NOVEL APPLICATIONS OF LOCALLY SOURCED MONTMORILLONITE (MMT) CLAY AS A DISINTEGRANT IN THE FORMULATION OF PHARMACEUTICAL PRODUCT

*Okolo, P.O., Omonmhenle, S.I., Abdulsalaam, A.O.and Ofunne, C.N.
Materials Testing Research Centre, Department of Chemistry, University of Benin, Benin City. Nigeria.
Correspondence author: okolopao@yahoo.com

ABSTRACT
This work explores the application of a locally sourced raw material, montmorillonite (MMT) clay, as a disintegrant in the formulation of an analgesic pharmaceutical product - paracetamol. The raw MMT was refined and treated with 0.IM NaCl to yield sodium montmorillonite (NaMMT) and the powder properties established in this work were compared with those of purified kaolinite (KO) clay and a reference standard disintegrant – maize starch (MS). Separately, the NaMMT, KO and MS powders were employed as disintegrants to compound paracetamol tablets. Some of the physical properties of the tablets were determined. Results of some powder properties showed that NaMMT and KO had superior angles of repose (40.20^o and 34.40^o, respectively) compared with the reference standard disintegrant MS (56.00%). Sodium montmorillonite (NaMMT) showed better swelling capacity (1.81) than both KO and MS (1.40 and 1.56, respectively), while MS and NaMMT exhibited comparable water retention capacity (3.04% and 2.90%, respectively). The porosity of MS (31.94%) was only slightly better than that of NaMMT (30.00%). For the physical properties of the tablets, the dissolution characteristic of NaMMT was slightly better than that of MS: for example, the percentage amount of 15% NaMMT and MS dissolved in 0.1M HCl solution at 30minutes duration were 75.40% and 74.10%, respectively; and at 50minutes duration, it was 85.10% and 82.10%, respectively. On the other hand, the disintegration property of MS (1.54min) was slightly better than that of NaMMT (2.10min). Kaolinite (KO) failed both the dissolution and integration tests, with only 0.31% dissolving even after 1hr and requiring more than 30min to disintegrate. The friability and hardness tests showed that NaMMT was superior to both MS and KO. Overall, the sodium montmorillonite (NaMMT) was found to hold strong prospect as a disintegrant in the formulation and compounding of certain solid, compact pharmaceutical dosages.
Keywords: Compact dosages, disintegrants, local raw material, montmorillonite clay, pharmaceutics.

INTRODUCTON
The prohibitive cost of some drugs in certain third world countries necessitates the exploration of certain raw materials in the formulation of some pharmaceutical products. To formulate solid, compact dosages, the active principles are usually uniformly dispersed in an inert solid vehicle referred to as a disintegrant. When pharmaceutical preparations are administered in the form of tablets, the active principles (drugs) are liberated as the tablet absorbs liquid, swells, dissolves and eventually disintegrates in the patient's stomach. An ideal disintegrant would cause the tablet to release at least 70% of the drugs in not more than 30 minutes (Reghvendra and Saraswaithi, 2012; Amodu, 2011).

Materials that have been employed as disintegrants include starch from: maize, cassava, yam, wheat, rice, pepino fruit, e.t.c; others are microcrystalline cellulose and modified cellulose gum (Iwuagwu and Okoli, 1992; Olayemi, 2008; Saleemula *et al.*, 2010; Amodu, 2011). Some workers have used clay for different purposes in drug formulation. Kaolinite clay was found to possess superior lubricant properties in tableting at low concentrations (0.2 - 1.0%) compared with the familiar lubricants, such as stearic acid and talc (Onyekweli, 1985; Oladimeji *et al.*, 1997). Others have employed montmorillonite, polygorskite, kaolinite and talc as emulsifying, thickening or anticaking agents, due to their colloidal and thixotropic properties, in the preparation of syrups, suspensions, gels e.t.c.(Lagaly, 1989; Yuan and Murray, 1997; Van, 1977; Lagaly, 2006).

This work seeks to contribute to the search for the use of local raw materials in the formulation of cheap and effective pharmaceutical products. It specifically intends to employ montmorillonite clay as the sole disintegrant in the formulation and compounding of an analgesic drug – paracetamol tablets. Results would be compared with those of a reference standard disintegrant – the maize starch (MS).

MATERIALS AND METHODS
Pharmaceutical-grade powders of paracetamol B.P., maize starch B.P., magnesium stearate and analytical grade sodium chloride (BDH, England) were used as obtained.

Montmorillonite clay sample was collected from Okada in Ovia North East Local Government Area of Edo State, Nigeria, while kaolinite clay sample was collected from Okwaehe in Orionwo Local Government Area of Edo State, Nigeria. These clay samples were properly identified by experts in Geology Department, University of Benin, Benin City, Nigeria.

Purification and Modification of Clay Samples

The purification and chemical modification of the native montmorillonite clay were based on the methods of Bergaya *et al.*, 2006. Air–dried native montmorillonite clay sample was crushed in a mortar and 500.0g of the clay dispersed in 4.0L of deionize water. The suspension was swirled thoroughly for 5min, and then filtered at room temperature (28°C) through mesh size of 200µm in order to screen out non-clay materials. The sediments was dried in a hot-air oven (Drying Oven. DHG − 9023A. B. Bran Scientific & Instruments Company, England) at 105°C to constant weight. The dry sediment was then dispersed in 1.0L 0.1M NaCl aqueous solution and stirred for 5hrs and filtered again. The resulting sediment was washed with deionized water until free of chloride ions as tested by $AgNO_3$ solution, to obtain the Na-montmorillonite (NaMMT) (Bergaya *et al.*, 2006). The NaMMT was then oven dried at 105°C to constant weight, pulverized and sieved through 64µm mesh size to get fine powder. The native kaolinite clay sample was similarly purified, except that no sodium analogue was made.

Determination of Physicochemical Properties of NaMMT and the Purified Kaolinite Powders
Swelling Capacity:

The swelling capacity was estimated by the methods of Bowen and Vadino, 1984. Five grams (5.0g) of purified clay sample were placed in a 100.0mL measuring cylinder and the bulk volume (V_x) noted. Deionized water (85.0mL) was added and the measuring cylinder agitated to disperse the clay. The volume of the suspension was made up 100.0mL with more deionized water. The dispersion was allowed to stand for 24hrs after which the final volume of the sediment (V_y) was read and noted. The swelling capacity was calculated as:

Swelling capacity = V_y / V_x .
The swelling capacity tests were repeated in triplicates and the average value calculated.

Water Retention Capacity

The water retention capacity was determined based on the methods of Komblum and Stoopak, 1973 and Ring, 1985. One gram (1.0g) of the purified clay sample was placed in 15.0mL plastic centrifuge tube to which 10.0mL deionized water was added and then stoppered. The contents were mixed for 2min. The mixture was allowed to stand for 10min and then centrifuged at 5000 r.p.m. for 25min (CENTRIFUGE MPW 53/MED INSTRMENTS, POLAND). The resulting supernatant was carefully decanted and the sediment weighed. The water

retention capacity was taken as the ratio of sediment weight (W_y) to the dry sample weight (W_x).

Water retention capacity = W_y / W_x. Triplicate results were obtained and the average used.

Bulk and Tapped Densities

The bulk and tapped densities were determined using the methods described by Jideonwo *et al.*, 2013, and Alanzi, 2007. Ten grams (10.0g) each of the purified clay samples were weighed on the analytical balance (Mettler Instruments 163, Switzerland) and transferred into a 100-mL measuring cylinder. The bulk volume (V_b) was recorded. The cylinder was then gently tapped on the wooden platform until the volume occupied by the clay sample became constant. The tapped volume (V_t) was then recorded. The bulk and tapped densities (D_b and D_t, respectively) were calculated as the ratio of weight (w) to volume:

$D_t = W / V_t$; $D_b = W / V_b$ .Triplicate results were obtained and the average used.

True Density

Specific gravity bottle was filled with the liquid paraffin and the weight noted. It was then poured out and the bottle washed clean and dried. One gramme (1.0g) of the oven - dried powder was introduced into the bottle, liquid paraffin was then poured into the bottle until it was filled. The new weight was noted. True density was calculated using the formula (Olayemi, 2008):

$$D_t = \frac{w \times d}{(a + w) - b}$$

Where D_t = True density;   d = Specific gravity of liquid paraffin;

a = Weight of bottle + liquid paraffin; and

b = Weight of bottle + liquid paraffin + sample; w = Weight of sample.

Hausner's Ratio

Hausner's ratio was calculated from the ratio of the tapped density to bulk density (Nwuluka *et al.*, 2010):

Hausner's ratio = D_t / D_b

Angle of Repose

The angle of repose was determined using the methods of Odeniyi *et al.*, 2011. Ten grams (10.0g) of the purified (dry) clay samples were each poured via a funnel into an open ended glass tube (1cm internal diameter) with its bottom resting on a horizontal surface. On gradually raising the cylinder vertically, the purified clay flowed out and formed a conical heap as a result of gravitational force.The height (h) of the cone and the radius (r) of its circular base were measured. The angle of repose () was calculated using the relationship:

$$\alpha - \tan^{-1}\left(\frac{h}{r}\right) .$$

pH Determination

Two grams (2.0g) of the purified clay samples were each poured into 100-mL measuring cylinder. De-ionized water was added up to the mark. The suspension was then agitated for 5min and the pH determined with a pH meter (Raymond *et al.*, 2006).

Preparation of Granules

Paracetamol granules were produced using the net granulation techniques of Hill, 2006. Paracetamol granules of three disintegrant ratios (5%, 10% and 15%) were prepared from the sodium montmorillonite (NaMMT) clay and the refined kaolinite (KO) clay, respectively. The disintegrant properties of these ratios were compared with that of a reference standard disintegrant (maize starch, MS). For example, to produce 5% disintegrant (NaMMT) ratio in the paracetamol granule, 2.5g of NaMMT powder was mixed with 50.0g of paracetamol powder in a motar using small quantity of deionized water (10.0mL) as granulating liquid, to form` a smooth consistency. This was then used to produce the granules as listed bellow, in the case of the reference standard disintegrant.

The reference standard disintegrant granules were prepared by first mixing 10.0g of the maize starch B.P. with 10.0mL of deionized water to form a slurry, which was made up to 100-mL volume with boiling deionized water (100°C) to produce starch mucilage. The starch mucilage was added to 50.0g dry paracetamol powder B.P., mixed gently until a moist smooth mass was formed. Subsequently, 5.0g of additional dry maize starch B.P. was added extragranularly as the disintegrant. The entire mass was mixed thoroughly to produce a smooth consistency (10% MS, so called).

The smooth consistency was then screened through a 2-mm mesh, using a spatula. The resulting granules were dried in the hot-air oven at 40°C for 30min after which it was re- screened through a 170-mm mesh size using the spatula. Magnesium stearate (1%) was finally added as lubricant, with final mixing.

Compression of Granules into Tablets

The granules were compressed into flat-faced tablets using a single punch tablet press (Erweka 400, Germany). The punch diameter used was 12mm, while the compression pressure was 7.5 units (Anthony *et al.*, 2003).

Quality Standard for the Tablet
Weight Uniformity Test.

Ten tablets from each batch of formulation were weighed individually on a mettler balance (Mettler Instruments 163, Switzerland) and the mean tablet weight was calculated (Amodu, 2011).

Tablet Thickness

The tablet thickness was determined using the micrometer screw gauge. Ten (10) tablets were picked randomly from each batch, and their respective thicknesses measured and expressed in mm and the mean value calculated (Amodu, 2011).

Tablet Hardness

The hardness of the tablet, expressed as the crushing force, was determined using a Monsanto Hardness Tester, Model 2A (Manesty Machines Ltd, Spoke Liverpool, England). A tablet was held between a fixed anvil and a moving jaw and the force gradually increased until the tablet just fractured. The value of the force at this point gives a measure of the tablet's hardness in kg force. For each batch, the hardness of five (5) tablets were determined from which the average was calculated (Amodu, 2011).

Tablet Friability

Ten (10) tablets were randomly picked from each batch, dusted carefully and lightly until all surface powder was removed. The tablets were weighed (W_1) accurately with the mettler balance. They were placed inside the Friabilator (Erweka TA 48503, Germany) and operated (rotated) 100 times in 4 minutes, i.e 25 r.p.m.. After this the tablets were removed, dusted and reweighed (W_2). From the weight difference, friability (f) for each batch of tablets was determined as the percentage weight loss (Saleemula *et al.*, 2010).

Disintegration time for tablets

The time required for six tablet per batch to disintegrate was determined using the Disintegrator (Manesty Tablet Disintegration Test Unit, MK. 4, 10.T.183, Manesty Machines, England). Distilled water thermostatically maintained at 37°C was used as the disintegration medium. The disintegration apparatus was calibrated to operate at thirty cycles per minute. The time taken for the last tablet or its fragment to pass through the mesh into the disintegration medium was recorded as the mean of the disintegration time for six tablets (British Pharmacopoeia, 2002).

Dissolution rate for tablets

Dissolution rate tests were carried out on the tablets based on the methods of Bai *et al.*, 2011. A dissolution test apparatus (Multipurpose Drug Test Device, Model ST 7; G. B. CALEVA Ltd. Dorset, England) was used; six (6) tablets per batch were tested. The dissolution apparatus was set at a rotation speed of 100 r.p.m., maintaining the temperature thermostatically at 37 ± 0.5^{o}C. The sample medium consisted of 800mL of 0.1M aqueous HCl for paracetamol tablets. Ten millilitres (10.0mL) of the sample medium was withdrawn at 10min intervals. Each aliquot withdrawn was immediately replaced with an equal volume of dissolution medium maintained at the same temperature. A ten fold dilution of the withdrawn sample medium was done using deionized water before spectrophotometric determination of drug content, at λ_{max} of 242nm (UV/VIS Spectrometer T70. PG Instruments Ltd, England). The percentage drug released was plotted against time (min) to generate a dissolution rate curve (Bai *at al.*, 2011).

155

RESULTS AND DISCUSSION

The results of some physical characteristics of the two proposed disintegrant powders (NaMMT) and KO as compared with that of the reference standard disintegrant (MS) are presented in Table1.

The angle of repose is an indicator to the flow property of powders (Ring, 1985); good flow property may reduce the powder's ability to consolidate during vibrational flow and hence leads to production of uniform tablets. Table 1 reveals that NaMMT has superior angle of repose (40.20°) compared to the reference standard disintegrants MS (56.00°). The Hausner's ratio values are derived as the ratio of the tapped density over the bulk density and give an indication of the degree of densification of powder which could result from the vibration of the feed hopper during tableting. Since densification can adversely affect the uniformity of flow of powder into the die, the tablet uniformity may also be adversely affected. A high Hausner's ratio predicts significant densification of powders. It can be inferred from Table 1 that NaMMT powder favourably compares with MS with respect to densification phenomenon (Iwuagwu and Okoli, 1992).

Since water uptake invariably precedes the disintegration process, the determination of water retention capacity and swelling capacity of powders may predict their potentials as tablet disintegrants (Iwuagwu and Okoli, 1992). Table 1 reveals that NaMMT displayed a superior swelling capacity (1.81) than MS (1.56) and KO (1.40). Also, the NaMMT and MS exhibited better water retention capacities 2.90% and 3.04%, respectively, than KO (1.80%). The good swelling capacities of NaMMT and MS can easily be correlated with their high powder porosities (30.00% and 31.94%, respectively) as against 20.00% for KO. The excellent swelling capacity, water retention capacity and porosity displayed by NaMMT may be due to the smaller size of Na^+ ion compared with Ca^{2+} ion (Shannon, 1976) in the clay matrix: during modification of raw calcium montmorillonite (CaMMT), Na^+ ions replaced Ca^{2+} ions and invariably left behind porous structure that became NaMMT. Intuitively, it would appear that Na^+ ion being less electropositive and possessing higher hydration energy than Ca^{2+} ion (Lee, 1996) would readily bind onto the polar water molecules. This is in agreement with the findings of Kloprogge *et al.*, 1999, who aver that clays with univalent interlayer cations swell more readily in aqueous systems than divalent and trivalent cation analogues. These factors synegystically confer excellent porosity, water retention capacity and swelling capacity on NaMMT which may finally translate to superb disintegrant properties in some tablet formulation.

Table 2 presents some physical properties of the paracetamol tablets formulated and compounded with the proposed disintegrants (NaMMT and KO) at different disintegrant concentrations, and compared with those prepared with a reference standard disintegrant, MS. It shows that the hardness of the tablets generally improved as the concentration of the disintegrant increased, within the range studied. However, the hardness of the tablets prepared with 15% NaMMT closely matched those made with the reference disintegrant MS (8.50 and 8.01, respectively). Friability tests reveal the extent the tablets can resist abrasion and chipping that might arise due to handling, transportation, e.t.c. Table 2 also shows that the friability of the batches of tablets were not significantly affected by the change in concentration of disintegrants. Since the maximum limit for friability (weight loss) is 0.8% (Amodu, 2011 and Odeniyi *at al.*, 2011) all the tablets passed the friability tests; again the 15% NaMMT formulation emerged as the best (0.19%) compared with the 0.46% for the reference MS tablets.

The uniformity of tablets is important because it ensures that dosage of active ingredient does not vary from one tablet to another. Table 2 reveals that the uniformity of all the tablets, per batch was satisfactory. Hence the tablets' thickness, diameter and mean weight were uniform and favourably compared with the reference MS tablets. These good tablet qualities with respect to hardness, friability and uniformity are eloquent testimony of some superb powder properties of the disintegrants, such as angle of repose and Hausner's ratio (Ring 1985; Iwuagwu and Okoli, 1992). The good tableting quality displayed by kaolin in this work is in consonance with the findings of Anthony *et al.*, 2003.

Tablet dissolution and bioavailability of the active ingredients are always invariably preceded by disintegration of the tablet. For most uncoated tablets, the maximum disintegration period is 30min (Amodu, 2011). Table 2 reveals that the kaolinite (KO) tablets woefully failed the disintegration test, requiring more than 30min to disintegrate, irrespective of disintegrant concentration in the range studied. The predominant elements in kaolinite, Al and Si, (Lee, 1996) are known to be unfavourably disposed towards water absorption, probably due to their relative large atomic sizes and low hydration energies compared to Na (Shannon, 1976 and Lee, 1996). Conversely, the disintegration qualities of the NaMMT tablets improved with increasing concentration of disintegrant within the range studied, with 15% NaMMT formulation closely matching that of the reference MS tablets (2.10min and 1.54min, respectively). The sodium ions in NaMMT being small sized, reasonably electronegative with higher hydration energy, coupled with high powder porosity in the disintegrant, and capillary actions, probably encouraged absorption of water into the matrix, leading to fast disintegration of the tablets (Washburn, 1921; Selkirk and Ganderton, 1970; Lee, 1996; Shannon, 1976).The overriding quality of a tablet depends on the rate at which active principles are released in an appropriate medium through dissolution.

Figures 1 and 2 summarize the dissolution and drug release properties of paracetamol tablets compounded with the two proposed disintegrants (NaMMT and KO) as compared with those of the reference standard disintegration MS. An ideal tablet releases at least 70% of the active ingredient in not more than 30minutes (Amodu, 2011). Figures 1and 2 show that the percentage drug released by the tablets generally increased with time, but the rate of this release is slowest with the kaolinite (KO) tablets which woefully failed the dissolution/drug release tests - it required 60min to release a maximum of 0.39% of the active ingredient, compared to MS tablets which released 74.10% within 30min (Fig. 1). This result is in tandem with the findings of Anthony *et al.*, 2003, who observed that even though kaoline enhanced good quality tableting, it adversely affected the tablet dissolution and release of the active drug. This property of KO is not unconnected with the adsorptive property of kaolinite, particularly the silica moiety in the structure (Windholz, 1976; Depasse, 1978).

On the other hand, the 15% NaMMT tablets easily passed the dissolution/drug release tests, having released 75.40% of the active ingredient within 30min. This fares even better then the MS tablets (reference standard) which released 74.10% within 30min. A graph of percentage drug released vs time (min) (Fig. 2) clearly shows that the rates of drug release (slopes) due to the 15% NaMMT and MS tablet are in tandem. The impressive dissolution/drug-release characteristics of NaMMT tablets are correlated with the high powder porosity and disintegration quality of NaMMT. This may be attributed to reasonably high electronegativity, high hydration energy and the small size of Na ions (compared with that of Al and Si ions in kaolinite), coupled with capillary actions; these most likely encouraged large water uptake leading to fast disintegration and dissolution of the tablets with the attendant bioavailability of the active ingredients (Washburn, 1921; Selkirk and Ganderton, 1970; Lee, 1996; Shannon, 1976).

Table 1: Some physical characteristics of NaMMT, KO and MS powders.

S/N	Physical characteristics	Sodium montmorillonite (NaMMT)	Kaolin (KO)	Reference standard: Maize Starch B.P. (MS)
1	Swelling capacity (degree)	1.81 (0.025)*	1.40 (0.30)	1.56 (0.31)
2	Water retention capacity (%)	2.90 (0.45)	1.80 (0.38)	3.04 (0.35)
3	Bulk density	0.40 (0.03)	0.50 (0.04)	0.56 (0.03)
4	Tapped density	0.63 (0.02)	0.83 (0.01)	0.71 (0.04)
5	True density (g/cm^3)	2.00	2.50	1.72
6	Hausner's ratio	1.56	1.43	1.27
7	Angle of repose (degree)	40.20	34.40	56.00
8	pH	8.49	4.95	6.90
9	Powder porosity (%)	30.00	20.00	31.94

*Standard deviation in parenthesis.

Table 2: Some physical characteristics of paracetamol tablets compounded with NaMMT, KO or MS as disintegrant at different concentrations.

| S/N	Tablet properties	Sodium montmorillonite (NaMMT)			Kaolinite (KO)			Reference standard: Maize starch B.P (MS)
		5%	10%	15%	5%	10%	15%	10%
1	Hardness (kg/N)	5.00 (0.02)*	7.00 (0.01)	8.50 (0.01)	4.00 (0.02)	7.00 (0.01)	6.50 (0.02)	8.01 (0.01)
2	Friability (%)	0.20	0.19	0.19	0.23	0.20	0.25	0.46
3	Thickness (mm)	0.33 (0.01)	0.33 (0.01)	0.33 (0.02)	0.33 (0.01)	0.30 (0.01)	0.30 (0.01)	0.33 (0.02)
4	Diameter (mm)	12.32 (0.01)	12.32 (0.01)	12.32 (0.01)	12.32 (0.02)	12.32 (0.01)	12.32 (0.02)	12.32 (0.01)
5	Mean weight (g)	0.52 (0.02)	0.52 (0.02)	0.52 (0.02)	0.52 (0.01)	0.52 (0.01)	0.52 (0.01)	0.52 (0.02)
6	Disintegration time (min)	31.00	12.00	2.10	45.00	46.00	48.00	1.54

*Standard deviation in parenthesis
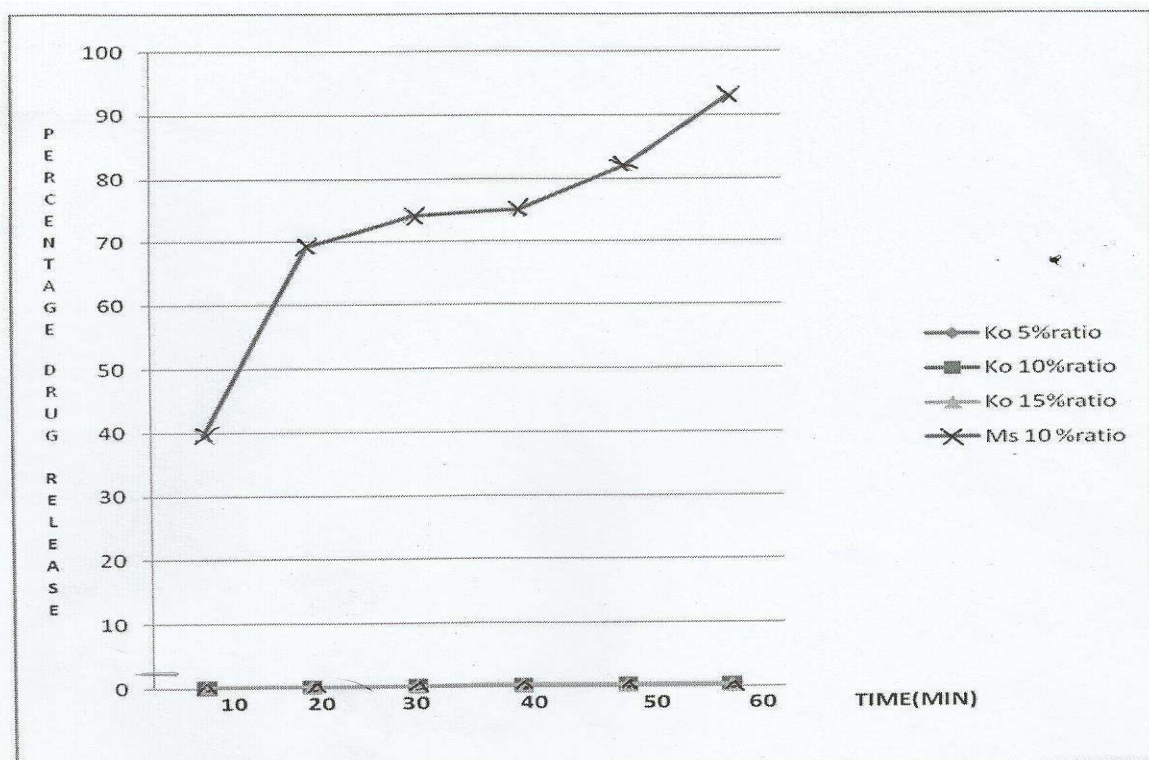
Fig. 1: Percentage drug-release during the dissolution test of KO relative to MS.
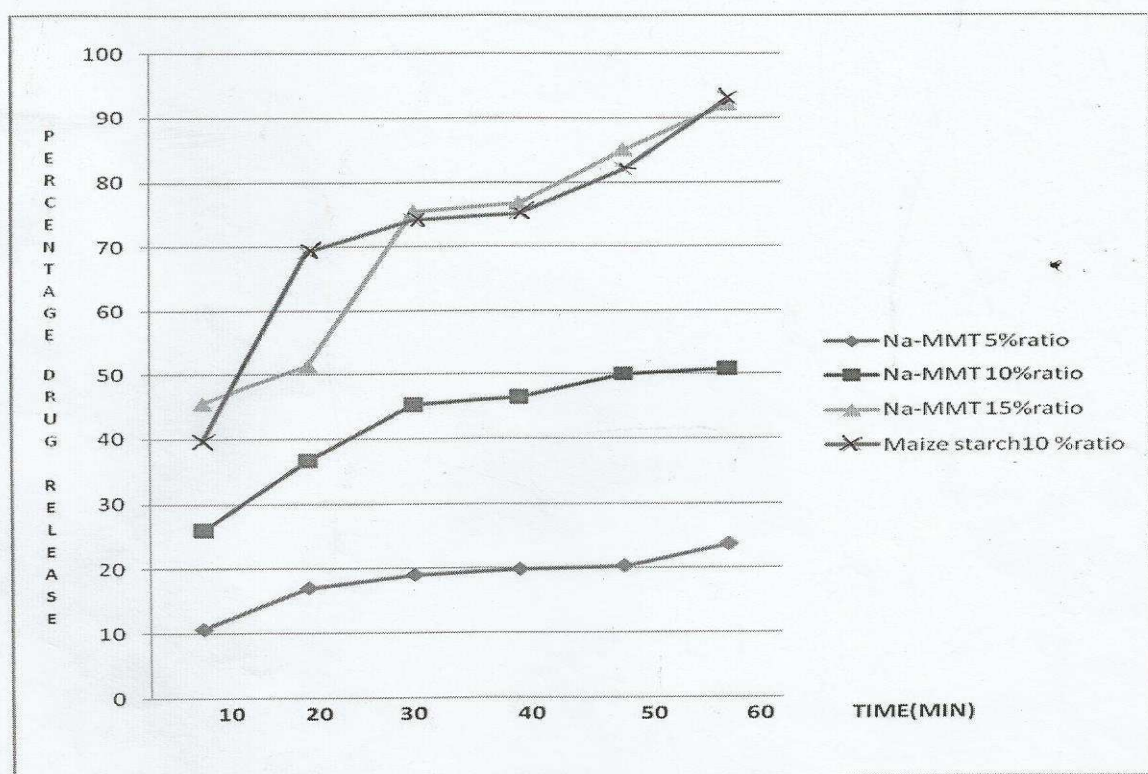

Fig. 2: Percentage drug-release during the dissolution test of NaMMT relative to MS.

CONCLUSION
In the light of the powder properties of the disintegrants, tablets qualities and dissolution/drug-release characteristics of the various tablets, it is clear that the sodium montmorillonite (NaMMT) may hold great prospect as a disintegrant in formulating and compounding some compact, solid dosages. In this work the paracetamol tablets compounded with 15% NaMMT emerges as the optimum formular.

REFERENCES

Alanzi, F.K. (2007). Evaluation of spray and freez dried excipient bases containing disintegration accelerators for the formulation of metoclopramide orally disintegrating tablets. *Saudi Pharm*. J. **15**:105-119.

Amodu, Y. (2011). Evaluation of millet starches as tablet binders and disintegrants. M.Sc. Thesis in Pharmaceutics. Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria Nigeria.

Anthony, O.O., Cyril, O.U., Lucky, O.O. and Jessica, D.Z. (2003). Adsorptive property of kaolin in some drug formulations. *Tropical J. Pharm. Res.***2** (1): 155-159

Bai, G., Wang, Y, and Armenante, P.M. (2011). Velocity profile and shear strain rate variability in the USP dissolution testing apparatus at different impeller agitation speeds. *Int. J. Pharm.***403** (1-2):1-14.

Bergaya, F., Theng, B.K., Lagarly, G. (2006). Hand book of clay science, 1st edn. Elsevier Publications, Amsterdam. Pp. 717-741.

Bowen, F.E. and vadino, W.A.(1984). A simple method for differentiating sources. *Drug. Dev. Ind. Pharm.***10**:505-511.

British Pharmacopoeia (2002). Vol. 1I. Stationary Office Ltd. St. Clement House, 2-16 Colegate, Norwich. P. A236.

Depasse, J. (1978). Interaction between silica and hydrophobic cations. *Br. J. Ind. Med.***35**(1): 32-34.

Hill, P.M. (2006). Effect of compression force and cornstarch on tablet disintegration time. *J. Pharm. Sci.***65**(11):1694 – 1697.

Iwuagwu, M.A. and Okoli, P.C (1992). Disintegrant properties of pregelatinized cassava and white yam starches. *Pharm. World J.* **9** (2):49-53.

Jideonwo, A., Okolo, P.O. and Osuoji, O.U. (2013). Powder properties of blends of starch and polyvinyl alcohol and their biodegradation characteristics. *Biol. and Environ. Sci. J. for the Tropics (BEST)*. **10** (2): 268-271.

Kloprogge, J.T., Komarneni, S. and Amonette, J.E. (1999). Clays. *Clay Miners*. **47:** 529.

Komblum, S.S. and Stoopak, S.B. (1973). A new tablet disintegrant agent: scrosslinked polyvinylpyrrolidone. *J. Pharm. Sci*. **62** (1): 43-49.

Lagaly, G. (2006). Colloidal clay science in: Handbook of clay science. Elsevier, Amsterdam. Pp. 141-245.

Lagaly, G. (1989). Ingredients of flow of kaolin and bentonite dispersion. *Applied Clay Science***4**:105-123.

Lee, J.D. (1996). Concise inorganic chemistry. 5th edn. Blackwell Science, Ltd. Oxford. Pp 160, 164,441.

Nwuluka, N.C., Idiakhoa, B.A., Nep, E.I., Ogaji, L. and Okafor, I.S. (2010). Formulation and evaluation of paracetamol tablets manufactured using the dried fruit of *Phonix dactyl lifera linn* as an excipient. *Research in Pharm. Biotech*. **2** (3): 25-32.

Odeniyi, M.A., Onu, R.N. and Adetunji, O.A. (2011). Evaluation of bioadhesive of natural and modified banana starches. *East and central African J. of Pharm. Sci.***14**,34-42.

Oladimeji, O.O., Ifudu, N.D. and Ojo, A. (1997). Evaluation of kaolin powder as a lubricant in tableting. *J. Pharm. Sci. Pharm. Prac*. **3** (1): 13-16.

Olayemi, O.J. (2008). Comparative binding effects of wheat, rice, and maize starches in chloroquine phosphate tablet formulation. *Res J. App. Sci. Eng. & Tech.***1** (2): 77-80.

Onyekweli, A. O. (1985). Binding disinterant properties of a local starch obtained from *Musa Sapientum. Nig. J. App. Sci*. **3**(1): 33-43.

Raymond, C.R., Paul, J.S. and Scian, C.O. (2006). Handbook of pharmaceutical excipient, 5th edn. Pharmaceutical Press, London. P.82.

Reghvendra, D. and Saraswathi, R. (2012). Nanoclay and drug delivery system. *Int. J. Phar. World Research*. **3** (3): 19-23.

Ring, S.G (1985). Some studies on gelatine. *Starch.***37**:80-87.

Saleemula, K., Ramu, G., Krisha, G.M., Jayaveera, K.N. and Chetan, B. (2010). Tablet disintegrant activities of new starch from immature pepino fruit. *J. Sci. Ind. Res*. **70**: 149-155.

Selkirk, A.B. and Ganderton, D. (1970). Influence of wet and dry granulation methods on the pore structure of lactose tablets. *J. Pharm. Pharmacol*, **22** (S):86-94

Shannon, R.D. (1976). Revised effective ionic radii. *Acta Cryst*., A **32**: 751-767

Van, O.H. (1977). An introduction to colloidal chemistry, 2nd edn. John Wiley. New York. Pp. 318.

Washburn, E.W. (1921). The dynamics of capillary flow. *Phys. Rev*. **17**: 273-283.

Windholz, M. (1976). The mark index – an encyclopaedia of chemicals and drugs, 9th edn. Merk & Co. Ind., Ralway, USA. P. 693.

Yuan, J. and Murray, H.H. (1997). The importance of crystal morphology on the viscosity of concentrated suspensious of kaolin. *Applied Clay Science*. **12:** 209-219.