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Formulation and Evaluation of Metronidazole Tablets using Co-processed *Caesalpinia* Gum and Annealed Maize Starch as a Direct Compression Excipient

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Abstract:
Background: *The shortcomings of existing excipients such as low dilution potential and poor die filling as a result of poor flow properties have been a problem in direct compression tableting. Direct compression excipients are specially processed to obtain almost spherical shaped powders. Existing direct compression excipients are very costly; as a result, there is need for the search for such excipient from local sources. Hence, this study was designed to assess the suitability of co-processed caesalpinia gum and annealed maize starch as a direct compression excipient.*
Materials and Methods: *Caesalpinia gum was co-processed with the annealed maize starch at ratio*1.25:98.75 *in a co-solvent system consisting of acetone and distilled water (2:1). The physical properties of the co-processed excipient were determined using standard methods. The flow properties of microcrystalline cellulose PH 101 were determined using standard methods. The co-processed excipient and microcrystalline cellulose PH 101 were used in the formulation of metronidazole tablets and the tablet properties were evaluated.*
Results: *FTIR spectral study showed that there was no chemical interaction between the constituents of the co-processed excipient, and between the co-processed excipient and the model drug. The dilution potential of the co-processed excipient with respect to metronidazole was 70:30 with a tensile strength of 0.65 MN/m^2 respectively. The tablet properties of metronidazole tablets formulated with the novel co-processed excipient (1.25:98.75) met the requirements in the British Pharmacopoeia. The dissolution studies showed that the co-processed excipient (1.25:98.75) gave better results than microcrystalline cellulose.*
Conclusion: *The novel co-processed excipient performed better than microcrystalline cellulose PH 101 as a filler-binder-disintegrant in the investigated formulations. It can serve as a locally sourced alternative to costly commercially available directly compressible excipients such as microcrystalline cellulose PH 101 for immediate release tablets.*
Keywords: *Caesalpinia gum, annealed maize starch, co-processed excipient, metronidazole, direct compression*

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I. Introduction

Tablets are the most commonly used solid pharmaceutical dosage form[1,2]. Tablets comprise of a mixture of active pharmaceutical ingredients and excipients, usually in powder form, compressed from a powder into a solid dosage form.

Direct compression is the process by which tablets are prepared directly from the powder blends of active ingredients and suitable excipients without a preliminary granulation step [2,3,4]. In recent years, most of the pharmaceutical manufacturing industries opt for direct compression tableting due to the fact that it requires fewer processing steps, elimination of heat and moisture, economy, and improved drug stability compared with wet granulation technique. Nevertheless, direct compression is more prone to segregation due to the difference in density of the active pharmaceutical ingredients and excipients. Most of the directly compressible materials can accommodate only 30-40 % of the poorly compressible active ingredients and are relatively costly [2,4,5,6]. Consequently, there is need to develop affordable excipients. In addition to the development of directly compressible excipients by the modification of a single substance, co-processing of two or more components is used to prepare directly compressible excipients. Co-processed excipients are combinations of two or more

excipients that possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients.

The co-processed excipients are introduced to achieve better flow, better dilution potential, and reduced fill weight variation in comparison with a single substance or the physical admixture. Several of these excipients are commercially available. Examples include Cellactose® (lactose-cellulose), Avicel® CE-15 (microcrystalline cellulose and guar gum), Ludipress® (lactose, polyvinylpyrrolidone, and crosspovidone), and Prosolv® (microcrystalline cellulose and silicon dioxide)[4,7,8].

The search for excipients for pharmaceutical formulations is an ongoing one. It is most appropriate to find a local substitute for directly compressible excipients. There has been a radical change in tablet manufacturing due to the introduction of processes such as direct compression method and use of high-speed machines. The shortcomings of existing excipients such as low dilution potential and poor die filling as a result of poor flow properties have been challenges in direct compression tabletting. Single-component excipients such as gums and starches do not always provide the required performance to allow certain active pharmaceutical ingredients to be manufactured adequately[9,10]. In response to these deficiencies, it is necessary to co-process two excipients such as a gum and starch which is expected to possess performance advantages that cannot be achieved using a physical admixture of the same combination of these two excipients.

Nigeria has the natural resources for preparation of co-processed excipients for direct compression. Natural polymers are in abundance locally in Nigeria, and as a result co-processing two or more polymers will be of great advantage in direct compression tabletting process in the pharmaceutical companies. *Caesalpinia pulcherrima*plant (Family Caesalpiniaceae) is widely cultivated in Nigeria. The seed gum from this plant co-processed with starch is expected to possess performance advantages that cannot be achieved using a physical admixture of the same combination of these two excipients. If the research work is successful, this product would add to the current local content initiative of the Federal Government of Nigeria.

II. Materials and Methods

Materials

Maize starch (Sigma-Aldrich, France), metronidazole (Fluka, China), magnesium stearate (Aldrich, Germany), talc (Sterling Organics, England), potassium bromide (Guangdong GuanghuaSci-Tech Co. Ltd,China), hydrochloric acid (BDH laboratory supplies, England), microcrystalline cellulose PH 101 (AcrosOrganics,USA), caesalpinia gum locally processed from the fresh seeds of *Caesalpinia pulcherrima* plant (Family Caesalpiniaceae) in western region of Nigeria and authenticated by Ibhamesebhor G and Omomoh B.E, Botany Department, Obafemi Awolowo University, Ile-Ife (authentication no IFE 17226).

Methods

Preparation of co-processed *Caesalpinia* gum-annealed maize starch

The method of Chandile *et al*[11] was adapted. Homogeneous mixture of *Caesalpinia* gum and annealed maize starch of ratio 1.25: 98.75 was added 10 mL solution of acetone and distilled water in ratio 2:1 respectively. The content of the beaker was mixed thoroughly and stirring was continued to form a wet coherent mass which was passed through a 500 µm mesh sieve. The wet granules were dried in an oven drier (Gallenkhamp BS, England) at 50 ^{o}C for 1 h. The dried granules were then size-reduced by passing it through 250 µm mesh sieve and stored in an airtight bottle.

Physical properties of Excipients

The particle size and shape were carried out using microscopy method. The angle repose was determined using fixed height method. The bulk and tapped density were determined using the measuring cylinder.

Compatibility study

Fourier transform infrared spectra of *Caesalpinia* gum, annealed maize starch, *Caesalpinia* gum-annealed maize starch co-processed excipient (1.25:98.75) metronidazole as well as mixtures of the co-processed excipient with metronidazole (1:1) were obtained using Fourier transform infrared spectrophotometer (ThermoFisher Scientific, Nicolet iS5, USA). Thin pellets containing the material and potassium bromide in ratio 1:50 were used and the spectra were obtained at room temperature as an average of 32 scans in the 500 to 4000 cm^{-1} range with a spectral resolution of 6 cm^{-1}.

Determination of dilution potential of co-processed excipient

Binary mixtures of the co-processed excipients and metronidazole were prepared as compacts in ratios (60:40, 70:30, 80: 20) at compression pressure of 273 MNm^{-2}. A single punch hydraulic hand press (Carver Laboratory Press, Model C, USA) which was fitted with 8.4 mm die and flat-faced punches lubricated with a 1 % w/v dispersion of magnesium stearate and talc in acetone was used to make the compacts. The target weight

of the compact was 250 mg. The compacts were stored for at least 24 h to allow for elastic recovery and hardening, after which they were analyzed. The crushing strength, diameter and the thickness of the compacts were determined. The tensile strength of the group of three tablets was calculated.

Preparation of metronidazole tablets by direct compression

Table 1 shows the formula used for preparing metronidazole tablets. The powder mix of the excipents and drug individually passed through 250 µm aperture sieve, without lubricants were blended for 4 min in a closed jar using doubling up technique. The sieved lubricants (250 µm aperture sieve) were added and tumbled for 30 secs. The powder mix was compressed into tablets on a single punch hydraulic press (Carver press, USA) at compression pressure of 273 MNm^{-2}. The target weight was 689.66 mg for metronidazole tablets containing the co-processed excipient (1.25:98.75) using 11.7 mm die and flat-faced punch and die. Microcrystalline cellulose was used as basis for comparison. The tablets were evaluated for weight uniformity, thickness, friability, crushing strength, and disintegration time.

Table 1: Formula for preparation of metronidazole tablet directly compressed with the excipients

Ingredients (mg)	F1	F2
Metronidazole	200	200
Co-processed excipient	482.76	-
Microcrystalline cellulose	-	482.76
Talc	3.45	3.45
Magnesium stearate	3.45	3.45
Target weight	689.66	689.66

Evaluation of Tablet Properties

Tablet weight

Twenty tablets randomly selected from each batch of the tablets containing metronidazole were weighed as a whole and individually, after which the average tablet weight was determined. The percentage coefficient of variation was calculated from the equation below.

$$\% \text{ Coefficient of variation} = \frac{\text{Standard deviation}}{\text{Mean weight}} \text{ X } 100 \qquad (3)$$

Tablet Crushing Strength

The crushing strength of ten tablets selected from each batch of metronidazole tablets was carried out Using Monsato hardness tester (Monsato, England). The force at which the tablet fractured was read as indicated by a pointer that moved along the gauge on the barrel of the tester. The average value was calculated.

Friability Test

The friability of ten tablets from each batch of metronidazole tablets was determined using Erweka Friabilator (TA3R Erweka, Germany) at a rotation speed of 25 rpm for 4 min. The tablets were introduced into the friabilator after taking the initial weight of the tablets. The tablets were removed at the end of 100 rpm, dusted and re-weighed. The average weight was calculated. The per cent friability was then calculated using the equation below:

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Initial weight}} \text{X} 100 \qquad (4)$$

Disintegration time

Disintegration test using Manesty disintegration apparatus (Manesty Machines Limited, Liverpool, UK) was performed on metronidazole tablets at 37 ± 1 ^{o}C in 200 mL of distilled water. The time taken for each tablet to disintegrate and pass through the mesh was noted. The average of the disintegration time for six tablets was obtained.

Total drug content

The quantity of active ingredient in each tablet formulation was determined spectrophotometrically. Five tablets selected from each batch of the tablet were crushed in a mortar. The powdered drug equivalent to weight of one tablet was weighed, triturated with 0.1 N HCl and transferred into a 1000 mL volumetric flask. The volume was made up to 1000 mL with 0.1 N HCl and then shaken. Some quantity of the mixture was filtered through Whatman number 1 filter paper. One millilitre of the filtrate was diluted with 9 mL of distilled water

before analyzing spectrophotometrically. The absorbance of the filtrate was determined spectrophtometrically at 277 nm for metronidazole and the average drug content per tablet was calculated.

Dissolution studies of tablets

Dissolution studies were carried out on each batch of metronidazole tablets using Erweka rotating basket dissolution apparatus (Erweka, GmbH, Germany). The dissolution medium used was 0.1 N HCl. One thousand millilitres of the dissolution medium was used during each study. The rotation speed was 50 rpm and the temperature was maintained at 37 ± 1 ^{o}C. In each case, one tablet taken from each batch was placed in the basket and then lowered into the vessel containing 1000 mL of the dissolution medium. Five millilitres of each sample was withdrawn at intervals of 5 min for 45 min. The initial volume of the vessel was maintained by replacing with 5 mL of the dissolution medium, maintained at 37 ± 1^{o}C after each sampling. This was filtered through a Whatman number 1 filter paper. One millilitre of the filtrate was diluted with 9 mL of distilled water before analyzing spectrophotometrically. The samples containing metronidazole were analysed spectrophotometrically at 277 nm respectively to determine the percentage drug released. The experiment was performed in triplicate for each batch and the average was taken. The percentage drug released was calculated from the formula:

$$\% \text{ Drug release} = \frac{\text{Concentration of drug in the withdrawn sample at a given time}}{\text{Maximum concentration}} \text{x } 100 \qquad (5)$$

Statistical Analysis

Analysis of variance (ANOVA) was used to analyze the results obtained for the dissolution studies using Statistical Package for the Social Sciences (SPSS) software. This was used to determine if there are any statistically significant differences between the means of three groups.

III. Results and Discussion

The physical properties of co-processed excipient containing *Caesalpinia* gum and annealed maize starch at ratio 1.25:98.75 respectively and that of microcrystalline cellulose are presented in Table 1 [12].

Table 3: Physical properties of excipients[12]

Property	Co-processed Excipient (1.25:98.75)	Microcrystalline Cellulose
Angle of repose (^{o})	40.99±1.66	42.69±2.65
Bulk density (g/cm^3)	0.52±0.20	0.37± 0.15
Tapped density (g/cm^3)	0.64±0.12	0.49±0.20
Particle density (g/cm^3)	1.55±0.05	1.51±0.04
Carr's index	36.66	23.54
Hausner ratio	1.24	1.33

Fourier transform infrared spectra of the excipients and that of the mixture of the co-processed excipient with the metronidazole (1:1) are presented in Figures 1 to 5. It was observed that the prominent peaks of annealed maize starch at 2930, 2359, 1643, and 1018 cm^{-1} were present in the co-processed excipient containing *Caesalpinia* gum and annealed maize starch. It was also found that the characteristic peaks of *Caesalpinia* gum at 2359, 1642 and 1025 were present in the co-processed excipient. It was also observed that the peaks reflected in the Fourier transform infrared spectra of the drug, that is, metronidazole were characteristic to the drug. The Fourier transform infrared spectral study showed that there was no chemical interaction between the constituents of the co-processed excipient, that is, *Caesalpinia* gum and annealed maize starch due to the fact that the prominent peaks were retained after co-processing. The absence of any chemical change is an essential property desirable for co-processed excipient [12]. It was also observed that the peaks reflected in the Fourier transform infrared spectra of the drug, that is, metronidazole were characteristic to the drug. These peaks were also found in the physical mixtures containing the drug and the co-processed excipient (1:1). Thus, indicating that the Fourier transform infrared spectral study reflected no chemical interaction between the co-processed excipient and due to the fact that the characteristic peaks of the drug as well as that of the co-processed excipient were retained. Consequently, the co-processed excipient could be used in the formulation of directly compressible tablets containing metronidazole.

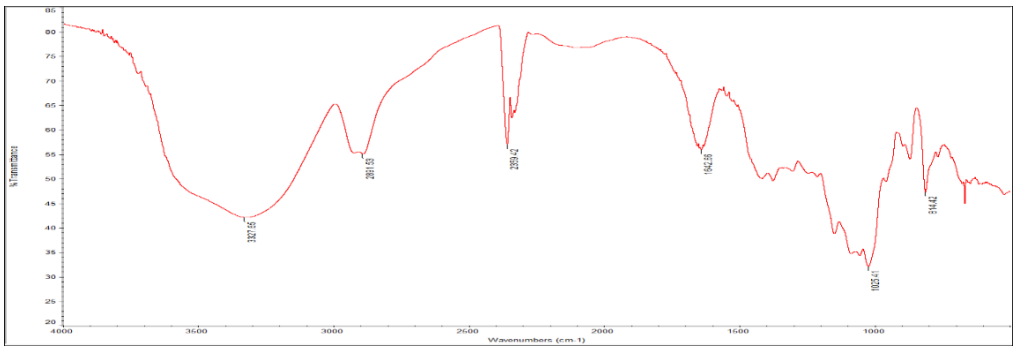

Figure 1: Fourier transform infrared spectrum of dried powder of *Caesalpinia* gum

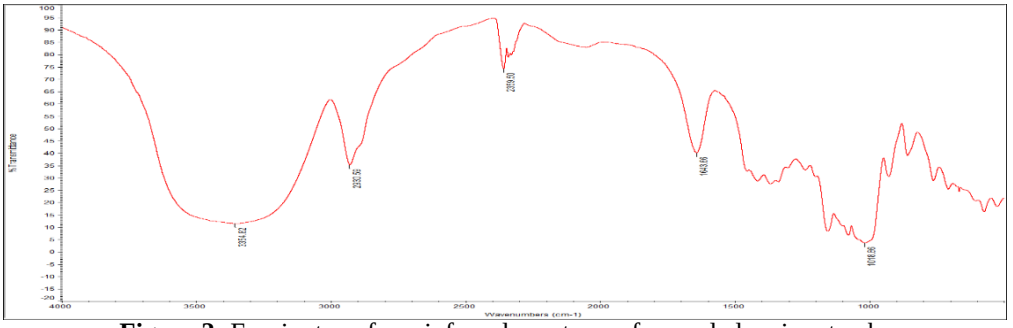

Figure 2: Fourier transform infrared spectrum of annealed maize starch

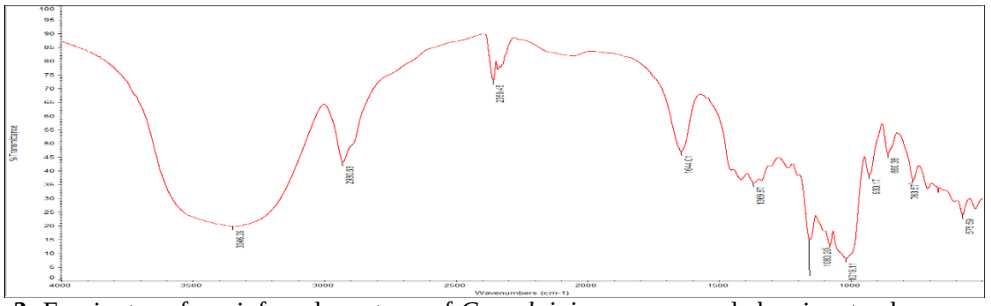

Figure 3: Fourier transform infrared spectrum of *Caesalpinia* gum – annealed maize starch co-processed excipient (1.25:98.75)

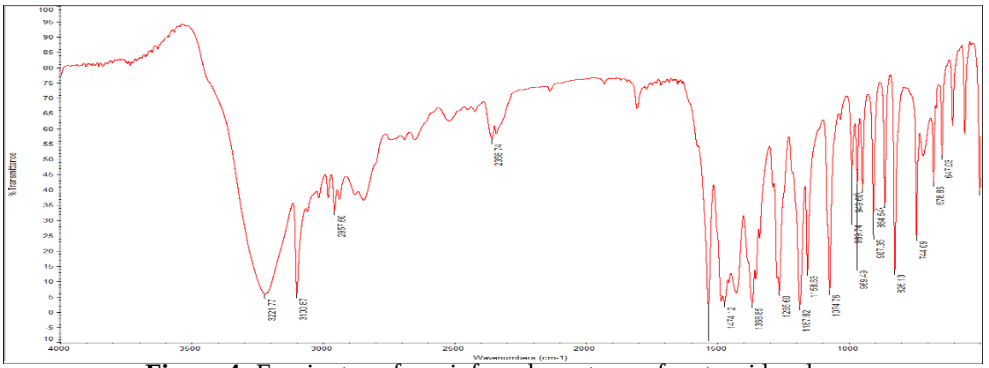

Figure 4: Fourier transform infrared spectrum of metronidazole

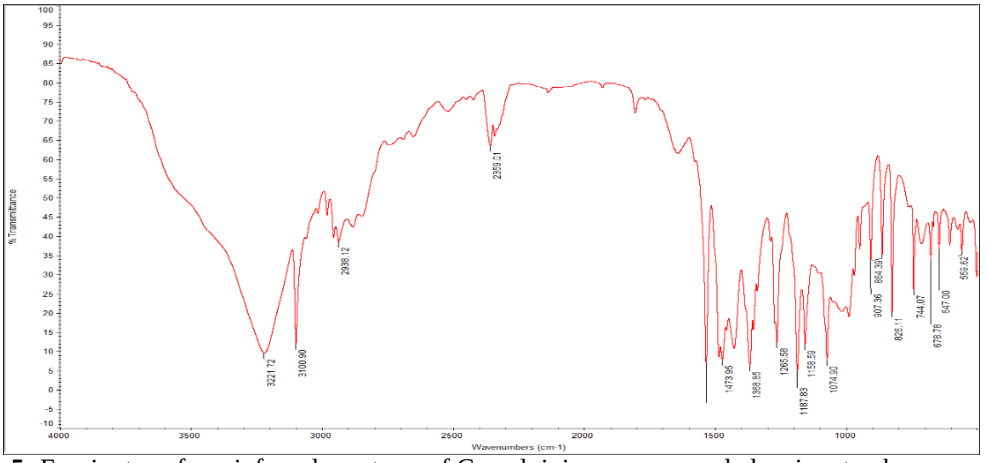

Figure 5: Fourier transform infrared spectrum of Caesalpinia gum – annealed maize starch co-processed excipient and metronidazole (1:1)

Dilution Potential of Co-processed Excipient

Dilution potential is an important property of excipient for direct compression. Dilution potential reflects the amount of an active ingredient that can be satisfactorily compressed into tablets with the given directly compressible excipient. A directly compressible excipient should have high dilution potential so that the final dosage form has a minimum possible weight. Generally, the more the drug that can be added to an excipient, the higher the dilution potential [4,10,13].

Table 2 reflects the diametrical crushing of tablets made from binary mixtures of the excipients and ascorbic acid. Generally, it was observed that the tensile strength of the tablets increased as the ratio of the excipient increased relative to the drug. Ascorbic acid or metronidazole tablets produced with the novel co-processed excipient yielded reasonable tensile strength at a dilution potential of 70:30 (excipient: drug). This indicates that up to 30 % of ascorbic acid, a low-dose drug and metronidazole, medium-dose drug could be satisfactorily compressed into tablets with the co-processed excipient. This percentage is within the range (30-40%) of established result in the literatures [4,13,14].

Table 2: Tensile strength of compacts of binary mixtures of the co-processed excipient and drug

Tensile strength (MNm^{-2})	Excipients : Drug 60:40	70:30	80:20	100:0
Metronidazole	0.56±0.51	0.65±0.12	0.95±0.27	1.12±1.04

Physical properties of metronidazole tablets

The results of the physical properties of metronidazole tablets containing the co-processed excipient (1.25:98.75) or microcrystalline cellulose are shown in Table 3. Low values of percent coefficient of tablet weight variation were obtained for the batches indicating good flow of powder mix. On the basis of weight uniformity and percent drug content of metronidazole tablets containing co-processed excipient (1.25:98.75) and that containing microcrystalline cellulose, it can be concluded that the powder blends flowed well. The result showed that the percent drug content of metronidazole tablets formulated with co-processed excipient (1.25:98.75) was higher than that of metronidazole in the tablets. This indicates good flow of the powder mix. Metronidazole tablets containing the co-processed excipient (1.25:98.75) reflected good crushing strength. It was observed that for metronidazole tablets containing microcrystalline cellulose, crushing strength could not be obtained due to the fact that it did not break even at 137.29 N. The low friability of tablets from each batch is in conformity with the crushing strength of the tablets. This is expected, due to the fact that the harder the tablet, the less likely it is for the tablet to chip, cap or break. Hence, the tablets will be able to withstand abrasion, friction and shock during packaging, handling, shipping [15,16]. The harder the tablet the more prolong is the disintegration time. Also, the hard core of the tablet will delay the ingress of the dissolution medium thus the rate of release of the drug into the dissolution medium will be slow.

Metronidazole tablets formulated with co-processed excipient (1.25:98.75) gave disintegration time of 2.25 min. This is in conformity with the pharmacopoeia requirement for immediate release tablets [1]. But the tablets formulated with microcrystalline cellulose did not meet up with the official requirement for immediate release tablets due to the fact that the tablet did not disintegrate within 15 min. The disintegration time of the tablets formulated with microcrystalline cellulose was prolonged. This may be attributed to the hardness of the

tablets. These tablets exhibited hardness values of more than 137 N, whereas that containing the co-processed excipient was 52.27N. The harder the tablet, the less pores available for ingress of the disintegration fluid. This may be responsible for the long disintegration time. The co-processed excipient compared well with microcrystalline cellulose as a directly compressible excipient in the formulation of immediate release tablets.

Table 3: Physical Properties of Metronidazole 200 mg Tablets

Tablet properties	Co-processed Excipient (1.25:98.75)	Microcrystalline cellulose
Weight uniformity (mg) (n = 20)	660.50±2.17	666.00±1.91
Crushing strength (N) (n = 10)	52.27±0.56	> 137.29±0.00
Thickness (mm) (n = 10)	4.59±0.03	4.49±0.88
Friability (%) (n = 10)	0.79±0.00	0.20±0.00
Disintegration time (min) (n = 6)	2.25±0.09	>15±0.00
Drug content (%)	101.20	90.64

Values are Mean ± S.D, except for average weight where values are Mean ± % coefficient of variation

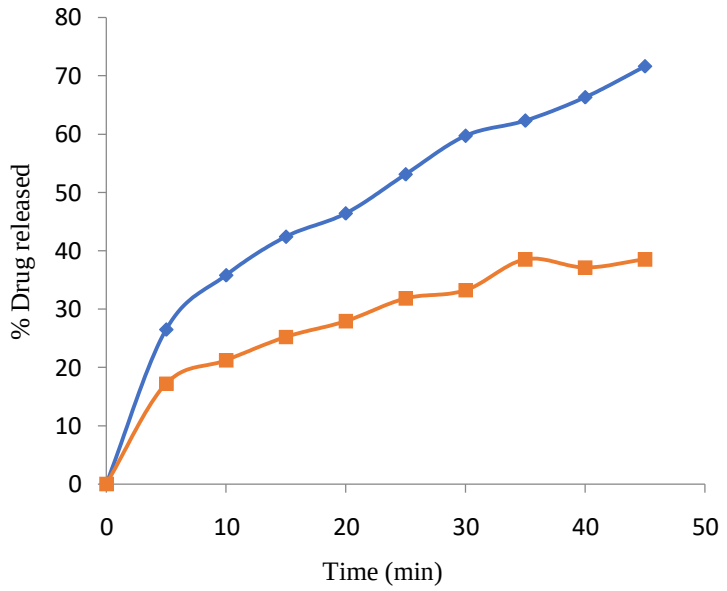

Figure 6: Dissolution Profile of Metronidazole Tablets made from Directly Compressible Excipients

Table 4: Dissolution Parameters of Metronidazole 200 mg Tablets

Parameters	Co-processed Excipient (1.25:98.75)	Microcrystalline cellulose
$T_{50\ \%}$(min)	23.00	-
$T_{70\ \%}$(min)	43.50	-
$T_{90\ \%}$ (min)	-	-
Drug released at 45 min (%)	71.60	38.50

KEY: - means no drug was released

Dissolution studies of metronidazole tablets made from directly compressible excipients

The dissolution parameters in Table 4 showed that the $T_{50\ \%}$ as well as $T_{70\ \%}$ for metronidazole tablets formulated with co-processed excipient (1.25:98.75) was 23.00 and 43.50 min respectively, while none was obtained at $T_{90\ \%}$. Metronidazole tablets containing microcrystalline cellulose reflected no $T_{50\ \%}$, $T_{70\ \%}$, and $T_{90\ \%}$. This may be due to the delay in release of the drug into the dissolution medium as a result of very high crushing strength of the tablets. The percent drug release at 45 min was found to be 71.60 and 38.50 % ($p < 0.05$) for metronidazole tablets containing the co-processed excipient and microcrystalline cellulose respectively. Even though the tablets were hard, they were not impervious to water. Microcrystalline cellulose is a hydrophilic excipient. As a result, it will not hinder the dissolution of drugs but metronidazole is poorly soluble in water thus the rate of release of the drug into the dissolution medium will be slow. The hard core of the tablet will also delay the ingress of the dissolution medium. The British Pharmacopoeia specifies that not less than 70% of the stated amount of active pharmaceutical ingredient should have been released at 45 min. This indicates that tablets containing the co-processed excipient (1.25:98.75) passed the dissolution test, while that containing microcrystalline cellulose failed the test. The dissolution studies showed that the co-processed excipient (1.25:98.75) compared well with the microcrystalline cellulose as a directly compressible excipient for immediate release tablet.

IV. Conclusion

It can be concluded that the co-processed excipient containing *caesalpinia* gum and annealed maize starch can serve as a multifunctional direct compression excipient in the formulation of metronidazole tablets due to the fact that it exhibited good flow properties, reasonable dilution potential, and excellent disintegration property.

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