Compressibility, Solubility

INTRODUCTION

In the realm of powder technology, efforts are made to develop pharmaceutical substances in order to produce a powder of good flowability and acceptable bulk density for direct compression (DC), relatively large particle must be used which may be difficult to mix to a high homogeneity and may be prone to segregation (Chen *et al.,* 2018). Many active pharmaceutical ingredients (APIs) have problems of inappropriate physical and mechanical properties, as well as low aqueous solubility. The micromeritic qualities of drug particles, such as size and shape, are essential for the formulation of solid high-dose units (Allen *et al.,* 2004; Chandran *et al.,* 2016). Hence, the CCA technique is required to impart numerous qualities such as improved solubility, acquiring the right polymorph, improving micromeritics and compression properties. Particle size enlargement has emerged as a key technique in modifying the primary and secondary qualities of active pharmaceuticals (Pawar *et al.,* 2004; Patel *et al.,* 2018).

Crystallo-co-agglomeration (CCA) technology, created by Kadam *et al.,* is a variant of the spherical crystallization process whereby a drug is crystallized and agglomerated with another drug or an excipient, which may or may not be crystallized in the system (Kadam *et al.,* 1997). Crystallo co-agglomeration is a cutting-edge technique of particle design that has shown to boost the efficiency of the earliest stages of the manufacturing. It combines the process of crystallization (primary particles design) and agglomeration (secondary particles design), and raises the added quality of the product by providing the primary and secondary particles with more functionality which is critical for the formulation of solid dosage forms (Dongare *et al.,* 2017; Deshkar *et al.,* 2017).

Drugs exhibiting poor compressibility and flowability are least suitable for DC. The process of crystallo co-agglomeration produces crystals of drug aggregate in the form of small spherical particles together with excipients and solvents that were used to develop and improve flow ability, mechanical and compression properties of the pharmaceutical solids (Ting *et al.,* 2018). Hence, it is emerging as potential area of research in particle designing employed in development of tablet dosage forms via direct compression (Kovacici *et al.,* 2012; Mihir *et al.,* 2020).

It is very desirable to simultaneous improve the extent and rate of dissolution of poorly soluble APIs as well as the mechanical properties. This would boost oral bioavailability, make it more reproducible, allow for clinically meaningful dose reductions, and improve the efficacy of therapy (Chandran *et al.,* 2016; Li *et al.,* 2021). The goal of physical modification focuses to produce amorphous states or reduce particle size. Formulation of co-agglomerates using various hydrophilic polymers improves drug solubility, dissolution rate, micromeritic properties, and physical properties for use in DC tablets (Deshkar *et al.,* 2017; Mahapatra, 2020). In particular, this technique can achieve a high degree of particle functionality and improvement in the efficiency of the manufacturing process (Raval *et al.,* 2020).

DC method is preferred for producing tablet because of it ease in processing, the lower number of unit operations and economic effectiveness. However, for applying DC in tablet production, the API/drug used should have acceptable flow qualities and compaction properties (Ankita *et al.,* 2011). Many drugs lack these qualities making it impossible to compress them directly into tablets. Metronidazole has a poor flow attribute and compressibility qualities making it a least suitable DC candidate.

Metronidazole (1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole), an anti-bacterial for treating infections caused by Gram negative anaerobic bacteria, is a poor water-soluble drug (5–10 mg/mL). It is a cohesive powder with high bulk density and poor flow property, and compressibility which makes DC difficult (Khalid *et al.,* 2018; Abdullahi *et al.,* 2023). This study explores the crystallo-co- agglomeration approach to boost the physico-mechanical and tabletting properties of the model drug, metronidazole.

METHODOLOGY

Materials

Pure Metronidazole powder (CDH Chemicals Ltd. New Delhi, India), Lactose (Nice Chemicals PVT. Ltd., Kerala, India), 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), Distilled water (Dept. of Pharm. and Ind. Pharm, A.B.U. Zaria), Polyethylene Glycol PEG 6000 (Shanghai Yuchuang chemical Tech. co., Ltd, China), Poly vinyl Pyrrolidone PVP K30 (Shanghai Yuchuang chemical Tech. co., Ltd, China).

Method

Preparation of Metronidazole co-agglomerates

The composition for the preparation of metronidazole co-agglomerates was adopted from Abdullahi *et al.* Pure metronidazole powder was accurately measured in to a beaker, this was dissolved in sufficient quantity of dichloromethane (good solvent) and was saturated at 50°C. Polyethylene glycol PEG 6000 and Polyvinyl pyrrolidone PVP K30 were weighed, transferred in another beaker and dissolved in sufficient quantity of poor solvent (water). The two dispersions were immediately added together under fixed agitation with a magnetic stirrer at 700 revolutions per min for 20 min after which the bridging liquid (ethanol) was added dropwise to generate co-agglomerates. The generated agglomerates were then filtered and dried in a hot dry oven for 24 h (Abdullahi *et al.*, 2023).

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 mixtures were compressed into tablets (500 ± 2mg) at 5.5 to 8 kN on a single stroke tablet press fitted with 12 mm circular flat-faced punches which were lubricated with 2% w/w dispersion of magnesium stearate in acetone. The tablet weight, diameter, thickness, crushing strength, friability and disintegration time were evaluated.

Formulation of Metronidazole tablets using Direct Compression method

To evaluate the direct compression propensity of the crystallo co-agglomerates, metronidazole crystallo co-agglomerates was selected at optimal dilution level for tableting via direct compression method. The tablets were formulated according to the formula in table 1 below. The metronidazole co-agglomerates tablets were formulated with Ludipress® and Starlac®. 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 was directly compressed into tablets (500 ± 2mg) on a single stroke tablet press equipped with 12 mm punch at a compression pressure of 5.5 to 8.0 kN. The same procedure was used to tablet pure metronidazole powder (Table 1) using same direct compression excipients for comparison.

Table 1. Composition of various batches of metronidazole Tablet (Batch F1 – F4)

Ingredients	F1	F2	F3	F4
Metronidazole Co-agglomerates 40% (mg)	—	—	200	200
Pure metronidazole 40% (mg)	200	200	—	—
Ludipress® 58% (mg)	290	—	290	—
Starlac® 58% (mg)	—	290	—	290
Magnesium Stearate 0.5% (mg)	2.5	2.5	2.5	2.5
Talc 1.5% (mg)	7.5	7.5	7.5	7.5
Total	**500**	**500**	**500**	**500**

omeritic Studies of pure metronidazole powder and its co-agglomerates:

Angle of repose, bulk density, Carr's Index and Hausner's ratio was used to determine the flow properties of metronidazole bulk and metronidazole agglomerates. To determine angle of repose, fixed funnel method was used, agglomerate size distribution was determined by sieving method, while Carr's Index and Hausner's ratio were calculated using bulk and tapped densities.

A. Bulk density (Db) and Tapped density (Dt) determination:

Using a large funnel, a 20 g powder sample was transferred into a dry measuring cylinder (100 mL) after which the initial bulk volume was measured as the loose volume occupied by the powder. Db was calculated by;

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

The cylinder was tapped 100 times after which the final volume (after tapping) was recorded. The formula below was used to calculate tapped density.

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

Both studies were conducted three times each and were expressed in g/mL.

Where; Db = Bulk density (g/mL), M = mass of powder (g), Vo = powder bulk volume (mL) Dt = Tapped density (g/mL); Vt = tapped volume of powder (mL).

B. Compressibility index (CI):

Compressibility of a powder is the percentage difference between tapped and bulk density (Carr, 1965), and is calculated using the formula below. The studies were conducted in triplicate.

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

C. Hausner's ratio (Hr):

The ratio of the tapped density and bulk density is referred to as Hausner's ratio (Hausner, 1967). This study was conducted in triplicate and was calculated by,

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

D. Angle of repose (θ):

A 20 g powder sample was weighed and transferred into a glass funnel clamped to a retort stand at 90° to a white flat paper at the horizontal, in a way that the tip of the funnel was 10 cm from the white paper. The highest angle recorded between the surface of the powder pile and the horizontal plane is known as the angle of repose. Studies was conducted three times and was calculated using,

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

Where; θ = angle of repose; h = height of powder pile; r = radius of the powder pile.

E. Flow Rate (Fr):

The Erweka flow rate machine is attached with a vibrator and a recording device to facilitate flow from the container. The amount of time it took for a 20 g powder sample to travel through the vibrating metal funnel of 0.5 cm diameter was measured and recorded using the flow rate machine. The study was conducted in triplicate and was calculated using.

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

M= weight of powder sample (g); t= time (sec)

Compaction studies of pure metronidazole and its co-agglomerate

With the use of a 12 mm flat-faced punch and die assembly on a Hydraulic Press, pure metronidazole and metronidazole co-agglomerates compacts (500 ±5 mg) were prepared at different pressures (25, 50, 75, 100, 150, 200, 250, 300 kn/m^2) and the same compression speed. With a dispersion of magnesium stearate in ethanol, the die was lubricated prior to each compression. Loading of the powder sample (500 ±5 mg) was carried out manually into the die and the compression pressure was applied allowing a dwell time of 10 s which was kept constant for each compression. After ejection, the tablets were stored in a desiccator over silica gel for 24 h to allow for elastic recovery. Tablet dimensions (weight and thickness) for each compression pressure *P* were recorded and the study was repeated thrice. With the formulas described below, the compression behavior of metronidazole powder and its prepared co-agglomerates were evaluated for tabletability, compressibility and compactibility.

$$\text{Porosity } (\text{Ɛ}) = 1 - D \quad (7)$$

$$\text{Apparent density } (\rho A) = \frac{weight\ (g)}{volume\ ((\pi r^2 h))} \quad (8)$$

$$\text{Relative density } (D) = \frac{\rho_A}{\rho_T} \quad (9)$$

where ρ_T = Tapped density, Ɛ = Compressed powder bed porosity at applied pressure *P*.

The tensile strength (σ) of the compact (MPa) was calculated using the equation below.

$$\sigma = \frac{2F}{\pi Dt} \quad (10)$$

Where, F, *D* and t are crushing strength (N), compact diameter (cm) and thickness (cm), respectively.

Evaluation of tablet properties

Determination of Tablet Diameter and thickness

Using ten (10) randomly selected tablets, diameters and thickness was evaluated using a digital caliper. The mean and standard deviation was calculated.

Determination of weight uniformity

From each batch, ten (10) tablets were chosen at random and weighed using an analytical balance. The average weight of the 10 tablets served as the basis for determining the weight variation of each batch.

Friability Test

Ten tablets from each batch were weighed and meticulously placed in a friabilator. The friabilator was programmed to rotate at a rate of 25 revolutions per min for 4 min, with the tablets to fall from a height of 6 inches at each revolution. The tablets final weight was recorded, and the percentage weight loss calculated from the equation below.

$$Friability = \frac{Wo - W}{Wo} \times 100 \quad (11)$$

Where Wo: tablet weight before test, W: tablet weight after subjecting it through the friabilator.

Crushing strength

Using a monsanto tablet hardness tester, diametrical compression was used to evaluate the crushing strength of the tablets at room temperature. The tablet was positioned between the tester's platen and the adjustable knob that was screwed in order to make contact with the tablet, while ensuring that enough pressure was applied to break the tablet. Tablets which split clean into two halves without any sign of lamination were taken. The result was the average of 10 assessments.

Tablet Disintegration Test

Disintegration test apparatus containing 0.1 M HCl and maintained at 37 ± 1°C thermostatically was used. Six (6) tablets from a batch, were tested at a time by placing one per tube. The time taken for each was recorded for six tablets to disintegrate and pass through the mesh and the mean disintegration time was calculated for each batch.

2. A. Construction of Calibration curve for metronidazole:

The UV spectrophotometer was calibrated by preparing a serial dilution of metronidazole in 0.1 N HCl (medium). An accurately 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.

B. Dissolution studies:

USP Apparatus I (Basket type) with a rotation speed at 100 rpm and a dissolution medium of 900 mL (0.1 N HCl) and maintained at 37 ± 1℃ was used to assess the *in-vitro* dissolution performance of the produced tablet batches. A 10 mL samples were removed at pre-determined time interval (10 sec, 30 sec, 1, 2, 5, 10, 15 and 30 min) and each time the same quantity of fresh dissolution medium was introduced to replace the abstracted samples. Upon suitable dilution with dissolution medium, samples were analysed by 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.

C. Uniformity of content determination

From each batch, twenty (20) tablets were chosen at random, weighed on the analytical balance, and then powdered into fine powder in a clean ceramic mortar. A 0.50 g aliquot of the powdered tablets was weighed and dissolved in 200 mL 0.1N HCl, which was then filtered. This was diluted with 100 mL of the medium, UV-spectrophotometer at 277.0 nm was used to analyse the samples.

Statistical Analysis and Data Presentation

All experiments were conducted in replicates to ensure validity of statistical analysis. Statistical methods measuring Mean, Standard deviation and Percentages (%) was done using social sciences statistical package SPSS software version 25. Data differences were considered significant for *P* values < 0.05. The results obtained were presented as tables and figures.

RESULTS AND DISCUSSION

The physicochemical and tableting performance of metronidazole co-agglomerates was evaluated on the basis of micromeritics, dilution potential, agglomerate handling qualities and dissolution. Micromeritic qualities of the crystallo-co-agglomerates produced was assessed in terms of bulk and tapped densities, Carr's index, Hausner's ratio and angle of repose, the values of which are presented in Table 2 below. The co-agglomerates of metronidazole exhibited relatively low bulk and tapped densities, small angle of repose, as well as significantly lower Hausner's ratio and Carr's index.

Table 2. Micromeritics of metronidazole co-agglomerates and pure metronidazole powder

Parameters	metronidazole co-agglomerates	metronidazole powder
Bulk density (g/mL)	0.34±0.01	0.50±0.01
Tapped density (g/mL)	0.40±0.01	0.69±0.01
Flow rate (g/sec)	4.04±0.29	2.66±0.22
Angle of repose (θ)	25.17±0.36	40.87±1.85
Carr's index (%)	15.00±0.14	27.54±0.14
Hausner's ratio	1.18±0.03	1.38±0.04
Mean particle size (μm)	296.61	71.82

Figure 1 below illustrates the compressibility profile of both pure metronidazole and its co-agglomerates. This profile evaluates the propensity of the material to undergo volume changes under compression. As the applied compaction pressure increases, the solid fraction of the material also increases. The graph indicates that applying pressure on pure metronidazole leads to significant decrease in porosity, revealing the inherent compressibility of pure metronidazole. This phenomenon can be attributed to particle size; the small particle size of pure metronidazole allows for a densely packed arrangement with minimal air spaces, facilitating the achievement of reduced porosity even under minimal pressure.

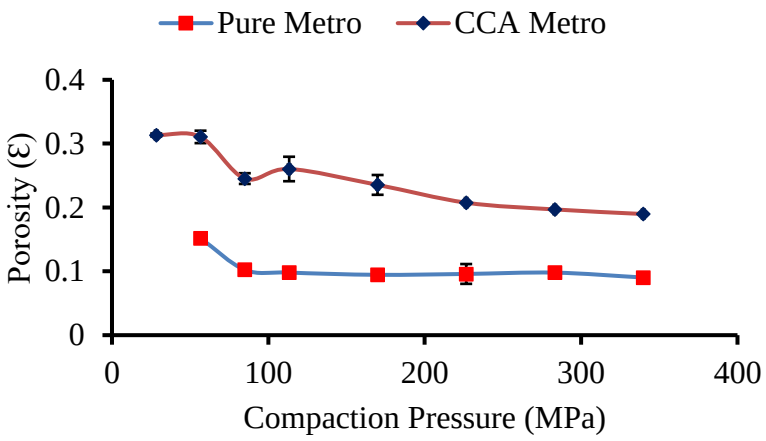

Figure 1. Compressibility profile of pure metronidazole and metronidazole co-agglomerates as it relates to porosity versus compaction pressure

As depicted in Figure 2 below, the compactability profile of pure metronidazole is contrasted with that of metronidazole co-agglomerates. This profile represents the tablet's tensile strength as a function of the solid fraction, which is the ratio of the tablet's density to its true intrinsic density. Notably, the metronidazole co-agglomerates demonstrated a significant elevation in tensile strength.

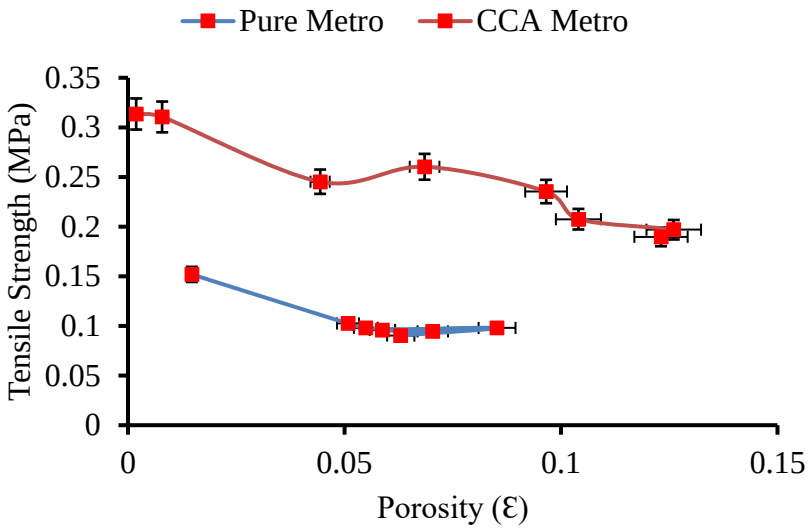

Figure 2. Compactibility profile of pure metronidazole and metronidazole co-agglomerates as it relates to Tensile strength versus porosity

Figure 3 presents the tabletability profile of both pure metronidazole and its co-agglomerates, as depicted by the relationship between tablet tensile strength and compaction pressure. This relationship symbolises the formation of inter particle bonds. Notably, these bonds appeared to be more robust and stronger in the metronidazole co-agglomerates than in the pure powder form. The enhanced bonding in the co-agglomerates suggests improved cohesive forces and a potential for producing tablets with better structural integrity under similar compression settings.

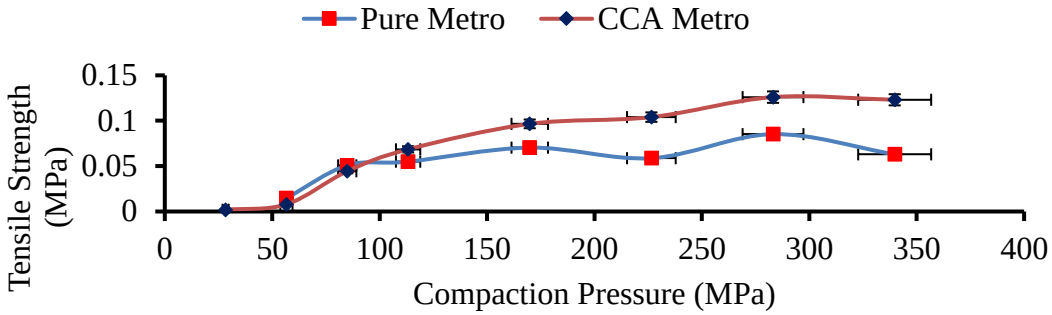

Figure 3. Tabletability profile of pure metronidazole and metronidazole co-agglomerates as it relates to Tensile strength versus compaction pressure

The data obtained in Table 3 below were generated from crushing strength (CS), friability (Fr) and disintegration time (Dt) of the solid compact of metronidazole co-agglomerates and excipient dilution in varying ratios. As concentration of metronidazole co-agglomerates increases, CS, and Dt decreases. The indices of CS/Fr and CSFr/Dt show 40% having the highest data value for dilution capacity of the co-agglomerates.

Table 3. Optimization of metronidazole co-agglomerates concentration using dilution potential

CCA (%)	CS (Kgf)	Fr (%)	CS/Fr	CSFr/Dt	Dt (min)
30	9.0±2.83	1.31	6.87	3.32	2.07±2.52
40	8.0±0.35	0.68	12.13	9.49	1.24±3.06
50	8.0±0.00	2.80	2.86	2.55	1.12±2.52
60	7.0±0.00	2.63	2.66	5.66	0.47±1.53
70	3.0±0.00	8.22	0.36	1.11	0.33±2.65

Key: Metronidazole crystallo co-agglomerates (CCA) Crushing strength (CS), Friability (Fr), Disintegration time (Dt)

The results of the physicochemical properties of the various batch formulation of metronidazole tablets are presented in Table 4 below, all batches showed acceptable uniformity of weight as none had percent deviation in weight > 5%. While all the batches showed a disintegration value of < 2 min, only batch F3 and F4 had an acceptable friability of < 1 %.

Table 4. Tablet Parameters for metronidazole tablet batches

Parameters	Pure Metronidazole F1	F2	Metronidazole co-agglomerates F3	F4
Weight (g)	490±0.00	502±4.47	498±4.47	494±5.48
Diameter (mm)	12.05±0.03	12.06±0.02	12.04±0.03	12.07±0.01
Thickness (mm)	3.09±0.04	3.09±0.05	3.13±0.02	3.06±0.03
Crushing strength (Kgf)	6.90±0.55	7.70±0.27	7.50±1.12	7.90±0.55
Friability (%)	2.15	3.20	0.82	0.80
Disintegration time (min)	0.48±0.56	1.17±0.11	0.48±0.44	0.59±0.11

Key: F = Formulation

Table 5 draws the relationship between the mechanical properties' (friability and crushing strength) and disintegration time of the produced metronidazole tablet formulations. Formulation batches F3 and F4 produced using metronidazole co-agglomerates show higher indices of CSFr and CSFr/Dt than formulation F1 and F2 that were produced using pure metronidazole.

Table 5. Crushing strength (CS), Friability (Fr), Disintegration time (Dt) Relationship for Metronidazole Tablets

Batches	CS (Kgf)	Fr	CSFr	CSFr/Dt	Dt (min)
F1	6.90±0.55	2.15	3.21	6.69	0.48±0.56
F2	7.80±0.27	3.20	2.44	2.08	1.17±0.11
F3	7.50±1.12	0.82	9.15	19.05	0.48±0.44
F4	7.90±0.55	0.80	9.88	16.74	0.59±0.11

Key: F = Formulation, Crushing strength (CS), Friability (Fr), Disintegration time (Dt)

The *In-vitro* dissolution study of metronidazole agglomerates showed significantly faster drug release profile as compared with pure metronidazole. Figures 4 and 5 presents the percentage metronidazole dissolved with time from tablet formulations produced via direct compression technique. The dissolution profiles of metronidazole exhibited improved dissolution behaviour for co-agglomerates batches than pure metronidazole batches.

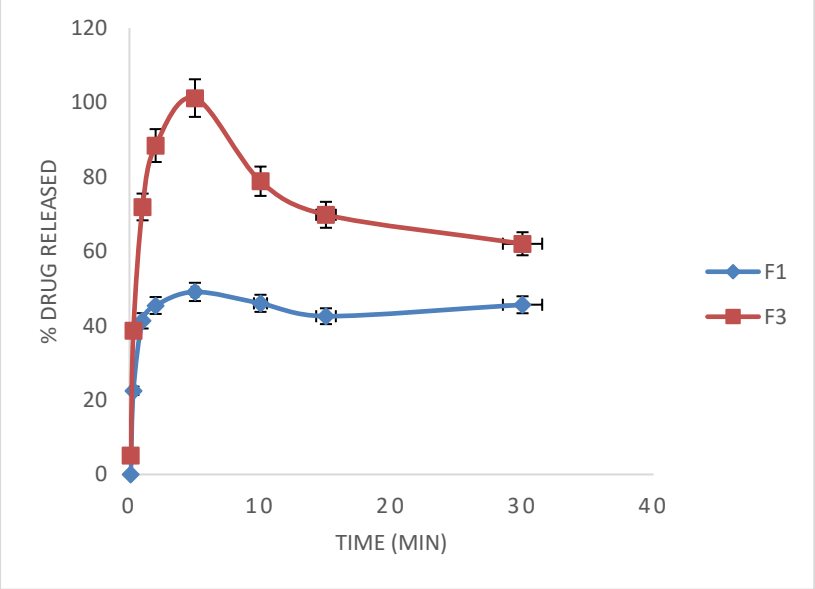

Figure 4. The drug release profile for pure metronidazole batch (F1) and metronidazole co-agglomerates batch (F3) tablets produced using Ludipress® via direct compression method

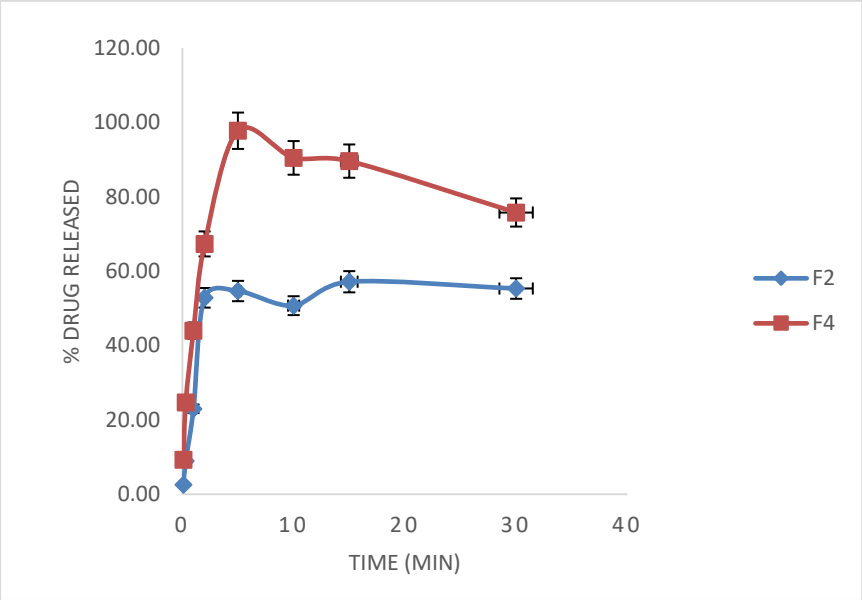

Figure 5. The drug release profile of pure metronidazole batch (F2) and metronidazole co-agglomerates batch (F4) tablets produced using starlac® via direct compression method

The data generated from the dissolution profiles of the various formulations of metronidazole tablet was used to generate the drug release indicator data. The $t_{50\%}$ and $t_{80\%}$ reflects the time taken for 50% and 80% metronidazole to dissolve, respectively, serve as empirical reflectors which assesses the onset of pharmacological action. The low values are indicative of fast drug release from the dose as observed in formulation F3 and F4.

Table 6. Drug release indicators of metronidazole tablet formulations

	Pure metronidazole		Metronidazole co-agglomerates	
Parameters	F1	F2	F3	F4
Dt (min)	0.48±0.56	1.17±0.11	0.48±0.44	0.59±0.11
$t_{50\%}$ (min)	--	1.45	0.30	1.22
$t_{80\%}$ (min)	--	--	1.26	2.57

***Key:** F = Formulation

DISCUSSION

Bulk and tapped densities are indirect measures of flow characteristics of powder, the values of which are presented in Table 2. This can be attributed to differences in the surface topography and intra-granular porosity caused by the hydrophilic polymers, which resulted in different packing characteristics and therefore low bulk density (Prescott and Barmum, 2008). The die fill volume is typically determined by the bulk and tapped densities. Materials with higher bulk density require lower die fill volume than those having small bulk density (Mahajan *et al.*, 2018; Khalid *et al.*, 2018). In Table 2, it can be observed that metronidazole co-agglomerates have lower values with respect to bulk and tapped densities, indicating higher die fill volume in comparison to those of the pure metronidazole powder.

The Hausner's ratio and Carr's indices of metronidazole agglomerates was 1.18±0.03 and 15.00±0.14% respectively, which falls within the theoretical limit for free flow characteristics of Hausner's ratio 1.12 - 1.18, and Carr's indices 11-15% respectively (Prescott and Barmum, 2008), compared to that of pure metronidazole (1.38±0.04 and 27.54±0.14%). Thus, indicating an increase in flowability of the metronidazole co-agglomerates. The reason for the improved flow of co-agglomerates is the significant reduction in the inter-particle friction because of the nearly spherical shape and the larger size of the crystals (Carr, 1965; Hausner, 1967; Mihir *et al.*, 2020). These could also be connected to the materials' particle size, shapes

and size distribution since they all have an impact on the flow of powder materials. The flow of powder typically reduces as the values of these indices (Carr's index and Hausner's ratio) rise, which might result in formulation problems like weight fluctuation, among others (Chen *et al.,* 2018; Khalid *et al.,* 2018).

The quality of the final product in terms of weight and content uniformity is predicted by the powder flow during manufacture (Prescott and Barmum, 2008). Material which possesses good flow property helps minimise weight variation in tablets and ultimately reduce content variation (Apeji *et al.,* 2017; Salim *et al.,* 2018). The difference in the value of angle of repose between pure metronidazole powder (40.87±1.85 º) and metronidazole co-agglomerates (25.17±0.36 º) was statistically significant ($p < 0.05$). The low values of angle of repose reported for metronidazole co-agglomerates can be attributed to the particle sizes. Angle of repose is an assessment of the flowability of a powdered or granular substance, it is affected by the cohesiveness of the powder. If the powder is cohesive, the value of the angle of repose will be high; whereas if the powder is not cohesive, it will be low (Bhimte and Tayade, 2007; Mihir *et al.,* 2020). Powders having an angle of repose tending to 50 º have unacceptable flow properties, while lower angles close to 25 º correspond to very good flow properties (Davies, 2009). When particles size is larger than 250 µm, the particles are often very free-flowing, but when the size is less than 100 µm, the powders become cohesive and flow issues are more likely to arise (Staniforth and Aulton, 2007).

Compressibility is the capacity of a material to undergo reduction in volume when subject to applied compression pressure (Alderborn, 2008). It assesses how readily the powder undergoes a change in volume with applied pressure. As the applied compaction pressure increases, so does the materials solid fraction. The plot in figure 1 shows a significant reduction in porosity was achieved with the application of pressure on the pure drug. The difference in compressibility value for pure metronidazole powder and metronidazole co-agglomerates was statistically significant ($p < 0.05$). The reduction of porosity of pure metronidazole at low pressure can be attributed to particle size, as the small particle size of pure metronidazole are closely packed with little air spaces and thus making it easy to achieve low porosity with the slightest applied pressure, Kedia *et al.,* made similar findings. The rate of decrease in porosity with rising compaction pressure is thought to be an expression of compressibility (Alderborn, 2008). The greater the compaction pressure, the lesser the value of porosity and the better the compressibility of the material. Figure 1 showed metronidazole co-agglomerates (CCA metro) as decreasing in porosity with rising compaction pressure while pure metronidazole maintained a fairly constant porosity at levels of increased compaction pressure. This shows metronidazole co-agglomerate having superior compressibility.

Compactibility of a powder material determines its capacity to generate tablets that will be strong enough under the effects of densification (Alderborn, 2008). Figure 2 depicts the compactibility profile of pure metronidazole and metronidazole co-agglomerate powder, which is the tablet's tensile strength as a function of the solid fraction (Ratio of tablet density to true density). The metronidazole co-agglomerates behaviour shows a statistically significant ($p < 0.05$) higher tensile strength. A study by Maghsoodi and Marghi observe a better compactability of co-agglomerated type crystal of ibuprofen as against the needle shaped crystals (Maghsoodi and Barghi, 2011).

Tabletability refers to a powdered material's ability to be transformed into a tablet of specific strength under the influence of compaction pressure (Alderborn, 2008). Figure 3 depicts the tabletability profile of pure metronidazole and metronidazole co-agglomerates and it is represented by a graph of tablet tensile strength against compaction pressure. This symbolises a significant increase $p < 0.05$ in formation of inter particle bonds which is more and stronger in metronidazole co-agglomerates. The fact that the compact produced from metronidazole agglomerates had higher tensile strength than pure metronidazole did suggest that the inclusion of hydrophilic polymers enhanced the inter-particulate bonding between the agglomerated crystals produced by crystallo- co-agglomeration technique (figure 3). The drug loading boosted the tensile strength of the compact due to more crystal bridges produced by the drug-drug molecules (Maghsoodi *et al.,* 2008). Also, positive drug-drug, polymer-drug, polymer-polymer interaction improves the tensile strength of the compact (Jadhav *et al.,* 2007).

Dilution potential assesses the quantity of an API that can be satisfactorily compressed into tablet with a given directly compressible excipient (Apeji *et al.,* 2017). The compressibility of the API influences the dilution potential (Olowosulu *et al.,* 2015; Salim *et al.,* 2018). The agglomerates of metronidazole were subjected to dilutions with direct compression excipient - Ludipress® to obtain an optimal percentage concentration yielding tablets of acceptable mechanical properties. To assess the dilution potential of DC active ingredients, many researchers have suggested an acceptable friability index of less than 1% (Salim *et al.,* 2018). But most frequently, however, crushing strength (or tensile strength) values is also used to evaluate dilution potential (Olowosulu *et al.,* 2015). The formulation batch with the lowest friability of < 1% and higher

crushing strength greater than 6 Kgf was chosen. The standard crushing strength range for uncoated tablets is typically between 4-8 Kgf (Ayorinde *et al.*, 2012).

The results obtained in table 3 showed 40% having the highest indices of CSFr/Dt which is a clearer indication of a robust and high-quality tablet. This further maintained the capacity and efficiency of Ludipress® as a good DC diluent for metronidazole co-agglomerates because it could produce tablets with acceptable strength and friability. High dilution potential is an important requirement of directly compressible diluents (Rojas and Kumar, 2011). Thus, metronidazole co-agglomerates 40% was used to formulate tablet batches with various direct compression excipients via DC method.

According to results on table 4, all the formulations prepared using the batch formula presented in table 1 met the established acceptable threshold for weight uniformity (mean ± 5%). To guarantee that each tablet's drug content is evenly distributed in a narrow range around it stated strength, weight uniformity test for tablets is necessary. This is because a tablet's weight can be a good indicator of the amount of active ingredient it contains. According to USP, in order for a drug product with a weight greater than 324 mg to pass the weight uniformity test, it must not exceed ± 5% of the average (USP, 2011). Thus, all the dilution potential formulations passed the official acceptable limit for uniformity of weight (mean ± 5%).

For uniformity of tablet weight, The B. P. stipulates that for tablets with mean weight higher than 250mg, not more than 2 tablets are allowed to deviate from the mean by more than ± 5% and no tablet by more than ±10% (BP, 2010). All batch of metronidazole formulation fell within the official weight range.

There was no discernible variance in the mean values of tablets thickness or diameter, as shown in Table 4 of the data. The use of lubricant (magnesium stearate) and glidant (talc) must have prevented friction between the die wall and improved the flow of the powder blend, respectively (Chen *et al.*, 2018). This guaranteed a uniform volume of the powder mixture to be fed into the die chamber, resulting in a consistent and homogeneous tablet diameter and thickness.

The mechanical characteristics of the tablets serve as a gauge of their resilience to withstand rigours of production, transit, dispensing and usage. Crushing strength and friability are two important metrics used to measure the mechanical characteristics of tablets. As the concentration of binder in the tablet increased, so did its crushing strength (Santosh *et al.*, 2017). Binders encourage the plastic deformation of particles, increasing the surface areas of contact available for inter-particulate bonding (Chandran *et al.*, 2016). More solid bonds will subsequently develop in the tablet as a result, leading to the formation of a cohesive and stable matrix in the tablet. Tablets must possess sufficient mechanical resistance to endure the stresses and strains of transportation and storage, hence the crushing strength of the tablets is assessed (Ayorinde *et al.*, 2012). It is a crucial factor in determining whether the tablets will be able to withstand chipping, abrasion, or breaking under storage, shipping, and handling conditions. Crushing strength CS represents how easily tablets can be handled as well as how they behave when compressed. Although there is no set standard for tablet hardness, crushing strength values of 4 – 15 Kgf (40 – 150 N) is generally recommended satisfactory for tablets (BP, 2010), while for uncoated tablets, values between 40 - 78 N are typically acceptable (Allen *et al.*, 2004). The values of crushing strength presented in table 4 for the metronidazole tablet batches produced 6.90 – 7.90 Kgf passed the crushing strength test. The good crushing strength obtained is a reflection of adequately dried granules and optimal compression force.

Friability, which gauges a tablet's susceptibility to wear and tear, is inversely related to its crushing strength (Apeji *et al.*, 2017). The better the tablet is able to tolerate mechanical manipulation, the lower the friability value. It was observed that all metronidazole co-agglomerates batches showed acceptable friability values below 1% (batch F3 0.82% and batch F4 0.80%). Friability value for tablet formulation batches F1 and F2, on the other hand, fails to meet the official set standard as the value was much higher 2.15% and 3.20% respectively, even though they had an acceptable crushing strength of 6.90 and 7.80 Kgf respectively. This failure may be due to post-compression elastic recovery of the active ingredient particles and can be related to poor bonding between the drug and model excipient composite particles, which is similar to the findings made by Khalid *et al.* Metronidazole exhibits plasto-elasticity behaviour, which means it will deform by plastic flow on compression and some of its particles may undergo elastic recovery on decompression (Olowosulu *et al.*, 2015). Tablet properties like crushing strength and friability are essential for patient acceptance.

In immediate release uncoated tablets, the tablets usually disintegrate into smaller particles, leading to increase in surface area around the drug particles (Chatterjee *et al.*, 2018). Disintegration time is a fundamental step for assessing dissolution and can determine the rate of drug absorption (Deshkar *et al.*, 2017; Chatterjee *et al.*, 2018). According to table 4, the disintegration time of metronidazole tablets batches produced in formulation F3, F4 and F1, F2 show no significant difference. All the metronidazole tablet batches produced displayed a rapid disintegration (< 2 min). Rapid disintegration is one benefit of tablets produced by DC method

which is in conformity with B.P (2010) specification for uncoated tablets.

The low values of friability in formulations F3 and F4 as contained in table 5 have shown to bring about a higher increase in the CSFr and CSFr/Dt relationship as compared to formulations F1 and F2 batches. CSFR provides a metric of assessment strength and weakness of tablet and has been described as a useful scale for tablet robustness (Ayorinde *et al.,* 2012).

CSFR/Dt is an indicator of strength of bond, and at the same time assesses any detrimental impact these parameters may have on disintegration time, which is a sign of breakdown of bonds. An optimum balance between binding and disintegration properties is indicated by high value (Ayorinde *et al.,* 2012). The CSFR/DT ratio was used to evaluate the disintegrant activity and strength of metronidazole tablets produced by DC method from metronidazole co-agglomerates and pure metronidazole. There was a general significant increase ($P < 0.05$) in the CSFR/DT ratio for batches produced from metronidazole co-agglomerates than those which contain pure metronidazole. From these, it can thus be said that a synergy of functionality improvement was achieved, when the metronidazole CCA were combined with commercially available DC excipient: Ludipress® and Starlac®. The commercial directly compressible (DC) excipients confers enhanced compactibility in the combination, whereas the co-agglomerates significantly enhance the disintegration efficiency of the combination due to their hydrophilic polymer content. Metronidazole calibration curve was prepared at wavelength 277.0nm, having satisfactory linearity and regression coefficient of 0.9795 (r^2 value) was found. The British Pharmacopoeia specifies that, for an immediate release tablet formulation, not less than 70% of the drug must dissolve in 45 min (BP, 2010). The *in-vitro* dissolution rate and consequently in-vivo absorption and bioavailability of the drug is a function that reflects the drug molecule solubility within the formulated tablet (Abdullahi *et al.,* 2023). As a result, the in-vivo performance is greatly influenced by the *in-vitro* dissolution studies.

In figure 4 and 5, the dissolution profiles of formulations of metronidazole tablet are depicted, and table 6 presents the data that was generated. The $t_{50\%}$ and $t_{80\%}$ are empirical reflectors which measures the onset of effect with low values indicating fast drug release from the dose form (Khalid *et al.,* 2018; Salim *et al.,* 2018). The time taken for 50% and 80% of the drug to dissolve ($t_{50\%}$) and ($t_{80\%}$) for metronidazole co-agglomerates containing batches (Batches F3 and F4) and pure metronidazole containing batches (Batches F1 and F2) were evaluated from the profile. The $t_{50\%}$ and $t_{80\%}$ of batch formulation of F3 and F4, were both attained in under 5 minutes, with a substantial difference, this immediately indicated that 75% of the active drug was released from these two formulations under 45 minutes as specified in the pharmacopoeia criteria for drug release from uncoated immediate-release tablets (USP, 2011). Given the improved wettability of the metronidazole co-agglomerates and the hydrophilic properties of PVP K 30 and PEG 6000 employed in co-agglomeration technique, the cause of this rapid dissolution may be explained by the fact that these substances were used (Deshkar *et al.,* 2017). On the other hand, only $t_{50\%}$ for formulations F2 was attained at 1.45 minutes, while $t_{50\%}$ and $t_{80\%}$ were not attained after 45 minutes for formulation F1. Therefore, F1 and F2 batches failed to meet BP requirements for dissolution. However, it is also clear that the dissolution pattern for each formulation corresponds to their specific disintegration scenario as the fast release could be associated to the short Dt.

CONCLUSION

This study revealed that co-agglomerates of metronidazole possessed increased particle size, excellent flowability, compressibility, tabletability, and packability due to reduced inter-particulate friction. The metronidazole co-agglomerates possess a significant tensile strength which indicated the formation of more and stronger inter-particle bonds. Furthermore, tablets made with metronidazole agglomerate exhibited improved compactability, high dilution potential and rapid disintegration as well as faster dissolution rate. The CSFr/Dt ratio for formulations F3 and F4 batches show functionality improvement with higher compactibility as well as having good resistance to handling. Thus, this technique can be utilised for preparation of tablets of metronidazole by DC with directly compressible tablet excipients.

ACKNOWLEDGEMENT

We wish to appreciate all the technical staff of the department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University Zaria for their support during the conduct of this research.

REFERENCES

Abdullahi, A.K., Olowosulu, A.K., and Allagh, T.S. (2023). Crystallo co-agglomeration technique for improving physicochemical properties, compressibility and solubility characteristics of metronidazole, *Brit. J. Pharm.* 8(1).1039

Alderborn, G. (2008). Tablets and compaction, in Pharmaceutics. The science of dosage form design, Aulton, M. E., Editor. Churchill Livingstone: Edinburgh p. 397-440.

Allen, L.V., Popovich, N.G., and Ansel, H.C. (2004). Ansel's pharmaceutical dosage forms and drug delivery systems. 8th edn. *Lippincott Williams and Wilkins, Philadelphia.* 236-238

Ankita, C., Pramod, K.S., and Mayank, B. (2011). A review on recent advancement in crystallo co-agglomeration, *Adv. Boil. Res*, 5(6):273-281.

Apeji, Y.E., Oyi, A.R., Isah, A.B., Allagh, T.S., and Modi, S.R. (2017). Development and optimization of a starch-based co-processed excipient for direct compression using mixture design. *AAPS Pharm. Sci. Technol.* 19: 866-880.

Ayorinde, J., Odeniyi, M., and Itiola, A. (2012). Evaluation of pharmaceutical and chemical equivalence of selected brands of diclofenac sodium tablets. *East and Central African J. Pharm. Sci. 15*, 3–9.

Bhimte, N.A., and Tayade, P.T. (2007). Evaluation of microcrystalline cellulose prepared from sisal fibres as a tablet excipient: A technical note. *AAPS Pharm. Sci. Technol*, 8 E1-7.

British Pharmacopoeia, Vol. 1 (2010). The Pharmaceutical Press, Her Majesty Stationery Office, London.

Carr, R. (1965). Evaluating flow properties of solids, *Chem. Eng.* 72, 163-168.

Chandran, C.S., Theju, J.T., Vipin, K.V., and Amitha, S. (2016). Crystallo-co-agglomeration: an effective tool to change the powder characteristics of indomethacin IP. *Int'l J. Pharm. & Pharm. Res*, *5*(4), 197–207.

Chatterjee, A., Shrivasttava, B, Sharma, G.N., and Gupta, M.M. (2018). Crystallo co-agglomeration of valsartan for improved solubility and powder flowability. *Asian J. Pharm.* 12(3), 182-195.

Chen, H., Aburub, A., and Sun, C.C. (2018). Direct Compression Tablet Containing 99% Active Ingredients: A Tale of Spherical Crystallization. *J. Pharm. Sci.* 1-5 https://doi.org/10.1016/j.xphs.2018.11.015

Davies, P. (2009). Oral solid dosage forms. In: Gibson, M. (Ed.), *Pharmaceutical preformulation and formulation*, 2nd edition, Informa Healthcare, USA. Inc. pp 367–430

Deshkar, S.S., Borde, G.R., Kale, R.N., Waghmare, B.A., and Thomas, A.B. (2017). Formulation of cilostazol spherical agglomerates by crystallo-co- agglomeration technique and optimization using design of experimentation. *Int'l J. Pharm. Invest.* 7 (4):164–73. https://doi:10.4103/jphi.JPHI_39_17

Dongare, T.D., Bhalekar, M.R., and Gandhi, S.V. (2017). Formulation optimization and pharmacokinetics of tinidazole crystallo–co–agglomerates. *MOJ Bioequiv. Availab.* 3(5):123–129. https://DOI:10.15406/mojbb.2017.03.00047

Hausner, H. (1967) Friction conditions in a mass. *Int'l J. Powd. & Metallurgy*, 3, 7-13.

Jadhav, N., Pawar, A., and Paradkar, A. (2007). Design and evaluation of deformable talc agglomerates prepared by crystallo-co-agglomeration technique for generating heterogeneous matrix. *AAPS Pharm. Sci. Technol. 8*(3).

Kadam, S.S., Mahadik, K.R., and Paradkar, A.R. (1997). inventors. A process for making agglomerates for use as or in a drug delivery system. *Indian patent*, 183036.

Kedia, K., and Wairkar, S. (2019). Improved micromeritics, packing properties and compressibility of high dose drug, cycloserine, by spherical crystallization. Powder technology, 344, 665-672. https://doi:10.1016/j.powtec.2018.12.068

Khalid, G.M., Musa, H., Olowosulu, A.K., Jatau, A.I., and Ilyasu, S. (2018). Comparative FTIR, Compaction and *In vitro* Dissolution Studies of *Plectranthus esculentus* Modified Starches in Metronidazole Tablet

Formulations by Direct Compression. *Pharm. Anal Acta*. 9: 577. https://doi:10.4172/2153-2435.1000577

Kovačič, B., Vrečer, F., and Planinšek, O. (2012). Spherical crystallization of drugs. *Acta Pharmaceutica*. *62*(1), 1–14. https://doi.org/10.2478/v10007-012-0010-5

Li, J., Hao, X., Wang, C., Liu, H., Liu, L., He, X., and Sun, C.C. (2021). Improving the Solubility, Dissolution, and Bioavailability of Metronidazole via Co-crystallization with Ethyl Gallate. *Pharmaceutics*, *13*, 546. https://doi.org/10.3390/pharmaceutics13040546

Maghsoodi, M., and Barghi, L. (2011). Design of Agglomerated Crystals of Ibuprofen During Crystallization: Influence of Surfactant. *Iranian J. Basic Med. Sci. 14*(1), 57–66.

Maghsoodi, M., Taghizadeh, O., Martin, G.P., and Nokhodchi, A. (2008). Particle design of naproxen – disintegrant agglomerates for directly compression by crystallo co-agglomeration technique. *Int'l J. pharm. 351:45-54.*

Mahajan, M.N., Malghade, D.A., Dumore, G.N., and Thenge, R.R. (2018). Design and development of CCA of ritonavir for the improvement of physicochemical properties. *Turkish J. Pharm. Sci.* 15(3): 248 – 255 https://doi:10.4274/TJPS.44227

Mahapatra, S.P., and Shashank T. (2020). Dosage Unit Dosages Form-Tablet: An overview. *Int'l Res. J. Hum. Eng. & Pharm. Sci.* 5(1): 9.

Mihir, K.R., Kevin, C.G., Jaydeep, M.P., Rajesh, K.P., and Navin, R.S. (2020). Functionality improvement of Chlorzoxazone by crystallo-co- agglomeration using multivariate analysis approach. *Particulate Sci. Technol.* https://10.1080/02726351.2020.1799126

Olowosulu, A., Oyi, A., Isah, A., and Ibrahim, M. (2015). The Use of Multifunctional Starch Based Co-processed Excipients (Starac) in the Formulation of Metronidazole Tablets by Direct Compression. *Afri. J. Pharm. Res. & Dev. 7*(2), 101–108.

Patel, C.P., Jivani, M., and Prajapati, B.G. (2018). Crystallo Co-Agglomeration: The Novel Approach For Micro particulation. *Res. & Rev. on Healthcare, 1*(3), 1–7.

Pawar, A., Paradkar, A., Kadam, S., and Mahadik, K. (2004). Agglomeration of ibuprofen with talc by novel crystallo-co-agglomeration technique. *AAPS Pharm. Sci. & Technol. 5*(4). https://doi.org/10.1208/pt050455

Prescott, J.K., and Barnum, R.A. (2008). Powder flowability. *Pharm. Technol.* pp: 60-84.

Raval, M.K., Garala, K.C., Patel, J.M., Parikh, R.K., and Sheth, R. (2020). Functionality improvement of Chlorzoxazone by crystallo-co-agglomeration using multivariate analysis approach. *Particulate Sci. & Technol. 0*(0), 1–23. https://doi.org/10.1080/02726351.2020.1799126

Raval, M.K., Garala, K.C., Patel, J.M., Parikh, R.K., Sheth, R., Raval, M.K., Garala, K.C., Patel, J.M., and Parikh, R.K. (2020). Functionality improvement of Chlorzoxazone by crystallo-co-agglomeration using multivariate analysis approach. *Particulate Sci. & Technol. 0*(0), 1–23. https://doi.org/10.1080/02726351.2020.1799126

Rojas, J., and Kumar, V. (2011). Comparative evaluation of silicified microcrystalline cellulose II as a direct compression vehicle. *Int'l J. Pharm.* 416:120-128.

Salim, I., Olowosulu, A.K., Abdulsamad, A., Mohammed, K.G., and Gwarzo, M.S. (2018). Physico-mechanical Behaviour of Novel Directly Compressible Starch-MCC-Povidone Composites and their Application in Ascorbic Acid Tablet Formulation. *Brit. J. Pharm.* 3(1) 527.

Santosh, V., Ganghi, R., Mutha, S., Mangesh, R.B., and Atul, P.C. (2017). Optimization of crystallo co-agglomerates of fenofibrate to improve flow properties and dissolution. *Res. pharmaceutica* 1(2), 21 – 26

Staniforth, J.N., & Aulton, M.E. (2007). Powder flow. In: Aulton, M.E. (Ed), *Aulton's Pharmaceutics: The design and manufacture of medicines*, Churchill Livingstone Elsevier, London, 3rd Edition. Chapter 13, pp 168-180.

United States Pharmacopoeia (USP) (2011). General Chapeters <711> Dissolution <701> Disintegration.

*Address for correspondence: Abba Khalid Abdullahi
Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University Zaria, Nigeria
Telephone: +2348030790928
E-mails: khalidabba90@yahoo.com

Conflict of Interest: None declared
Received: November 07, 2023
Accepted: February 17, 2024