Comparative Assessment of Ginger and Cassava Starch as a Binder on Ibuprofen Tablet Formulation

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ABSTRACT

Using the wet granulation method of tablet formulation, ibuprofen tablets were formulated with binder concentration of 2%, 4% and 6% w/w respectively. The compressional, mechanical and dissolution properties were analyzed using density, crushing strength and dissolution methods. The result obtained showed that tablets made with ginger starch had acceptable crushing strength and dissolution rate. The disintegration time for 2%, 4% and 6% w/w ginger starch were 22.25, 17.07 and 33.17 minutes respectively and that for cassava starch 34.24, 29.16 and 33.35 minutes respectively. The 2% w/w of the ginger and cassava starches did not fall within the standard limit of the hardness test (4–8 kg) but rather values of 8.55 kg and 8.45 kg respectively were obtained and this may be linked to the threshold of the concentration of the binder not being attained. All the formulations passed the qualitative analysis but that consisting of 4% w/w ginger starch performed excellently in the entire tests hence ginger starch of such concentration could be a very suitable excipient for ibuprofen tablet formulation as compared to cassava starch of the same percentage composition.

Key-words: Ginger, Cassava, Ibuprofen, Starch, Tablet, Natural biodegradable biopolymer

INTRODUCTION

Binders as agents impart cohesive qualities to powdered material during the production of tablet. They impact such properties to the tablet formulation by ensuring that the tablet remains intact after compression as well as improving free powder flowing quality [1]. Binders have been used as solutions and in dry form depending on nature of another ingredient in the formulation and method of preparation. The choice of a particular binding agent depends on the binding force required, compatibility with other ingredients, particularly the active pharmaceutical ingredient (API) [2]. Important materials commonly used as binders are starch, gelatin, natural gum, sugar, acacia, polyethylene glycol, water etc [3]. Starch is the most common binder and pharmaceutical excipient used in tablet formulation to impart cohesion on powder mix during tablet formulation. Starch as one of the most abundant organic chemicals on earth is found in the leaves of green plants and on the plastids where it is synthesized from seeds, roots, and tubers of most plants serving as the chemical storage form of energy [4]. Starch is a natural biodegradable biopolymer which has wide industrial application, a quantitatively important digestible polysaccharide regarded as nutritionally superior to low molecular weight carbohydrate or sugar [5]. Maize and potato starch has been in common use and recently cassava starch [6]. Another type of starch currently under study is ginger starch as a binder in the pharmaceutical industry. The type and binder concentration could impart a direct effect on tablet properties such as crushing strength, friability, disintegration and tablet dissolution.

Ginger (Zingiber officinale) is an herbaceous perennial plant belonging to the order zingiberaceae and family Zingiberaceae. Harvest of natural ginger is determined by the age of the leaves and bulb size and it contains such compounds as starch, fat, gingerol and volatile oil. The starch is mainly used as an indicator, the excipient in...
tablet formulation and also for other purposes where it serves as a thickening agent and binding agent [7]. Cassava (Manihot esculenta) is a perennial shrub with an edible root which grows in tropical and sub-tropical areas of the world. Cassava is propagated by stem cutting [8] and the major constituent is starch especially from the cassava tuber and this starch is often recommended for use in extruded snacks for improved expansion. The cassava starch is also used as a thickener in food not subjected to rigorous processing condition. It is very bland in flavor hence used in processed baby foods and as a filler material and binding agents in the confectionery industry [9]. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAIDs), a first member of the propionic acid derivative which occurs as a white powder or crystals with a characteristic odor.

Ibuprofen is soluble in aqueous solution of alkali hydroxide and carbonate but slightly soluble in water and has a melting point of about 76°C [10]. Ibuprofen has a prominent analgesic and anti-pyretic effect, which is due to the inhibitory action on cyclooxygenases involved in the synthesis of prostaglandin that plays important role in the production of pain, fever, and inflammation [11].

Ibuprofen is well absorbed orally, peak serum concentration is reached within 1–2 hours after drug administration and the drug is eliminated within 24 hours after the last dose through metabolism. The dose of ibuprofen for an adult is 1.2 g daily in divided doses, while that for children is 20 mg/kg body weight daily, but not above 500mg for children with weight less than 30kg, as overdose may lead to toxicity, such as acute renal failure, aplastic anaemia, neutropenia and thrombocytopenia. Ibuprofen decreases the effect of aspirin by blocking the active site of platelet cyclo-oxygenase, hence it should be administered 8 hours before aspirin, or at least 2–4 hours after aspirin. Ibuprofen is available in the following dosage forms as tablet, capsules, chewable tablets, and oral suspension and usually manufactured as 200 mg or 400 mg ibuprofen in a tablet and 100 mg/50 mg in oral suspension and it should be taken after a meal because it can lead to damage of stomach or intestinal lining, if taken before a meal.

Tablets are solid preparation each containing a single dose of one or more active ingredients and usually obtained by compressing uniform volumes of particles. It is the most popular dosage form in existence among all dosage forms because of the convenience of self-administration, chemical and physical stability, cheapness, versatile way of use and delivery, compactness and ease of manufacturing [12].

Certain numbers of chemically inert materials known as adjunct or excipients are added to the active pharmaceutical ingredient and their classification is based on their processing functions and finished products such as binders, lubricants, glidants, disintegrants, etc. Such excipients should be bound with certain quality criteria as non-toxic, physiologically inert, relatively cheap and acceptable to regulating agencies in all countries [13]. The aim of this study is to evaluate and compare the binding activity of extracted ginger and cassava starch on ibuprofen tablet formulation.

**MATERIALS AND METHODS**

**Experimental Materials-** Ibuprofen powder (BDH, England), magnesium stearate, lactose, maize starch, talc, pH meter (Jenway 3510, England), Electronic balance (Adventurer™ AR 2130, England) dissolution Apparatus (Erweka TBH 600, Germany), disintegration apparatus (Erweka ZT, 122, Germany), UV spectrometer (Jenway 6405, England), fribilator (Erweka TAR 220, Germany), hardness tester (Erweka TBH 100, Germany), Ginger and cassava starch (processed in pharmaceutical technology laboratory, University of Port Harcourt, Nigeria.

**Solubility determination of ibuprofen powder-** A 0.1 g quantity of ibuprofen powder was weighed (Table 1) and each transferred into six test tubes, various solvents (acetone, sodium hydroxide, water, n-hexane, HCL and chloroform) (10 ml each) were respectively introduced into each of the six test tubes, containing the drugs, shaken and observed for solubility.

![Fig. 1: Chemical structure of Ibuprofen](image)
Table 1: Preparation of Ibuprofen granules

| Ingredients               | Weight per tablet (mg) | Weight in 150 tablets (g) |
|---------------------------|------------------------|---------------------------|
| Ibuprofen                 | 400                    | 60                        |
| Maize starch              | 1.5% w/v               | 1.5% w/v                  |
| Lactose                   | 120                    | 10                        |
| Ginger/Cassava starch     | 2% w/v, 4% w/v and 6% w/v | Qs                        |

Exo disinfectants

| Lubricants/Glidants       |                         |                           |
|---------------------------|-------------------------|---------------------------|
| Dried maize starch        | 1.5% w/v                | 1.5% w/v                  |
| Magnesium stearate        | 2% w/v                  | 2% w/v                    |
| TALC                      | 3% w/v                  | 3% w/v                    |

Adopting the technique of wet granulation method of the tablet formulation, ibuprofen granules were made based on the formula in Table 1. Ginger starch was employed as the test binder while cassava starch was employed as the reference standard all incorporated in various concentrations as 2, 4, and 6% w/v.

Ibuprofen powder was geometrically diluted with dried maize starch (disintegrant) in a porcelain mortar. The binder paste prepared from the ginger and cassava starches respectively were incorporated into the content of the mortar until a wet coherent mass was obtained. The damp mass was then passed through a 2mm sieve aperture to break down the mass and then dried at 50°C in the oven (Mermett U-27, Germany) for 30 minutes. The granular mass obtained was again passed through a 1mm sieve aperture to ensure uniformly sized granules and this was further dried at 50°C for 1 hour. The dried granules were incorporated with the exo-excipients (disintegrant, lubricant and glidant) as dried maize starch, magnesium stearate and talc respectively.

Physico Technical Characterization of Granules

Flow rate Determination- Adopting the flow through the hoppers method, a funnel with an efflux tube length (3.9 cm) and orifice diameter (1.2 cm) was clamped on the retort stand and the distance between the funnel and surface is set at 6cm. Required weight of 30 g of granules per batch was allowed to pass through the orifice and the time taken for it to pass through was recorded. The flow rate was determined using the relation-

\[
\text{Quantity of granules (g) flow per unit time (sec)} = \frac{M \text{ (g)}}{T \text{ (sec)}}
\]

Where, \(M\) = Weight (Mass) of granules in the funnel

\(T\) = Time of granule flow through the hopper

Mean of the triplicate readings was taken as the flow rate of the granules. Characterization of other physico-technical properties such as angle of repose, bulk and tapped density, Hausner’s quotient and Carr’s index were carried out adopting the standard procedures.

Addition of Exo-excipients- The exo excipients [exo-disintegrant (dried maize starch), lubricant (magnesium stearate) and glidant (talc)] were added to the granule based on the formula as in Table 1 and the granules properly blended to obtain a randomly mixed powder suitable for Pharmaceutical tablet formulation.

Compression of tablets- After the addition of exo-excipients, the granules were compressed into a tablet using the single punch tableting machine (Erweka E PHI, Germany) at varying pressure until the best tablet was formed. The formed tablets were left for 24 hours before evaluation to allow for elastic recovery.

Quality control of tablets

Weight variation- The weights of 20 randomly selected tablets were determined as a whole and then individually using electronic balance (Adventurer Tm England) and the mean weight calculated. The variation
in weight of the individual tablets from the mean was determined.

**Friability test**- Ten tablets were randomly selected and placed in a sieve and loose dust removed with the aid of a soft brush. The dedusted tablets were weighed and caused to cascade in the drum of a friabilator rotated at 25 rpm for 4 minutes. The tablets were again dedusted and reweighed. The percentage friability was determined using the formula:

\[
\% \text{ Friability} = \frac{\text{Initial weight} – \text{final weight}}{\text{Initial weight}} \times 100
\]

**Crushing Strength (Hardness) test**- The crushing strength of each of 10 tablets was determined using the Erweka TBH Germany hardness tester and the mean crushing strength determined.

**Disintegration test**- The disintegration rate of six tablets randomly selected from each batch was individually determined in BP specified apparatus (Erweka ZT 122, Germany) containing purified water at 37±0.5°C and the mean disintegration time was calculated.

**Preparation of standard calibration curve**- 100 ml of pure ibuprofen powder was placed in a 100 ml volumetric flask dissolved in 0.1 N NaOH and made up to mark with the same solvent. Various dilutions of the stock were made to obtain 0.01, 0.02, 0.03, 0.04, 0.05 and 0.06 mg% with 0.1 N NaOH and the absorbance determined using UV spectrometer at 228 nm (wavelength for ibuprofen). A standard calibration curve of absorbance against concentration was plotted.

**Dissolution test**- The dissolution rates of the active drug from the tablet were determined using USP apparatus II (paddle). A 900 ml of freshly prepared dissolution medium (0.1N NaOH) was transferred into the dissolution jar and maintained at 37±0.5°C. The paddles were caused to rotate at 50 rpm. Samples were withdrawn at 10, 20, 30, 40, 50 and 60 minutes and analyzed spectrophotometrically (Jenway 6405 UV, England) for ibuprofen at 228 nm. 10 ml of samples removed for analysis were replaced immediately with fresh aliquot of the dissolution medium and the percentage drug dissolved calculated based on calibration curve result (Beer Lambert’s plot).

\[
\text{Concentration} = \text{slope} \times \text{absorbance} \pm \text{intercept}
\]

\[
\text{Amount of drugs released (mg/ml)} = \frac{\text{Concentration} \times \text{Dissolution bath volume} \times \text{Dilution factor}}{\text{Total amount dissolved}}
\]

**Drug content Determination**- Twenty tablets were randomly selected from each batch, weighed and crushed to fine powder. The powdered drug (50 mg) was weighed and transferred into a 50 ml volumetric flask and dissolved with 0.1 N NaOH shaken and made up to volume with same solvent. 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, and 6 ml of the solution was withdrawn and each made up to 50 ml with 0.1 N NaOH and then filtered. The drug content was determined by measurement of the absorbance of the filtrate at 228 nm using the UV-spectrophotometer.

**Assay of Ibuprofen**- The method involving acid-base titration (stoichiometric method) was modified and used. Twenty tablets were selected randomly from a batch of the formulation and weighed. A quantity of the powder equivalent to 0.5 g Ibuprofen was extracted with 20 ml chloroform for 15 minutes and then filtered using filter paper. The residue was washed thrice with 10 ml each of chloroform and the filtrate gently evaporated to dryness. The residue was dissolved in 100 ml of 96% ethanol and the solution titrated against 0.1N NaOH upon addition of 2 drops of phenolphthalein as indicator. The end point (pink color) was noted and content of ibuprofen calculated.

**RESULTS**

The result is given below in Table 1 has due to the effect of types of binder (ginger and cassava) and the varied percentage compositions.
Table 2: Physico-technical characterization of Ibuprofen granules

| Granules property               | 2% G  | 4% G  | 6% G  | 2% C  | 4% C  | 6% C  |
|--------------------------------|-------|-------|-------|-------|-------|-------|
| Flow rate (g/sec)              | 7.10 ± 0.96 | 6.70 ± 0.85 | 5.90 ± 0.45 | 6.30 ± 0.12 | 5.20 ± 0.12 | 4.50 ± 0.15 |
| Angle of Repose (°)            | 27.30 ± 0.64 | 25.60 ± 1.31 | 24.70 ± 3.79 | 27.80 ± 0.21 | 27.30 ± 0.17 | 26.90 ± 0.23 |
| Bulk density (g/ml)            | 0.68 ± 0.03 | 0.54 ± 0.06 | 0.50 ± 0.01 | 0.74 ± 0.01 | 0.74 ± 0.02 | 0.65 ± 0.00 |
| Tapped density (g/ml)          | 0.76 ± 0.02 | 0.64 ± 0.00 | 0.56 ± 0.05 | 0.81 ± 0.00 | 0.79 ± 0.01 | 0.72 ± 0.00 |
| Hausner’s quotient             | 1.12 ± 0.02 | 1.21 ± 0.13 | 1.12 ± 0.09 | 1.11 ± 0.02 | 1.07 ± 0.02 | 1.11 ± 0.01 |
| Compressibility index (kg)     | 10.79 ± 1.39 | 13.08 ± 9.26 | 13.80 ± 7.11 | 19.97 ± 1.41 | 12.10 ± 1.64 | 17.60 ± 0.31 |

Various solvents were used for the test so as to determine the suitable medium for dissolution of formulated ibuprofen tablets.

Table 3: Assay and Solubility Profile of Ibuprofen Powder

| Test                                           | Observation | Inference |
|------------------------------------------------|-------------|-----------|
| Ig of ibuprofen powder + 10 ml Acetone          | Soluble     | ++        |
| 1g of ibuprofen powder + 10 ml 0.1 NNaOH        | Soluble     | ++        |
| Ig of ibuprofen powder + 10 ml water            | Insoluble   | --        |
| Ig of ibuprofen powder + 10 ml 0.1 N HCl        | Insoluble   | --        |
| Ig of ibuprofen powder + 10 ml chloroform       | insoluble   | ++        |

++ = Highly soluble or insoluble, and -- = Insoluble

The formulated tablets based on various percentage compositions of the binders (ginger and cassava starches) were subjected to physicotechnical characterization to determine the strength, stability and ability of the formed tablet to breakdown at certain period of time.

Table 4: Evaluation of Tablet Properties

| Binder conc. | Hardness (Kg) | Weight variation (g) | Friability (% w/v) | Disintegration time (minutes) |
|--------------|---------------|----------------------|--------------------|-----------------------------|
| 2% w/w G     | 8.55 ± 0.26   | 4.10                 | 0.72               | 22.25                       |
| 4% w/w G     | 5.54 ± 0.29   | 4.08                 | 0.88               | 15.07                       |
| 6% w/w G     | 6.37 ± 0.19   | 5.45                 | 0.88               | 18.17                       |
2% w/w C  |  8.45 ± 0.32  |  2.34  |  0.93  |  29.24  \\
4% w/w C  |  5.80 ± 0.14  |  4.70  |  0.60  |  17.16  \\
6% w/w C  |  6.60 ± 0.26  |  2.50  |  1.30  |  23.25  \\

G=Ginger starch, C= cassava starch

This result in this figure shows the release profile of the API from tablet batches formulated using varied concentration (2–6%) of ginger starch.

**Fig. 2:** Standard calibration curve for pure ibuprofen powder at 228nm

This result in this table shows the effect of the binder and the binder concentration on the actual content of the active pharmaceutical ingredient (API) on the formed ibuprofen tablet.

**Table 5:** Drug Content for Ibuprofen Tablet Formulation

| Concentration of binder ( % w/v) | Drug content (mg) | Percentage drug content ( % w/v) |
|----------------------------------|-------------------|---------------------------------|
| Ginger                           |                   |                                 |
| 2                                | 277.6             | 90                              |
| 4                                | 340.8             | 96                              |
| 6                                | 372.0             | 98                              |
| Cassava                          |                   |                                 |
| 2                                | 250.0             | 89                              |
| 4                                | 300.0             | 93                              |
| 6                                | 357.2             | 94                              |

The result in this figure shows the release profile of the API from tablet batches formulated using varied concentration (2–6%) of ginger starch.
The result in this figure shows the release profile of the API from tablet batches formulated using varied concentration (2–6%) of cassava starch.

The result on table 6 shows the amount of the API that dissolved from the tablet in the chosen medium (0.1N NaOH) with time (minutes) using various concentrations (2–6% w/w) of ginger and cassava starches.

Table 6: Dissolution profile of ibuprofen with various Conc. of Ginger and Cassava starches

| Time (minutes) | Ginger starch | Cassava starch |
|---------------|--------------|---------------|
|               | Drug dissolved (%) |               |               |
|               | 2%G          | 4%G          | 6%G          | 2%C          | 4%C          | 6%C          |
| 10            | 62.0         | 72.1         | 87.4         | 53.6         | 64.9         | 79.5         |
| 20            | 63.2         | 77.6         | 89.1         | 56.5         | 68.2         | 80.7         |
| 30            | 65.9         | 80.5         | 89.8         | 58.7         | 70.7         | 83.3         |
| 40            | 67.3         | 81.7         | 91.7         | 60.6         | 71.6         | 85.2         |
| 50            | 68.5         | 83.6         | 92.7         | 62.0         | 73.5         | 87.2         |
| 60            | 69.4         | 85.2         | 93.7         | 62.5         | 74.5         | 89.3         |
DISCUSSION

Six batches of ibuprofen granules were formulated containing varying concentration (2% w/v, 4% w/v, 6% w/v) of the binding excipients (cassava and ginger starch). From the evaluation of tablet properties as in Table 4, there was an improvement in the flow behavior of the granules formed when compared to the mere powder initially used reference to such characterization properties as compressibility index and Hausner’s quotient \(^{[14]}\). Also from the results on the same table, it was observed that the flow rate decreases with increased percentage composition of the binders (ginger and cassava starches) although the flow rate of the granules made with ginger starch was higher than that of the cassava starch in all relative concentrations (2% w/v, 4% w/v and 6% w/v). The angle of repose from 2% w/v to 6% w/v for ginger starch, ranged from 27.3°–24.7° while for cassava starch (2% w/v to 6% w/v) the value varied from 27.8°–26.9°.

The values range as obtained for angle of repose indicated excellent flow characteristics of granules made using extracted ginger starch and already established cassava starch reference to standard value ranges. The ibuprofen granules formed with ginger starch and cassava starch has decreased bulk and tapped density with increase in binder concentration although the bulk density and tapped density values were higher in cassava starch granules than in ginger starch granules. This may due to the high porosity and fluffy nature of the cassava starch powder. Despite the difference in bulk and tapped density all the granules formulated from ginger and cassava starch had a Hausner’s ratio of <1.25, which was comparable to standard values and this is an indication of a good granule flow property and acceptable compressibility index relative to the reference standard values and this indicates the possibility of compact tablet being formed when the starches are incorporated as excipients in solid dosage formulation.

Quality control tests involve series of procedures intended to ensure that a formulated product (pharmaceutical tablets) adheres to defined sets of standards. The test included uniformity of weight, crushing strength (hardness), friability, disintegration, dissolution and assay of drug content. Friability test is an attrition resistance method that evaluates the characteristics of a formulated tablet upon subject to various forces during handling between the productions up to product administration. From the result, all the batches passed the test except for 6% w/v cassava starch with a value of 1.30% reference to standard values \(^{[15]}\).

The hardness test is an indication of the compatibility and intrinsic strength of the granules. A range of 4 to 8 kg has been recommended as values accepted for crushing strength of tablets \(^{[16]}\). All the tablets passed this test except for 2% w/v ginger and cassava starch with values of 8.55 kg and 8.45 kg respectively. This may be due to the inadequate threshold of the binder concentration being attained at 2% w/v concentration.

Disintegration test is a measure of the time taken for a tablet to be broken down into smaller particles in a physiological medium. The acceptable requirement for disintegration time of uncoated tablet was 15 minutes. From Table 4, it was observed that for the ginger and cassava starches and the composition of the various concentration, only tablets formed with ginger starch 4% w/v disintegrated without getting to the limit specified in reference book, while others failed the disintegration test. This effect could be as a result of thin film formation around the granules which could increase the thickness; hence probably the concentration of the lubricant (Magnesium stearate) needs to be adjusted down ward while the disintegrant (maize starch) concentration needs to be slightly increased to embrace adequate sorption and wicking of aqueous fluid and hence enhance quick disintegration of formed tablet \(^{[17]}\).

Dissolution studies provide an insight into the release or absorption of drugs component from a dosage form. Certain factors that affect drugs dissolution includes the types and nature of binders, hardness of tablets, surface area and composition, distance of diffusion, solubility of active drug and the formulation process \(^{[18]}\). The standard dissolution profile for uncovered ibuprofen tablets stipulates that not less than 85% of the labeled drug content is dissolved within 60 minutes. From the study, it was observed that all other tablets formed using other binder concentration (4% w/v and 6% w/v) of ginger and cassava starch dissolved within stipulated time (<60 minutes) while that formulated with 2% w/v binder concentrations failed to meet the required standard. This result could be linked to the binder concentration not being up to optimum value to impact a binding and disintegrant property and by not exerting adequate sorption and wicking mechanisms, which the starches
under study was assumed to influence although in other concentrations (4% and 6%) the ginger starch had better impact as shown in Fig. 3 & Fig. 4.

In the drug content evaluation, the official standard recommended a range of 90–110% drug content [19] and from the study, all ibuprofen tablets prepared using the various starches concentration of 2%, 4% and 6% w/v of ginger and cassava starches was within the recommended limits. This also depicts that no interaction occurred between the excipients and the active pharmaceutical ingredient (API).

CONCLUSIONS

Ginger starch has been assessed to have good binding property than cassava starch hence could be a good excipient with a probable disintegrant property, based on the physicochemical and qualitative analysis of the granules and tablets produced with it. With the result obtained from the analysis, therefore, use of ginger starch as a binder and a probable disintegrating agent is highly recommendable for the formulation of ibuprofen tablet especially at concentrations of 4 to 6% w/w.

Ginger starch should be sourced and formulated at the recommended percentage (4 to 6%) concentration so as to enhance a quality binding activity as this will help to cushion the economic effect of the imported synthetic pharmaceutical binding excipients especially in developing countries.

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CONTRIBUTION OF AUTHORS

The correspondence author made 60% contribution to the success of this research work by the conception /design of the work, data analysis and interpretation, drafting of the article, critical revision of the article and approval of the article for publication. The second author has 40% contribution by financial support and in both data collection and analysis.

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