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PREPARATION AND EVALUATION OF METRONIDAZOLE TABLETS PRODUCED WITH DIFFERENT BINDERS USING WET GRANULATION METHOD

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ABSTRACT

In tablet formulation, binders are essential for ensuring proper powder mix, granulation and overall tablet quality. Variations in binder quality and concentration can impact drug bioavailability, strength and manufacturing processes. The inconsistency in bioavailability and therapeutic response of metronidazole from different manufacturers highlights the importance of binder selection in tablet formulation. This study evaluates the impact of different binding agents on tablet quality. The optimum binder concentration for each of the binders was assessed to obtain suitable concentration that was used to prepare metronidazole tablets. Metronidazole tablets were formulated with four different binder vis, acacia, gelatine, PVP, maize starch at 3% concentration using wet granulation method after which the tablet properties were evaluated. Metronidazole powder exhibited poor flow indices, as indicated by angle of repose: 39.92 ± 1.85, Carr's compressibility index (CI): 20.13 ± 0.28 and Hausner's ratio (Hr): 1.26 ± 0.01, whereas its granules exhibited good flow properties. The crushing strength (CS), friability (FR), disintegration time (DT) (CSFR/DT) ratio for batches showed values in 3% binder concentration, indicating higher strength as compared to other concentrations. There was a significant increase (P < 0.05) in the CSFR/DT ratio for gelatine (2.22) in formulation F2 compared to maize starch in Formulation F4. The formulated tablets with the various binders have met with the British Pharmacopeial criteria of 80% drug release from uncoated immediate-release tablets. Amongst the four binders, gelatine was found to be the best in the formulation of robust metronidazole tablets by wet granulation method at an optimised concentration of 3% w/w. Tablets produced with gelatin exhibited greater mechanical strength than those produced with other binders, while also demonstrating a slightly longer DT. Metronidazole tablets

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produced with gelatine have met the British Pharmacopeial requirements including an acceptable in-vitro drug release profile.

Keywords: Metronidazole Tablet, Wet granulation method, Gelatin binder, Tablet formulation, Binder selection, Immediate-release tablets

INTRODUCTION

Metronidazole, a synthetic nitro-imidazole antibiotic, is versatile in its administration routes, including oral, which boasts an 80% bioavailability, making it the preferred method (Soni *et al.* 2021; Ezegbe *et al.* 2023). This antibiotic is primarily effective against anaerobic bacteria and protozoa. Given its widespread use and observed differences in therapeutic responses across various manufacturers, metronidazole was selected as a model drug for this study.

This variability highlights the critical need for research to optimise the formulation and manufacturing processes to ensure consistent drug efficacy and patient safety. However, an issue of paramount concern is the observed variation in drug bioavailability among different manufacturers, resulting in inconsistent therapeutic outcomes (Ezegbe *et al.* 2023; Khalid *et al.* 2018). Such disparities can result in diminished treatment effectiveness and patient discomfort. The increasing instances of substandard drug manufacturing further emphasise the need for meticulous research in pharmaceutical formulation and stringent quality control. These concerns are not unfounded, as the use of counterfeit or substandard drugs can have severe consequences for patient health, including compromised treatment outcomes, increased side effects and potential drug resistance. The need to address and mitigate these health implications underscores the importance of research in pharmaceutical formulation and quality control.

Tablets are formulated by compressing specified volumes of granules or a powder mix of an active ingredient and excipients. Excipients are indispensable in ensuring the production of quality tablets; they are incorporated into formulations to enhance processing, stability, bioavailability and the overall function of the drug dosage (Moreton 2004). Thus, excipients play a pivotal role, not merely as fillers, but as elements that support the drug's delivery (Apeji *et al.* 2019). Commonly employed in solid formulations like tablets, these excipients can range from lubricants, diluents, glidants, stabilising agents to disintegrants, binders, bulking agent and coating agents, among others (Darji *et al.* 2018). These excipients are either from natural, synthetic or semi-synthetic sources.

Binders, a type of pharmaceutical excipient, are r e q u i r e d in tablet formulations to guarantee an effective blend of powders, create good granules and generally enhance the flow characteristics of the granules (Ezegbe *et al.* 2023). They alter the binding attributes of the granules by fostering the development of robust inter-particular bonds (Parit, Chougule and Patil 2021). Depending on the other constituents in the formulation and the preparation method, binders can be utilised either in solutions or in dry forms (Das and Das 2019).

Our study focused on evaluating four distinct binding agents and their influence on the formulation of metronidazole tablets using the wet granulation method. Understanding the distinct properties of these agents is essential as they significantly influence the resulting tablet's physical and mechanical characteristics. Acacia, derived from the gum of acacia Senegal or acacia Seyal trees, is a natural binding agent frequently employed in pharmaceutical formulations. It is known for its adhesive properties and ability to create

strong bonds between particles. Acacia is particularly valued for its role in improving the flow properties of granules (Parit, Chougule and Patil 2021). Gelatine, a protein-based binding agent, is derived from animal collagen, typically sourced from cattle or pigs. It possesses excellent binding capabilities, resulting in robust tablet formulations. Gelatine is favoured for its versatility and compatibility with a wide range of pharmaceutical ingredients (Jackson *et al.* 2022). Polyvinylpyrrolidone (PVP) is a synthetic polymer commonly used as a binding agent in tablet manufacturing. It is known for its solubility in water and its capacity to create strong inter-particular bonds. PVP is valued for its ability to enhance the disintegration and dissolution properties of tablets (Apeji *et al.* 2019). Maize starch, a natural carbohydrate-based binder, is derived from corn. It is widely used in pharmaceuticals due to its adhesive properties, which aid in the agglomeration of powders. Maize starch is appreciated for its role in improving the flow properties of granules (Olowosulu *et al*. 2015).

The choice of these binding agents was motivated by their prevalent utilisation in tablet formulations and their diverse characteristics. Acacia, gelatine, PVP and maize starch were selected as binding agents to represent a distinct category of binding agents, including natural, animal-derived, synthetic and plant-based options. This diversity allows for a comprehensive evaluation of the binding agents commonly used in pharmaceutical tablet production.

The binder's selection is vital in tablet manufacturing as it directly affects the tablets mechanical properties, dissolution properties and, ultimately, the drugs bioavailability and therapeutic efficacy (Manyikana *et al*. 2016). By examining these binding agents in metronidazole tablet formulation, we aim to highlight their crucial role in the pharmaceutical manufacturing process, ensuring patients receive effective and high-quality medications.

The wet granulation technique was chosen for its established prominence in tablet production. The method excels in producing granules with favourable flow properties, ensuring even drug distribution and boosting tablet mechanical integrity. Furthermore, it facilitates the integration of various binding agents, enabling a detailed evaluation of their effects on tablet quality.

This research aims to identify the optimal binder for producing immediate-release tablets using the wet granulation approach. The core objective is to formulate and assess metronidazole tablets using four diverse binding agents.

MATERIALS

Materials used in the study were metronidazole powder (CDH Chemicals Ltd. New Delhi, India), acacia gum (Hopkins and Williams, England), distilled water (Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University Zaria), lactose (BDH Chemicals Ltd. Poole, England), talc powder (BDH Chemicals Ltd. Poole, England), magnesium stearate (BDH Chemicals Ltd. Poole, England), maize starch (BDH Chemicals Ltd. England) and gelatine (BDH Chemicals Ltd. Poole, England).

Equipment

Equipment used in the study were friabilator (type TA3R Erweka, Germany), flow rate meter (Erweka, type GDT, Germany), test sieve shaker (Endecotts Ltd., England), single stroke tablet press (Erweka, Type AR400, Germany), USP disintegration apparatus (Type ZT3, Erweka, Germany), USP dissolution apparatus (Type DT, Erweka, Germany), Gallenkamp

hot air oven (BS 7B993 8D, England), Monsanto tablet hardness tester (Monsanto Chemical Co., USA), digital balance top loading HF 2000 (USA), digital caliper (Fischer, Germany), tablet hardness tester (Monsanto Chemical Co. USA) a n d UV-visible spectrophotometer (UV-1601, Shimadzu, Japan).

METHODS

Evaluation of Physical Parameters of Granules

Micromeritic Studies

The flow characteristics of pure metronidazole powder and the prepared metronidazole granules were evaluated. These characteristics were analysed in terms of several parameters, including angle of repose, tapped density (Dt), bulk density (Db), Carr's compressibility index (CI) and Hausner's ratio (Hr).

Db and 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 taken up by the powder. Db was calculated by:

$$Db = \frac{M}{Vo} \hspace{4cm} \text{(Equation 1)}$$

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

$$Dt = \frac{M}{Vt} \hspace{4cm} \text{(Equation 2)}$$

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).

CI

Powder compressibility, as defined by Carr in 1965, is the percentage difference between its Dt and Db. These investigations were carried out three times for accuracy and consistency and was given by,

$$CI = \frac{(Dt - Db)}{Dt} \times 100 \hspace{3cm} \text{(Equation 3)}$$

Hr

Hr, as defined by Hausner in 1967, is determined by dividing the Dt by the Db. This specific study was replicated three times for robustness and reliability and was given by:

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

Angle of repose

A precise sample of 20 g of powder was transferred into a clean, dry glass funnel which was fixed to a retort stand at a 90° angle to a flat horizontal surface. Beneath the funnel, a piece of paper was set so that the funnel's tip was 10 cm above this surface. The powder was meticulously poured through the funnel, creating a heap on the paper. The angle of repose was then calculated as the greatest possible angle between the pile's surface and the horizontal plane. This experiment was performed three times for consistent and reliable results, and was given by,

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

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

Flow rate (Fr)

The Fr can be constantly monitored using an electronic balance that has a recording device and a vibrator attached to assist the flow out of the container. In this instance, a 20 g sample of the powder was fed through an Erweka Fr machine. The duration required for each type of powder to fully traverse the vibrating metal funnel was documented. This investigation was repeated three times to ensure accuracy and reliability.

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

where, M = weight of powder (g), t = time (sec)

Particle size analysis

This analysis was performed by sifting a powder sample through a stack of wire mesh sieves, separating it into discrete size ranges (500, 250, 150, 90, 75, 45) µm. A 20 g powder sample was sieved using an Erweka vibration sieve through a nest of standard sieves. The vibration rate was set at 200 strokes/min and the sieving time was 10 min. The percentage powder retained was multiplied by the mesh size and divided by 100 to determine the contribution of each size fraction to the overall mean diameter. The sum of the weight diameters calculated for each sieve size was calculated to give the mean particle size. Particles smaller than 45 µm on the pan were categorised as fines. This procedure was repeated three times to ensure robustness and reliability.

Formulation of Metronidazole Tablet by Wet Granulation Method

Metronidazole powder, sodium starch glycolate and lactose were weighed on a class B balance to the nearest gram and was dry mixed with pestle in a porcelain mortar using doubling up technique. Binder mucilage was prepared by weighing the binder, moistened with about 1 mL of distilled water and homogeneously mixed into a paste using a spatula in a 50 mL graduated beaker. Hot water near boiling pointing was added with stirring until 4 mL is reached. The beaker with its contents was placed on a hot plate with constant stirring until the liquid suddenly turns into a translucent, opaque appearance which appears to denote the formation of the mucilage. This was kept to cool to about 40°C before being added to the dry mix and massed in the mortar until a homogenous granular texture was formed. The wet mass was force-screened through 1.6 mm sieve mesh onto a tray and kept to dry in the Gallenkamp hot air oven thermostat at 40°C until a constant weight, which denotes complete drying was achieved. Magnesium stearate was then added to the granules and dry mixed (tumble mixing) in a jar for 5 min.

The lubricated granules were then compressed using the tableting machine of 12 mm punch and die assembly using 500 mg as the mean weight of the tablet. All the batches of granules were prepared using this procedure.

Optimisation of Binder Concentration in Wet Granulation

To evaluate the optimum concentration of binder needed in the formulation of immediate release metronidazole tablets using wet granulation method, different metronidazole batches were formulated with the different percentages (1%–5%) of wet granulation binders—acacia, gelatine, PVP and maize starch. The tablets were formulated according to the formula in Table 1. Extra granular excipients such as magnesium stearate and sodium starch glycolate were added. The granules were compressed using the tableting machine of 12 mm punch and die assembly using 500 mg as the mean tablet weight.

Table 1: Batch formula for metronidazole tablet prepared with various binders using wet granulation method.

Ingredients (mg)	F1	F2	F3	F4
Metronidazole 40%	200	200	200	200
Lactose 51%	255	255	255	255
Acacia 3%	15			————
Gelatine 3%		15		————
PVP 3%		————	15	
Maize starch 3%			————	15
Sodium starch glycolate 4%	20	20	20	20
Magnesium stearate 2%	10	10	10	10
Total	500	500	500	500

Evaluation of Tablet Properties

Determination of tablet diameter and thickness

A digital caliper instrument was employed to ascertain the diameters and thicknesses of 10 tablets selected at random. The mean and standard deviation (SD) of these measurements were subsequently calculated.

Determination of weight uniformity

An analytical top-loading balance was used to weigh ten randomly chosen tablets from each batch. The average weight of the 10 tablets was used to determine the weight variation of each brand. The SD for each batch was also calculated.

Friability (FR) test

A selection of 10 tablets from each batch was taken and securely placed into a friabilator. The device was set to operate at a speed of 25 rpm for a duration of 4 min, during which the tablets fell through a distance of 6 inch with every rotation. After this process, any dust was removed from the tablets, and a final weight was recorded. The weight loss percentage was then calculated using the corresponding formula.

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

where, Wo is the weight of tablets before test, W is the weight of the tablet after subjecting it through the friabilator.

Crushing strength (CS)

The CS of the tablets was assessed at ambient conditions using a Monsanto tablet hardness tester, which performs diametrical compression. Each tablet was placed in between the tester's platen and an adjustable knob was gradually tightened until it touched the tablet. Sufficient pressure was applied to break the tablet. Only results from tablets that cleanly broke into two halves without any signs of lamination were considered. The final result was obtained by averaging the values from 10 such measurements.

Tensile strength (TS)

The prepared tablets batches of metronidazole were stored in a desiccator (containing silica gel) for roughly 24 h. Following that, a Monsanto tablet hardness tester was utilised to apply a load across the diameter of each tablet to determine the hardness at the point of crushing. The TS was then calculated using a specific formula from Olowosulu *et al.* (2015).

$$Ts = \frac{6.24F}{Dt} \qquad \text{(Equation 8)}$$

where, F is the crushing force in Kgf, D is the diameter of the tablet in mm and t is the thickness of the tablet in mm.

Disintegration test (DT)

The DT of the tablets was conducted using a testing apparatus filled with 0.1 M HCl and temperature-controlled at 37 ± 1°C. Six tablets from a single batch were tested simultaneously, with each tablet placed in a separate tube. The duration needed for each of the six tablets to disintegrate and move through the mesh was recorded. The average DT for each batch was then calculated.

Crushing strength-friability (CSFR) ratio

The CSFR ratio was calculated by dividing the CS by the FR value. This was carried out three times to ensure accuracy and consistency.

$$CSFR \text{ ratio} = CS/FR$$

CSFR ratio to DT

The CSFR/DT was calculated by dividing the CS by the product of FR and DT. This investigation was done three times for ensuring consistency and accuracy.

$$CSFR/DT \text{ ratio} = CS/FR*DT$$

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 nine serial dilutions were obtained. The dilutions were analysed 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 and the following linear regression equation was used to compute the concentration of the unknown samples. This investigation was repeated three times in order to ensure accuracy and consistency.

$$y = 0.0521x + 0.1826 \qquad \text{(Equation 9)}$$

correlation coefficient (R^2) = 0.9795.

Dissolution studies

The in vitro dissolution studies of the prepared tablets were carried out using a USP Apparatus I (Basket type) operating at a rotational speed of 100 rpm. The apparatus contained 900 mL of dissolution medium (0.1 N HCl), which was maintained at a consistent temperature of 37 ± 1°C. A total of 10 mL samples were taken out at pre-specified time intervals (1, 5, 10, 15, 20, 30) min and for each withdrawn sample, an equivalent volume of fresh dissolution medium was supplemented.

The withdrawn samples, after adequate dilution with 0.1 N HCl, were evaluated using a UV-spectrophotometer at a wavelength of 277.0 nm. The 0.1 N HCl was used as a control and the quantity of metronidazole released at each time point was measured. From these measurements, the percentage of drug release was calculated. This investigation was carried out three times to ensure accuracy and consistency of results.

Assay of metronidazole tablets

Twenty tablets from each batch were selected at random, weighed using an analytical balance and then pulverised into a powder using a ceramic mortar. A sample of 0.50 g from the powdered substance was weighed and dissolved in 200 mL of 0.1N HCl, then filtered. The filtered solution was further diluted with an additional 100 mL of the medium. The resulting solutions were assessed using a UV-spectrophotometer at 277.0 nm wavelength.

Statistical Analysis and Data Presentation

Each experiment was performed multiple times to confirm the reliability of the statistical analysis. The properties across varying data sets were compared using Analysis of Variance (ANOVA) via SPSS software. Differences were deemed substantial when *P*-values fell below 0.05. The collected data was then articulated as mean, SD and percentages in tables and illustrative figures.

RESULTS

The physicochemical properties of metronidazole granules formulated with different wet granulation binders are presented in Table 2. The granules prepared from all the binders vis; gelatine, acacia, PVP, maize starch were characterised by relatively low bulk densities 0.38, 0.40, 0.43 and 0.43 ranked as gelatine < acacia < PVP < maize starch, respectively. This indicates good granules. Similarly, the tapped densities were 0.42, 0.45, 0.46 and 0.49, respectively. The Hr and CI of granules of the various wet granulation binders can be ranked as PVP < gelatine < acacia < maize starch.

The FR of the various granules was found to be very good as indicated by the low angle of repose. The angle of repose of the various granules of the wet granulation binders ranged from 25.34° to 26.68°. The angle of repose can be ranked in the order PVP < acacia < gelatine < maize starch. This indicates a good flowability of the granules, thus further supporting the FR measurement which is ranked; acacia > maize starch > PVP > gelatine.

Also, low percentage of fines (< 2%) across all the granules of the various binders was observed as showed in Table 2 and Figure 1. The percentage fines can be ranked as gelatine < acacia < PVP < maize starch.

Table 3 draws the relationship between the mechanical properties (FR and CS) and DT of metronidazole tablets produced using various wet granulation binders. The low FR values have been observed to cause a greater increase in CSFR and CSFR/DT relationship.
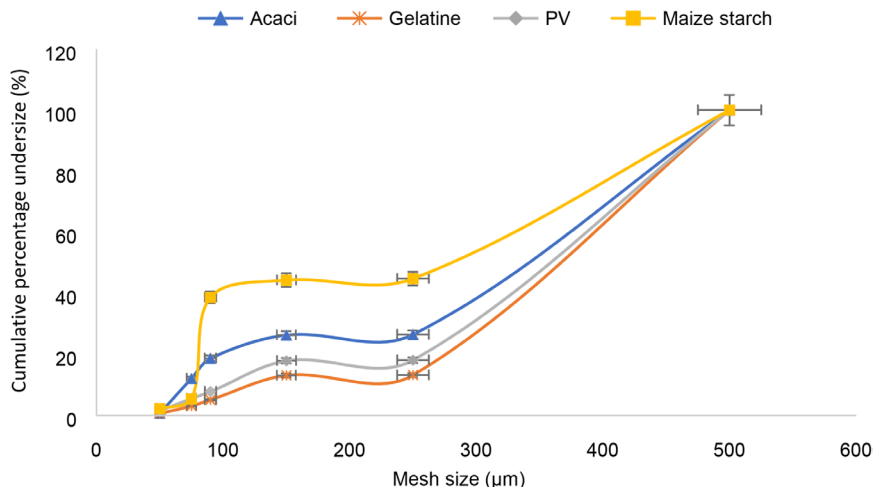
Figure 1: Cumulative percentage undersize against the particle size (mesh size) of the granules produced using four wet granulation binders (mean ± SD, *n* = 3).

From the test of FR results, it is evident that tablets produced with maize starch binder have failed FR assessment owing to its FR values > 1%. The result showed that good CS of the tablets and low FR values increases the CSFR indices. Hence, a good mechanical strength which was observed in tablets produced with acacia, gelatine and PVP. Amongst the three wet granulation binders that produce tablets of acceptable FR and high values of CSFR, only gelatine yielded a significantly (*P* < 0.05) high value of CSFR/DT. It can, then, be inferred that the wet granulation binder—gelatine have a superior balance between the mechanical strength and DT.

The DT of metronidazole tablets made using model wet granulation binders: acacia, gelatine, PVP and maize starch are as follows: 10.52 min, 11.05 min, 9.22 min and 6.20 min, respectively. All the DT values were within the official limits of 15 min.

Table 4 presents the release indicators for metronidazole tablet batches formulated with different binders (acacia, gelatine, PVP and maize starch). The values for dissolution time (td), time for 25% dissolution ($t_{25\%}$), time for 50% dissolution ($t_{50\%}$) and time for 70% dissolution ($t_{70\%}$) were provided. Gelatine (F2) exhibited a slightly longer td (11.05 min) compared to other binders but achieves the highest maximum release (103.83%). Acacia (F1), PVP (F3) and maize starch (F4) demonstrated varying dissolution profiles with differences in td and maximum release percentages as observed in Figure 2.

Table 2: Physicochemical properties of metronidazole granules produced using various binders via wet granulation method (mean ± SD).

Parameters	Metronidazole powder	Acacia (F1)	Gelatine (F2)	PVP (F3)	Maize starch (F4)
Bulk density (g/mL), n = 10	0.673 ± 0.08	0.40 ± 0.01	0.38 ± 0.01	0.43 ± 0.01	0.43 ± 0.01
Tapped density (g/mL), n = 10	0.842 ± 0.13	0.45 ± 0.01	0.42 ± 0.01	0.46 ± 0.01	0.49 ± 0.01
Flow rate (g/sec), n = 3	3.45 ± 0.07	3.89 ± 0.05	3.43 ± 0.03	3.53 ± 0.06	3.78 ± 0.08
Angle of repose, n = 3	39.92 ± 1.85	25.57 ± 0.66	25.72 ± 0.26	25.34 ± 1.35	26.68 ± 0.71
Carr's index, n = 3	20.13 ± 0.28	11.24 ± 0.18	9.64 ± 0.17	6.60 ± 0.11	12.37 ± 0.18
Hausner's ratio, n = 3	1.26 ± 0.01	1.13 ± 0.00	1.11 ± 0.00	1.07 ± 0.00	1.14 ± 0.00
Mean particle size (μm)	69.72	394.30	450.11	427.39	318.40
Fines (%)	45.05	0.9	0.4	0.7	1.5

Notes: ± = standard deviation, n = replicates.

Table 3: Comparative analysis of tablet properties produced with different binders (mean ± SD).

Binders	Weight (g)	Diameter (mm)	Thickness (mm)	CS (kgf)	FR (%)	DT (min)	CSFR	CSFR/DT	Ts (MN/m²)	Assay (%)
Acacia (F1)	504.00 ± 5.48	12.04 ± 0.02	3.12 ± 0.04	5.50 ± 0.87	0.80	10.52 ± 1.23	6.88	0.65	0.91	94.32
Gelatine (F2)	510.00 ± 18.71	12.05 ± 0.03	3.13 ± 0.03	9.80 ± 1.10	0.40	11.05 ± 3.42	24.50	2.22	1.58	102.37
PVP (F3)	502.00 ± 8.37	12.04 ± 0.02	3.12 ± 0.02	4.70 ± 0.76	0.40	9.22 ± 1.81	11.75	1.27	0.77	99.12
Maize starch (F4)	498.00 ± 8.37	12.02 ± 0.04	3.12 ± 0.04	6.60 ± 1.14	1.19	6.20 ± 2.01	5.55	0.89	1.06	95.66

Notes: ± = standard deviation (SD), CS = crushing strength, FR = friability, DT = disintegration time, tensile strength.

Table 4: Release indicators of metronidazole tablet batches prepared using different binders.

Binders	t_d (min)	$t_{25\%}$ (min)	$t_{50\%}$ (min)	$t_{70\%}$ (min)	Maximum release (%)
Acacia (F1)	10.52	4.23	8.20	11.00	99.37
Gelatine (F2)	11.05	3.27	8.35	13.25	103.83
PVP (F3)	9.22	3.26	7.11	10.41	101.13
Maize starch (F4)	6.20	0.52	4.00	6.53	100.04

Notes: t_d = dissolution time; $t_{25\%}$ = the time at which 25% of the drug has dissolved in the dissolution medium; $t_{50\%}$ = the time at which 50% of the drug has dissolved in the dissolution medium; $t_{70\%}$ = the time at which 70% of the drug has dissolved in the dissolution medium.
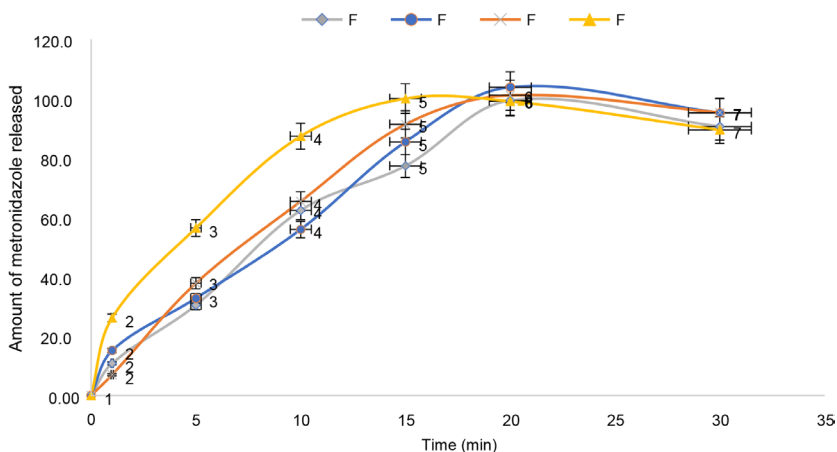

Figure 2: Dissolution profile of metronidazole tablet batches prepared using different binders (mean ± SD, *n* = 3).

DISCUSSION

Micromeritic properties of the pure metronidazole was studied in terms of Db, Dt, CI, Hr and angle of repose, as contained in Table 2. The high values of CI and Hr of the pure metronidazole can be attributed to the inherent high cohesive nature of the drug which hindered its flowability. These could also be related to the particle size, shape and particle distribution of the drug because these are factors that affect the flow of powder material (Wells and Aulton 2007).

This study elucidates various binding agents used in producing metronidazole tablets through wet granulation. In tablet formulations, excipients are purposefully included alongside the active ingredient to improve the drugs stability and therapeutic efficacy. Such enhancements include better drug absorption and reduced viscosity (Das and Das 2019).

The binders (acacia, gelatine, PVP and maize starch) were utilised to optimise and obtain the ideal binder concentration for an immediate release tablet formulation. The micromeritic properties of the granules produced at the different binder concentrations were assessed in terms of Db, Dt, CI, Hr and angle of repose. The resulting granules

demonstrated consistently low bulk and Dt characteristic of free-flowing granules. Indeed, the Db and Dt densities of a powder significantly influence its flowability and compressibility (Aulton 2013). These qualities can be further quantified using CI and Hr (Carr 1965; Hausner 1967).

Tablets produced with varying binder concentrations (1%–5%) underwent mechanical evaluation to identify the concentration optimal for a robust, immediate-release metronidazole tablet. The mechanical properties denote the tablet's ability at 3% concentration across all the binders exhibiting ability to withstand potential stresses during its lifecycle, from manufacturing to consumption. Thus, on this basis, this concentration of binder was adopted for continued study.

Table 2 elucidates the physico-mechanical properties of the granules formed with different binders. Variations in bulk densities can be attributed to distinct particle behaviours and packing characteristics, affecting granule interactions and consequently, differing Db (Haritha 2017). Typically, Dt exceeds Db due to a reduction in void spaces, leading to a denser powder bed (Staniforth and Aulton 2007). Low Db granules exhibit better flow properties, with FR correlating with the angle of repose. The angle of repose serves as a measure for the flowability of a granular substance, affected by its cohesive nature. Cohesive powders result in higher angles, while non-cohesive powders lead to lower angles. Angles greater than 50° typically signify poor flow, while those close to 25° reflect excellent flow properties (Olowosulu *et al*. 2015; Apeji *et al*. 2022).

Higher Db result in lower die fill volumes, a principle further demonstrated in Table 2, where all granules exhibited lower Db and Dt, implying a higher die fill volume (Wells and Aulton 2007). Both CI and Hr relates compressibility and flowability to Db and Dt (Carr 1965; Hausner 1967). Improved flowability in the prepared granules stemmed from reduced interparticle friction due to their shape and size (Ezegbe *et al.* 2023).

A meaningful statistical difference in mean particle size was noted ($P < 0.05$), with over a four-fold increase in the average diameter of granules compared to pure drug particles, indicating impact of granulation and hence, particle growth. Generally, particles larger than 250 µm flow freely, while sizes under 100 µm can cause cohesion and flow issues. Extremely cohesive powders with sizes under 10 µm often resist gravitational flow (Staniforth and Aulton 2007).

The powder's flow properties during production are indicative of the final product's quality, specifically in weight and content uniformity (Prescott and Barnum 2008). All the tablet batches produced using the different binders met the official accepted limit of uniformity of weight (mean ± 5%) according to the United States Pharmacopoeia (USP) (2011) and British Pharmacopoeia (BP) (2010).

CS of a tablet is an important parameter, reflecting the ease of tablet handling as well as its compressional behaviour. The values of CS for the tablet batches produced, from the different binders ranges between 5.50 Kgf–9.80 Kgf (Table 3) have passed the CS test. The CS of 4 Kgf–15 Kgf (40 N–150 N) is recommended satisfactory for tablets (British Pharmacopoeia 2010). The good CS obtained is a reflection of good binding agent, optimal binder concentration, good method of binder incorporation, adequately dried granules and optimal compression force. The CS of a tablet serves as an indicator of its capacity to endure mechanical stresses during handling, manufacturing, packaging and shipping (Ayorinde, Odeniyi and Itiola 2012). This factor plays a vital role in evaluating the tablet's resistance to damage such as chipping, abrasion or fracturing while being stored, transported or handled prior to usage. Notably, the impressive CS displayed by the tablets made with gelatine binder (F2) could be attributed to an increased cohesive interaction leading to improved binding (Alawode, Eselem-Bungu and Amiandamhen 2020).

FR assesses a tablet's resistance to mechanical wear and tear, such as abrasions, chipping and breakage (Eraga, Arhewoh and Uhumwangho 2015). Typically, a tablet's quality is deemed acceptable if the FR value does not exceed 1% (British Pharmacopeia 2010). Failure to achieve this standard might be attributed to insufficient binder concentration, which leads to weak inter-particle bonding or the application of inadequate compression pressure during the tablet-making process. In this study, it was noted that only the batch of tablets formulated with maize starch as a binder (F4) did not meet the standards FR criteria. There's an inverse correlation between FR and tablet CS.

The TS was determined using Equation 8. The higher TS values (1.58) in the formulations F2, which were created using gelatine binder (as shown in Table 3), point to a robust bonding between the particles of the granules. This signifies an enhancement in the mechanical properties of the tablets during handling (Haritha 2017). The increase in TS in the compact is attributed to the formation of more crystal bridges due to drug-drug molecule interactions. Additionally, synergistic interactions between binder molecules, drug molecules, and the combination of both contributed to a further increase in the tablet's TS (Noor *et al.* 2017).

DT is critical for drug dissolution and might determine drug absorption rates. Tablet disintegration is characterised as the collective result of adhesive and disintegrating forces that come into play when the tablet encounters an aqueous environment (Adebayo and Itiola 1998). According to the BP, the maximum DT for uncoated tablets should be 15 min (British Pharmacopoeia 2010). Tablets formulated with the four different wet granulation binders were characterised by DT < 15 min. The prompt disintegration seen in all the batch formulations can be credited to the granulation process's capacity to enhance the solubility and dissolution of the formulations. This improvement leads to the quick absorption of water molecules into the tablet structure, resulting in the tablet's structural breakdown in the medium (Onyishi, Chime and Ugwu 2013).

The CSFR serves as an overall indicator of a tablet's resilience and robustness, acting as a valuable benchmark for evaluating tablet quality (Ayorinde, Odeniyi and Itiola 2012). Additionally, as reported by Alebiowu and Itiola (2003), a higher value of this index is indicative of a stronger tablet. The formulation batch containing gelatine as the binder had the highest value of 24.50 as contained in Table 3. This parameter shows the superior quality of gelatine as a suitable binder in the tablet formulation of metronidazole via wet granulation method.

Another metric introduced is the CSFR to DT ratio. This ratio, CSFR/DT, offers a more comprehensive measure of tablet quality by factoring in both strength and disintegration behaviours (Alebiowu and Itiola 2003). The ratio of CSFR to DT was employed to evaluate the disintegrating efficiency and robustness of metronidazole tablets, crafted using different binders through the wet granulation technique. There was a significant increase ($P < 0.05$) in the CSFR/DT ratio for gelatine (2.22) in formulation F2 compared to those made using maize starch (F4), acacia (F1) and PVP (F3) (refer Table 3). A higher CSFR/DT ratio suggests an optimal balance between the tablet's binding and disintegration characteristics (Ayorinde Odeniyi and Itiola 2012). This suggests that for the creation of high-quality metronidazole tablets with superior mechanical attributes, gelatine has demonstrated superior quality and emerges as the most suitable binder for immediate release tablet formulations.

The calibration curve for metronidazole established within a concentration range of 50 µg/mL to 0.781 µg/mL at a wavelength of 277.0 nm, established strong linearity, reflected by a regression coefficient of 0.9795 (r^2 value). The drug dissolution pattern, illustrated in Figure 2, revealed that all the tablet formulations displayed a comparable

release behaviour. Key metrics including DT and specific drug release indicators ($t_{25\%}$, $t_{50\%}$ and $t_{70\%}$) are detailed in Table 4.

Dissolution testing serves as an essential tool in assessing drug release from dosage forms, providing insight into the drug's release in the gastro-intestinal tract. A positive relationship was observed between the DT and dissolution rates. The tablet batches produced from the different wet granulation binders were subjected to dissolution studies to understand their pharmacokinetics and thereby bioavailability. The British Pharmacopoeia stipulates that for an immediate release formulation, not less than 70% of drug must be dissolved in 45 min (British Pharmacopoeia 2010). *In vitro* dissolution rate influences the solubility of a drug molecule within a tablet, which subsequently impacts *in vivo* absorption and bioavailability. Thus, *in vitro* dissolution study plays an important role in predicting the *in vivo* performance of tablet dosage forms (Alshehri *et al*. 2017).

The values $t_{25\%}$, $t_{50\%}$, and $t_{70\%}$ serve as practical markers for the beginning of drug's action, indicating its release from the dosage form (Khalid *et al.* 2018). These values clearly demonstrated that 75% of the active ingredient was released from every formulation in under 45 min, aligning with the BP specifications for immediate-release tablets. All the tablets formulated with different binders have complied with the Pharmacopeial standard, which requires an 80% drug release from uncoated immediate-release tablets (United States Pharmacopoeia 2011).

CONCLUSION

Metronidazole tablets were successfully formulated using four different binders via the wet granulation technique, yielding tablets with optimal granular and mechanical attributes. Measurements for hardness, FR and DT all complied with established standards. The binder—gelatine at an optimised concentration of 3%, showcased superior performance. Tablets formulated with gelatine exhibited enhanced mechanical strength, suggesting its pre-eminence as the most suitable binder for immediate release metronidazole tablets. Furthermore, the *in vitro* dissolution profile of these tablets underscores their promising potential, reinforcing gelatine's pivotal role in achieving desirable drug release characteristics.

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