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Formulation Development and Application of Natural Clay as Binder in Metronidazole Tablets

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Authors' contributions

This work was carried out in collaboration between all authors. Author ECI designed the study. Authors MAM, SAC, IVO, ALEU, BBK and MKM performed the statistical analysis, wrote the protocol and managed the analyses of the study and literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of the work is to study the binder properties of native clay in metronidazole tablets.
Study Design: Extraction of clay, formulation of tablets and *in vitro* evaluation of the formulations.
Place and Duration of Study: Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka 410001, Nigeria. The study was carried out from August 2011 to September 2012.
Methodology: Granules were prepared by wet granulation using 7.5, 10 and 12.5% w/w clay and gelatin as binders respectively. The pre-compression test was performed on the granules including

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the flow rate and the loose densities. The tablets were analysed by determining the weight, disintegration time, friability, hardness and drug content. *In vitro* drug release was also studied in 0.1 N HCl.

Results: Results show that drug content ranged from 195.3 ± 0.07 to 208.2 ± 0.03 mg in all the formulations and show that metronidazole was not degraded by the clay. Tablets hardness range of 2.38 ± 0.55 to 5.99 ± 0.10 kgf for tablets formulated with 12.5 and 10% w/w of clay, while tablets formulated with gelatin had hardness of 5.99 ± 0.10 and 5.69 ± 0.99 kgf. Tablets containing 7.5, 10 and 12.5.5% w/w of clay exhibited disintegration time of 1.4, 3.6 and 24 min while. About 80.3, 58.2 and 36.8% of metronidazole were released from C1, C2 and C3 tablets formulated with 7.5, 10 and 12.5% of clay as binder respectively at 5 min, while 42.1 and 10.1% were released from tablets formulated with 7.5 and 10% w/w of gelatin as binder. Tablets formulated with clay had higher release of drug than those formulated with gelatin ($p < 0.05$).

Conclusion: Therefore, clay could be used as binder in formulating metronidazole tablets.

Keywords: Native clay; clay minerals; metronidazole; tablets binder.

1. INTRODUCTION

Pharmaceutical excipients are inert materials which provide additional desirable characteristics to the dosage form. Although these additives are said to be inert, but they have great influence on stability, bioavailability and the process by which the dosage forms are prepared. Natural excipients are those excipients which are from natural origin. Natural excipients may be derived either from plant, e.g. acacia, starch, pectin, cissus gum, etc.; animals e.g. gelatin, egg yolk, wool fat; minerals e.g. bentonite, veegum, kaolin etc. In comparison to synthetic excipients, natural excipients are nontoxic, less expensive, compatible and widely available [1]. Binders from plant and animal origin have vast application in tableting; however, clays (minerals) have minimal utility in tableting hence the need to study its application as binder in tablets.

Clay refers to natural materials composed of very fine-grained minerals, with some plasticity when mixed with water and which harden on drying. It is, therefore, applicable to all small-sized particles, normally < 2 μm, found in soils, sediments or as alteration products of rocks, including, small quantities of other minerals and/or organic products such as quartz, feldspars, carbonates, sulphates, Fe and/or Al oxide and humus [2]. Clay mineral is a mineralogical term referring to part of a family (the phyllosilicates) consisting of hydrated aluminosilicates containing considerable amounts of Mg, K, Ca, Na and Fe and, occasionally, less common ions such as Ti, Mn, or Li. Despite their varied chemical composition, they can be classified into: Smectites, micas, kaolin, talcum, chlorites, vermiculites, fibrous and interstratified [2]. Some clay minerals used in pharmacy and cosmetics, include: kaolinite, talc, smectites and fibrous clays. Their specific function in any particular formulation depends on both their physical properties (particle size and shape, specific surface area, texture, color and brightness) and chemical features (surface chemistry and charge). The kaolin group is a family including kaolinite, halloysite, dickite and nacrite, of which kaolinite is the most common mineral [2-3].

Clay minerals and clays are used in Pharmaceutical Technology and Dermopharmacy as ideal excipients and as substances with suitable biological activity in the formulation of dosage forms that are either solid (tablets, capsules and powders), liquid (suspensions, emulsions) or semisolid (ointments, creams) [2]. These are used for either topical or oral administration [2,4-9], they can be used as abrasives, absorbents, adsorbents, anticaking agents, glidants, coating agents, opacifying agents, viscosity-increasing agents, emulsion stabilizers, binders, suspending agents, therapeutic agents, tablets and capsule diluents or lubricants [2].

The use of clay in achieving and maintaining human health have focused on the ancient practice of geophagy, which is the practice of eating earth materials containing clay minerals [10-12]. The purpose of geophagy is to elicit a healing response in humans through ingesting the easily available materials that may physically soothe an infected and inflamed gastrointestinal lining [13]. The ingestion of dried clay minerals or a clay suspension is commonly used as a source of dietary elements, as a detoxifying agent, and

Table 1. Composition of metronidazole tablets

Batch	Metronidazole (mg)	Maize starch (mg)	Magnesium stearate (mg)	Native clay (mg)	Gelatin (mg)	Lactose qs (mg)
C1	200	30.0	3.0	22.5	-	300
C2	200	30.0	3.0	37.0	-	300
C3	200	30.0	3.0	29.5	-	300
C4	200	30.0	3.0	-	22.5	300
C5	200	30.0	3.0	-	37.0	300

C1, C2 and C3 were formulated with 7.5, 10 and 12.5% w/w of clay as binder, while C4 and C5 were formulated with 7.5 and 10% w/w gelatin as binder

as an allopathic treatment of gastrointestinal illnesses and acute and chronic diarrhea [5,10]. In the acidic environment of the stomach, the clay minerals could bind to positively charged toxins and serve as detoxifying agents [10]. Over the counter pharmaceuticals that originally contained kaolinite, attapulgite, or clay-like substances (i.e. Kaopectate®) represent classic examples of the use of clay minerals by human populations to treat diarrhea and intestinal illnesses [14] and soothe gastrointestinal ailments [10]. Metronidazole is an antiprotozoal and anti parasitic agent that is very effective in the treatment of intestinal amoebiasis, trichomoniasis, giardiasis and many other parasitic diseases [15]. Hence the rational combination of this drug and natural clay should over synergistic effect in the treatment of diarrhea due to intestinal protozoa. Therefore, the aim of this work is to investigate the binder properties of native clay in metronidazole tablets.

2. MATERIALS AND METHODS

The materials used include: Metronidazole (Evans Pharmaceutical Ltd., England), hydrochloric acid, lactose (Merck, Germany), maize starch, lactose, gelatin, magnesium stearate (BDH, Poole, England), distilled water (Lion water, Nsukka, Nigeria) and native clay (purchased from Ogige Market, Nsukka, Nigeria in the month of February, 2012).

2.1 Purification of Clay

The native clay was powdered using mortar and pestle and passed through sieve number 10 (Turgens & Co., Germany) in order to remove stones and large particles. It was soaked in water for 24 h, sieved using sieve no. 40 to remove small stones and tiny particles. The clay was lather dried in a tray dryer (Manesty Ltd, Liverpool, England) at 40℃ and stored in an air tight container until used.

2.2 Formulation of Metronidazole Granules

Granules were prepared by wet granulation (aqueous granulation) using clay and gelatin as the binders respectively at 7.5, 10 and 12.5% w/w. Lactose (diluents) was mixed with the drug and the disintegrant maize starch in a tumbler mixer, the powder blend was moisten with the binder solution and passed through a 1.7 mm sieve. The granules were dried in a tray dryer at 60℃ for 1 h and dried screened using a 1.0 mm sieve. The lubricant (magnesium stearate) was mixed with the granules and compressed after pre-compression tests using a Manesty F3 Single Punch tabletting machine, using a 9.0 mm Punch and die.

2.3 Pre-compression Tests

2.3.1 Flow rate and angle of repose

The flow rate and angle of repose was determined by dynamic method [16]. The accurately weighed granules (20 g) were placed in a funnel. The height of the funnel was 11 cm from the bench. The granules were allowed to flow freely onto a surface and time of flow was noted. The height of the powder heap was measured with a cathetometer and the diameter of the powder cone was measured. Angle of repose was calculated using the following equation [16].

$$\text{Tan}\,\theta = \frac{h}{r} \quad (1)$$

where h and r are the height and radius of the powder cone. Flow rate was determined by dividing the mass of powder by the time of flow.

2.3.2 Compressibility index

To calculate the Carr's compressibility index, both bulk density (BD) and tapped density (TD) was determined as previously described [17-18]. A quantity of 20 g of powder from each batch, previously shaken to break any agglomerate, was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. BD and TD was calculated and used to calculate the Carr's index and Hausner's ratio.

The compressibility index of the granules was determined by Carr's compressibility index [6].

$$\text{Carr's index } (\%) = \frac{[(\text{TD} - \text{BD})\text{x } 100]}{\text{TD}} \qquad (2)$$

2.3.3 Hausner's ratio

Hausner's ratio was calculated by making use of bulk and tapped densities of powder samples,

$$\text{Hausner's ratio } = \frac{\text{TD}}{\text{BD}} \qquad (3)$$

2.4 Post Compression Tests

2.4.1 Uniformity of weight

Twenty tablets randomly from each batch were weighed together and individually using an electronic balance (Ohaus Adventurer, China) and the percentage deviations determined according to official methods [19].

2.4.2 Friability test

The test was performed using a friabilator (Erweka GmbH, Germany) rotated at 25 rpm for 4 min as stipulated in BP, 2009. The tablets were weighed before and after rotation and the percentage friability calculated using:

$$\text{Friability } = 1 - \frac{\text{W}_\text{f}}{\text{W}_\text{o}} \text{ x } 100 \qquad (4)$$

where W_o and W_f are the initial and final weights of the tablets respectively.

2.4.3 Determination of hardness

Ten tablets form each batch of the tablets was tested for the diametrical crushing strength using Monsanto hardness tester. The crushing strengths (hardness values) were determined (kgf) and compared with official specification [19].

2.4.4 Disintegration time test

The disintegration times of the tablets were determined in 0.I N hydrochloric acid maintained at 37.0 ± 1.0℃ using the disintegration tester (Erweka ZT 120 basket and rack assembly). Six tablets were selected at random from each batch and the machine operated until all the tablets disintegrated.

2.4.5 Drug content analysis

Twenty tablets were selected at random and carefully pulverized using mortar and pestle. An amount of the resulting powder equivalent to 200 mg of metronidazole was accurately weighed, dissolved in 20 ml of 0.1 N HCl in 100 ml volumetric flask and made up to volume with 0.1 N HCl. Thereafter, the mixture was filtered using Whatman no 1 filter paper and the resulting filtrate was diluted appropriately and the absorbance readings was determined using a spectrophotometer (Jenway 6305, UK) at predetermined wavelength of 320 nm. The concentration of metronidazole was calculated using Beer-Lamberts plot for metronidazole determined in 0.1 N HCl at 1.0 to 5.0 mg%. The test was performed in triplicates and the mean determined.

2.4.6 Dissolution test

Tablet dissolution test was carried out using the USP XXIII basket method (Erweka Germany Type: DT 600) operated at 100 r/min for 60 min in 900 ml of 0.1 N HCl maintained at 37±0.5℃ (United States Pharmacopoeia, 2004). At certain time intervals, 5 ml of dissolution fluid was withdrawn and replaced with an equal amount of fresh prepared 0.1 N HCl dissolution medium. Each withdrawn sample was filtered and the amount of metronidazole released was determined using the UV-Visible spectrophotometer (Jenway 6305, UK), at 320 nm and concentration calculated with reference to Beer-Lamberts plot.

2.5 Analysis of Mechanisms of Drug Release

In order to study the kinetics and drug release mechanisms, the *in vitro* data was applied to three kinetic models including first order, Higuchi and Korsmeyer-Peppas release models.

$$\text{Log } Q_0 - \text{Log } Q_t = k_1 t / 2.303 \quad (5)$$

$$Q = K_2 t^{1/2} \quad (6)$$

$$M_t/M_\infty = K_3 t^n \quad (7)$$

where Q is the amount of drug released or dissolved at time t, Q_0 is the initial concentration of drug, k_1, k_2 and k_3 are first-order, Higuchi and Korsmeyer-Peppas kinetic constant. M_t/M_∞ is fraction of drug released at time *t*, *n* is diffusion exponent and is indicator of the mechanism of transport of drug through the polymer [20-22]. The following plots were made: log cumulative of % drug remaining vs. time (first order kinetic model), cumulative % drug release vs. square root of time (Higuchi model) and the integral form of Higuchi, log cumulative % drug release vs. log time and log fraction of drug release versus log time (Korsmeyer-Peppas model).

2.6 Statistical Analysis

The results were subjected to one way ANOVA. Differences in mean were assessed using a two tailed student's T- test. $P < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Micromeritic Properties of Granules

The results of the micromeritic properties of metronidazole granules formulated with clay as the binder are shown in Table 2. The flow properties was analyzed by using two different methods; direct method of flow under gravity and an indirect method that uses densification and packing geometry. Bulk and tapped densities (loose density) was used as indirect method of assessing flowability and results are shown in Table 2. The results of the loose densities were applied to flow indices to determine the flowability of the granules. The results show that the metronidazole granules prepared with clay as binders (C1 - C3) have poor flowability which may be improved by addition of flow agent such as magnesium stearate. However, the granules formulated with the reference binder, gelatin had excellent flowability as shown in Table 2. Hausner's ratio ≤ 1.25 indicates good flow, while > 1.25 indicates poor flow [16]. Carr's index in the range of 5 – 16 indicates excellent flow, 12 – 16 shows good flow, 18 – 21 shows fair flow, 23 - 35 show a poorly flowing powder that can be improved using glidants, while values above 38 shows very poor flow [16]. Flow properties of granules is important in tableting and capsule filling because it affects the weight of the tablets, drug content and bioavailability of the drug.

3.2 Properties of Tablets

Results of the tablets weight uniformity test are shown in Table 3. It indicate that batches C1 and C4 formulated with 7.5% of clay and gelatin respectively passed the test with percentage deviation of 3.5% in each batch, this deviation is within the official specification [19]. All the other batches failed the test with percentage deviation > 5%. The BP specified that tablets with average weight of 250 mg or more should have percentage deviation not greater than 5% [19]. Variation in weight leads to variation in active ingredient content and could be a function of poor flowability of granules, particle size, particle shape and particle size distribution.

3.2.1 Drug content

The results of the content of metronidazole in tablets formulation was analyzed by UV-method and results are shown in Table 3. Drug content ranged from 195.3 ± 0.07 to 208.2 ± 0.03 mg in all the formulations. The results show that metronidazole was not degraded by the excipient used, hence the formulations complied with BP specifications. Therefore, the clay did not degrade metronidazole. Clay being a natural excipient is affordable and widely distributed in nature. The use of clay as binder in metronidazole could have a synergistic effect in the treatment of intestinal amoebiasis, clay being used natively in the treatment of diarrheal [10]. The antibacterial properties of some clay minerals have also been reported [10].

3.2.2 Tablets hardness

The results of tablets hardness are shown in Table 3 and show that tablets formulated with clay as binder (C1, C2 and C3) had hardness range of 2.38 ± 0.55 to 5.99 ± 0.10 kgf of C3 and C2 respectively formulated with 12.5 and 10% w/w of clay, while tablets formulated with gelatin had hardness of 5.99 ± 0.10 and 5.69 ± 0.99 kgf for C4 and C5 formulated with 7.5 and 10% w/w of gelatin respectively. Therefore tablets formulated with 10% of clay as binder (C2) had hardness that was comparable to those formulated with gelatin. Clay could therefore be used as binder in metronidazole tablets.

Table 2. Micromeritic properties of metronidazole granule

Batch	Flow rate (g/s)[*†]	BD (g/ml) [*†]	TD (g/ml) [*†]	AR (°) [*†]	Carr's index (%)	Hausner's ratio
C1	5.62 ± 0.04	0.65 ± 0.05	0.95 ± 0.01	15.95 ± 0.42	31.57	1.46
C2	5.01 ± 0.04	0.64 ± 0.03	0.95 ± 0.07	14.47 ± 0.32	32.60	1.48
C3	6.73 ± 0.02	0.66 ± 0.03	0.96 ± 0.10	17.97 ± 0.27	34.40	1.45
C4	5.54 ± 0.06	0.62 ± 0.02	0.74 ± 0.02	17.01 ± 0.15	16.20	1.21
C5	7.09 ± 0.05	0.57 ± 0.05	0.64 ± 0.04	17.30 ± 0.17	10.90	1.12

[*]n = 3; [†]mean ± standard deviation; C1, C2 and C3 were formulated with 7.5, 10 and 12.5% w/w of clay as binder, while C4 and C5 were formulated with 7.5 and 10% w/w gelatin as binder. BD: Bulk density, TD: Tapped density, AR: Angle of repose

Table 3. Properties of metronidazole tablets

Batch	Tablets weight (mg ± CV%) [a]	Hardness (kgf) [b, †]	Friability (%) [b, †]	Drug content (mg) [a, †]
C1	306.2 ± 3.5	3.33 ± 0.59	0.73	207.9 ± 0.05
C2	307.0 ± 6.6	5.99 ± 0.10	5.50	208.2 ± 0.03
C3	287.5 ± 5.5	2.38 ± 0.55	7.47	195.3 ± 0.07
C4	303.3 ± 3.5	5.90 ± 0.33	0.29	202.1 ± 0.07
C5	287.5 ± 5.5	5.69 ± 0.99	0.30	196.3 ± 0.08

[a]n = 20, [b]n = 10; [†]mean ± standard deviation; C1, C2 and C3 were formulated with 7.5, 10 and 12.5 % w/w of clay as binder, while C4 and C5 were formulated with 7.5 and 10% w/w gelatin as binder

3.2.3 Disintegration time

The results of the disintegration time of metronidazole tablets formulated with clay and gelatin respectively as binders are shown in Fig. 1. Results showed that batches C1, C2 and C3 containing 7.5, 10 and 12.5.5% w/w of clay exhibited disintegration at 1.4, 3.6 and 24 min while, C4 and C5 formulated with gelatin as binder (10 and 12% w/w) had disintegration times of 31.7 and 68.2 min. The results however, showed that gelatin is a stronger binder than clay and the concentrations used were not adequate enough for normal release tablets. The gelatin tablets therefore failed the disintegration time test for normal release tablets. The tablets formulated with 10 and 12.5% w/w clay passed the disintegration time test, while batch C3 containing 12.5% of clay as binder failed the test with disintegration time > 15 min. Therefore, metronidazole normal release tablets could be formulated with 7.5 and 10% w/w of clay as binder in order to enhance the oral bioavailability of this drug.

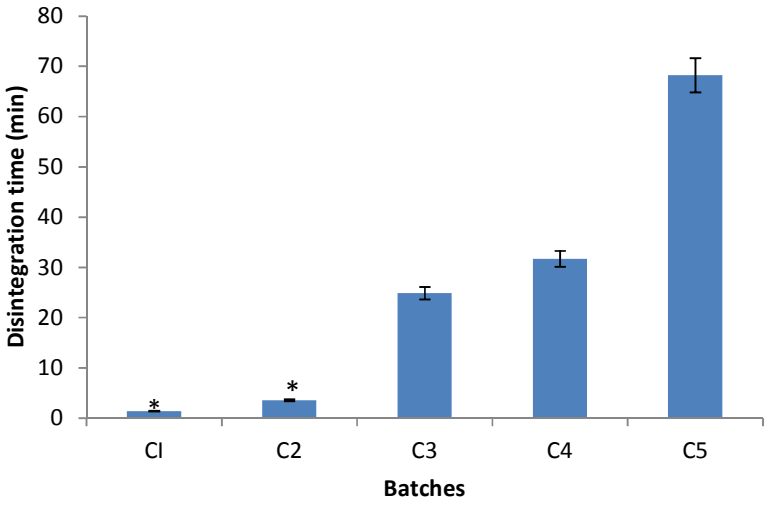

Fig. 1. Disintegration time of metronidazole tablets

*C1, C2 and C3 were formulated with 7.5, 10 and 12.5% w/w of clay as binder, while C4 and C5 were formulated with 7.5 and 10% w/w gelatin as binder (reference). *Significant at p < 0.05 compared to reference tablets*

3.2.4 *In vitro* drug release

The results of the *in vitro* release profile of metronidazole from tablets are shown in Fig. 2. A total of 80.3, 58.2 and 36.8% of metronidazole were released from C1, C2 and C3 tablets formulated with 7.5, 10 and 12.5%, of clay respectively at 5 min, while 42.1 and 10.1% were released from tablets formulated with 7.5 and 10% w/w of gelatin (C4 and C5). More so, at 35 min, 99.1, 98.9 and 50.4% of metronidazole were released from C1, C2 and C3 tablets formulated with 7.5, 10 and 12.5% of clay as binder respectively, while 80.2 and 51.9% were released from tablets formulated with 7.5 and 10% w/w of gelatin as binder (C4 and C5). The results show that increase in binder concentration increased significantly the time of release of drug with formulations containing 12.5% of clay showing more prolonged drug release. The results also suggest that clay could be used in formulating normal release metronidazole. However, gelatin (10% w/w) showed significantly low drug release of drug ($p < 0.05$) than the tablets formulated with clay with 54.2% drug release at 55 min. However, there was an initial fast release on the batches formulated with clay, which could be due to drug on the surface of the tablet. In other words, it can be said that there was a burst effect. The burst effect could be of clinical importance when managing infectious case.

3.2.5 *In vitro* release kinetics

The results of the *in vitro* release kinetics of metronidazole from tablets formulated with 10% w/w of clay as binder are shown in Table 4. The results show that First order plot of log cumulative drug release versus time was linear (r^2 = 0.982) showing that drug release followed first order release. Also plot of the integral form of Higuchi gave n < 0.5 showing that drug release followed Fickian diffusion release mechanism. The release rate constant (*k*) also showed that first and Higuchi models gave high *k* values. The results showed that drug release followed mixed mechanism of drug release. The Korsmeyer-Peppas model confirmed Fickian diffusion shown by Higuchi models in their r^2 and the *n* value. The results showed that drug release from tablets formulated with clay as binder followed Fickian diffusion release predominantly [20-22].

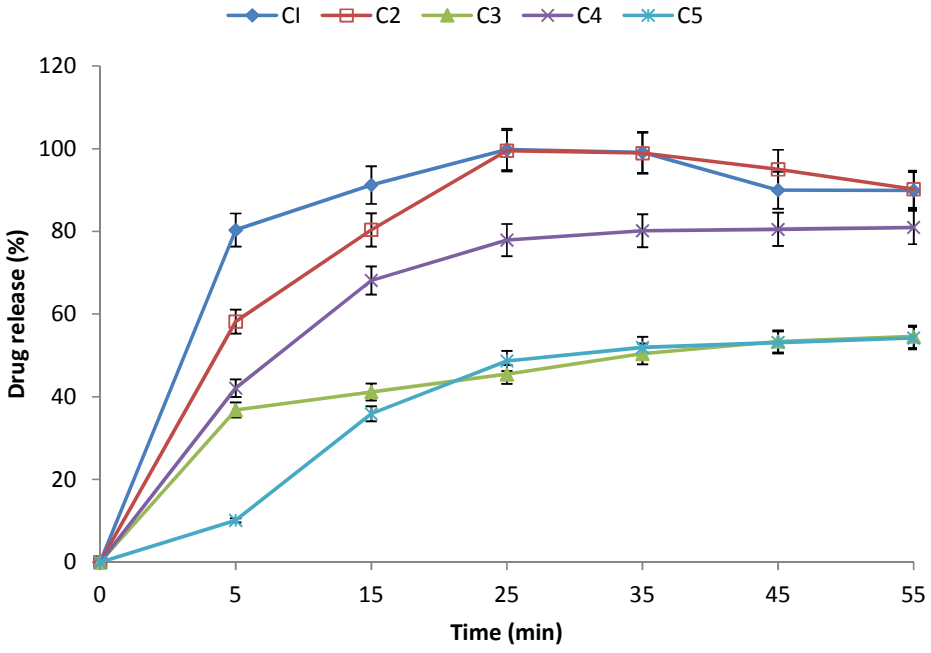

Fig. 2. *In vitro* release profile of metronidazole tablets

C1, C2 and C3 were formulated with 7.5, 10 and 12.5% w/w of clay as binder, while C4 and C5 were formulated with 7.5 and 10% w/w gelatin as binder (reference)

Table 4. Drug release kinetics of tablets formulated with 10%w/w of clay (C3)

Model	*r*	*N*	*K* (h^{-1})
First order	0.982	-	64.9
Higuchi	0.942	0.172	27.0
Korsmeyer-Peppas	0.941	0.170	0.50

4. CONCLUSION

Native clay showed good binder properties in metronidazole tablets and have advantages over gelatin in metronidazole tablets. It is particularly good for normal release tablets and could have some synergistic effect in intestinal amoebiasis due to its anti diarrheal properties. It has better biocompatibility compared to synthetic binders and is relatively cheap and readily available. However, further study into this area is highly encouraged so as to effectively study and scale up the use of native clay as binder in tablets.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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