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Original Research Article

Super-disintegrant activity of acid-modified millet starch in diclofenac tablet formulations

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Abstract

Purpose: To determine the effect of acid modification on the disintegrant activity of native millet starch in diclofenac sodium tablet formulation in comparison with sodium starch glycolate.
Methods: Diclofenac sodium tablets were prepared by direct compression using sodium starch glycolate, native and acid-modified millet starches at concentrations of 2.5 and 5 %w/w. The granules were evaluated for their flow properties while the tablets were evaluated for tablet dimensions, uniformity of weight, crushing strength, friability, disintegration time, wetting time and dissolution studies. Drug-excipient interaction using DSC and FTIR was also investigated.
Results: All the granules were free flowing with angles of repose and Carr's indices of < 31° and < 21 % respectively. The tablet hardness was between 4.3 - 6.5 kp while the friability values were < 1.0 %. They all showed good wetting and disintegration time of < 3 min and 7.5 min respectively. Only batches of tablets formulated with 5 %w/w of sodium starch glycolate and acid-modified millet starch met official specification for fast disintegrating tablets. Dissolution studies showed that all batches achieved over 90 % drug release in 30 min except tablets prepared with 2.5 %w/w of the native millet starch. DSC and FTIR analyses revealed no drug interactions with excipients.
Conclusion: The acid-modified millet starch showed a shorter disintegration time and a better dissolution profile when compared with the native millet starch. Acid modification imparts better disintegration and dissolution properties to the starch. The acid-modified millet starch can also be used as a cheaper alternative to sodium starch glycolate because of the comparable disintegration times and dissolution profiles of diclofenac sodium tablets formulated with these disintegrants.

Keywords: Acid modification, millet starch, disintegrant, diclofenac, tablets

Indexing: Index Copernicus, African Index Medicus

Introduction

An oral fast-dissolving dosage form is the product of novel dosage technologies that involve the fast disintegration and dissolution of the dosage form into a solution or suspension in the mouth without the need for water. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within seconds after administration. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect [1].

Pearl millet (*Pennisetum glaucum*) is the most widely grown type of millet. Millet is an important staple food throughout large parts of Asia and western Africa containing more protein than rice. Millet is one of the oldest foods known to humans and possibly the first cereal grain to be used for domestic purposes. Millet has been used in Africa and India as a staple food for thousands of years. Today millet ranks as the sixth most important grain in the world, sustains one third of the world's population and is a

significant part of the diet in northern China, India and Nigeria [2]. The dry grain of pearl millet contains about 70% of carbohydrate which consists almost exclusively of starch [3].

Acid hydrolysis of starch has been used extensively in the food, textile and paper industries for many years to produce soluble thin-boiling starch [4]. Acid modified starches are produced commercially by hydrolyzing the starches with hydrochloric or sulfuric acid at temperatures below the gelatinization temperatures of the starch for a period of time. The process involves the cleavage of the glycosidic bonds between the monomeric units which involves both protonation of the glycosidic oxygen and addition of water to yield the reducing sugar end of the starch [5]. This leads to an increase in the relative crystallinity of starch since acid preferentially attacks the amorphous regions, while the crystalline regions remain intact [6-8]. The physiochemical properties of the starch is changed without destroying its granule structure, yielding starch with increased solubility and gel strength, and decreased viscosity [9,10]. The aims of the study were to develop fast disintegrating tablets of diclofenac sodium using acid modified millet starch as the disintegrant and to compare the physicochemical properties of the formulated granules and tablets with those formulated with sodium starch glycolate, a known super-disintegrant.

Methods

Materials

Diclofenac sodium powder was a gift sample from Edo Pharmaceuticals Ltd, Benin City, Nigeria, hydroxypropyl methylcellulose (HPMC) (Qualikems Pvt Ltd, Delhi, India), sodium hydroxide (CDH Ltd, New Delhi, India), sodium starch glycolate, α-lactose monohydrate, magnesium stearate and talc (BDH Chemicals Ltd, Poole, England). Pearl millet (*Pennisetum glaucum*) was purchased from a local market in Benin City, Edo State, Nigeria.

Extraction of millet starch

About 2 kg of the dry millet grain was washed to remove all extraneous materials and soaked in water for 24h. The steeped grains were milled into a paste using an electric grinder (Moulinex, France). The paste was mixed with sufficient water and then strained through a muslin cloth to remove the grain chaff. About 100ml of 0.1N NaOH was added to separate the starch and proteineous materials and to neutralize the prevailing slight acidity. Excess sodium hydroxide was removed by washing several times with distilled water. The clear supernatant fluid was then poured away while the sedimented starch was collected. The collected starch was spread to dry in an oven at 40 ºC. The dried starch lumps were size-reduced to a fine powder using a blender.

Acid-modification of extracted starch

Three hundred grams (dry basis) of native millet starch was hydrolyzed by suspending the starch powder in 600 ml 6 % HCl solution at 23 ± 1.0 ºC for 8 days without stirring [11]. The suspension was neutralized with 10 %w/v NaOH solution, and the starch slurry was washed five times with distilled water and dried in a hot air oven at 40 ºC for 24 h. The starch was powdered with a laboratory ball mill and passed through a 125 μm mesh sieve.

Preparation of granules and tablets

Six batches of diclofenac sodium granules and tablets were prepared with the formula outlined in Table 1. The required quantities of the ingredients needed for each batch were weighed and screened through a 125 μm sieve. The diclofenac sodium and lactose powders were dry mixed in a mixer for 5 min, then the other ingredients except the lubricant and glidant, previously mixed together were incorporated into the powder mix in geometric proportion and mixed intimately. The powder blend was slugged in a heavy-duty tableting machine (Kilian and Co, GmbH, Köln, Germany) and the resultant slugs were broken down into granules with a mortar and pestle. The screened quantities of magnesium stearate and talc were added stepwise to the granules and mixed thoroughly.
The granules were subjected to drug-excipients compatibility studies and various flow properties evaluations before being compressed by direct compression into tablets. The tablets were stored in an air tight container for further evaluation.

Drug-excipient interaction studies

DSC and FTIR compatibility studies were carried out on the native and acid modified

Table 1: Formula of prepared diclofenac sodium powder mixes and tablets

Ingredients	Quantities (mg/tablet)					
	A	**B**	**C**	**D**	**E**	**F**
Diclofenac sodium	50	50	50	50	50	50
Lactose	55	52	55	52	55	52
Hydroxypropyl methylcellulose	6	6	6	6	6	6
Sodium starch glycolate	3	6	-	-	-	-
Native millet starch	-	-	3	6	-	-
Acid-modified millet starch	-	-	-	-	3	6
Magnesium stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total	**120**	**120**	**120**	**120**	**120**	**120**

millet starch granules obtained to investigate any interaction between the drug and the starches.

The DSC analysis was carried out using a Netzsch DSC 204F1 Phoenix apparatus (Netzsch Germany). Four milligrams of the granules was weighed into an aluminium pan and sealed. The seal was pierced and calibration of the calorimeter was carried out with indium. Heating of the sample was carried out at the rate of 10 °C per min from 30 to 350 °C under nitrogen at a flow rate of 70 ml/min. FTIR analysis of the sample was done using FTIR-4100 Spectrophotometer (Shimadzu Co. Japan). The potassium bromide (KBr) tablet method was used; five milligrams of the sample was blended with KBr to 200 mg. The powder was compressed using a Sigma KBr press into a tablet shape. The tablet was placed in the sample compartment and scanned at a range of 4000 - 750 cm^{-1}.

Pre-compression (granule flow) evaluations

Bulk and tapped densities: A 30 g quantity of the granules was poured gently into a graduated measure. The volume of the granules was read and the bulk density calculated. The measure containing the 30 g of the granules was tapped 100 times on a wooden platform. The volume was noted and used in calculating the tapped density.

Carr's index and Hausner's ratio: The difference between the tapped and bulk density of the granules divided by the tapped density was calculated and the ratio expressed as percentage to give the Carr's index. The ratio of the tapped density to the bulk density of the granules was calculated as the Hausner's quotient.

Angle of repose: The fixed funnel and free standing cone method was used [12]. A transparent glass funnel was clamped at 2.7 cm above a flat horizontal surface. Granules were carefully poured through the funnel onto the horizontal surface until the apex of the cone made by the heap of granules touched the tip of the funnel. The height of the heap and the diameter of the cone base were measured. The angle of repose, θ, was calculated using Equation 1.

$$\theta = \tan^{-1}(h/r) \quad \ldots . \ (1)$$

Where h is the height of the heap of granules and
r is the radius of the circular base

Flow rate: The funnel method was employed [13]. A glass funnel was clamped to a retort stand at a certain distance from a horizontal surface. Fifty grams of granules was poured into the funnel with its orifice blocked with a glass sheet. The glass sheet was withdrawn and the granules allowed to fall freely under the influence of gravity. The time taken for the entire granules to pass through the orifice was recorded. This was carried out in triplicate and the mean values recorded.

Post compression (tablet) evaluations

The following tests were carried out on the compressed tablets using standard procedures: tablet dimensions, weight uniformity, crushing strength, friability, disintegration time, wetting time and dissolution studies [14].

Dimensions: The thickness and diameter of each of ten tablets per batch were measured using a micrometre screw gauge and their mean and standard deviation values recorded.

Weight uniformity: The weight of each of 20 tablets was determined from each batch using an electronic balance (College B154, Mettler Toledo, Switzerland) and the mean weight and standard deviation were computed.

Friability: Ten pre-weighed tablets were placed in the drum of a friabilator (Erweka GmbH, Germany) revolving at 25 rpm. After 4 min, the

tablets were brought out, de-dusted and reweighed. Their percentage loss in weight value was calculated. Triplicate determination was carried out and the mean and standard deviation were reported.

Crushing strength: Using a motorized tablet hardness tester (Campbell Electronics, Model HT-30/50, India), the crushing strength of ten individual tablets per batch was determined by diametric compression. The mean and standard deviation values were calculated.

Disintegration time: The time taken for six tablets per batch to disintegrate in distilled water at 37 ± 0.5 °C were determined using the BP disintegration tester (MK IV, Manesty Machines, UK). The mean or average time and standard deviation were calculated.

Wetting time: A weighed tablet was placed on a soaked mass of cotton wool in a petri dish and a small amount of amaranth powder was placed on the upper surface of the tablet. The time taken for the development of a red colour on the upper surface of the tablet was taken as the wetting time [15]. Triplicate determinations were carried out and the average wetting time with the standard deviations were calculated.

Dissolution studies: The dissolution profiles of the diclofenac sodium tablets were determined using the USP dissolution test apparatus (Type II) for the various batches of the tablets (Labindia-DS 8000, Mumbai, India). A dissolution medium of 900 ml of phosphate buffer solution pH 6.8 maintained at 37 ± 0.5 °C with a paddle revolution of 50 rpm was used. A 5 ml volume of dissolution medium was withdrawn at various intervals over a period of 60 min and replaced with an equivalent volume of fresh dissolution medium maintained at same temperature (37 ± 0.5 °C). The samples withdrawn were filtered and suitably diluted with phosphate buffer solution. The absorbances of the resulting solutions were measured at λmax of 276 nm (T70, PG Instruments Ltd, USA). The concentration and the percentage of drug released at each time interval was determined using the equation from the standard calibration plot obtained from the pure drug.

Statistical analysis

Descriptive statistics was done for all data using Microsoft Excel (2007). Mean and standard deviations of triplicate determinations was computed and reported. Differences between mean was determined using one-way ANOVA while $p < 0.05$ was considered significant.

Results and Discussion

Pre-compression parameters

The results of the granule flow properties are shown in Table 2. The bulk and tapped density, Carr's index and Hausner's ratio values of the granules indicated a decrease in close packing of the granules with increase in the amounts of the disintegrants in all the batches. The granules also exhibited variable flow rate that increase with increased in the quantity of disintegrants. The angle of repose values ranged from 22.22 - 30.15° and indicated that the diclofenac sodium granules had excellent flow properties.

Compatibility studies

DSC analysis: Figure 1 (a), (b) and (c) shows the DSC thermograms of pure diclofenac sodium powder and its granules prepared with native and acid modified millet starches respectively. The pure diclofenac sodium thermogram shows two endothermic peak, a sharper one at 82 °C and a

Table 2: Pre-compression properties of the different batches of diclofenac sodium granules

Batch	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (°)	Flow rate (g/sec)
A	0.50 (0.02)	0.67 (0.03)	20.32 (0.11)	1.26 (0.11)	26.27 (0.11)	5.11 (0.62)
B	0.51 (0.02)	0.61 (0.02)	16.39 (0.10)	1.19 (0.12)	22.22 (0.12)	5.24 (0.10)
C	0.49 (0.05)	0.54 (0.01)	20.53 (0.02)	1.25 (0.11)	30.15 (0.11)	4.30 (0.35)
D	0.51 (0.04)	0.60 (0.01)	17.00 (0.01)	1.20 (0.11)	28.52 (0.11)	4.50 (0.72)
E	0.53 (0.03)	0.64 (0.01)	17.18 (0.02)	1.23 (0.15)	29.13 (0.12)	5.31 (0.82)
F	0.53 (0.02)	0.62 (0.03)	16.64 (0.02)	1.17 (0.11)	26.24 (0.12)	5.96 (0.64)

Standard deviation in parenthesis

semi-broad one at 122 °C. The sharp peak may be attributed to the loss of water by the powder while the broad peak corresponds to the melting point of the amorphous diclofenac sodium powder. The thermogram of the granules prepared with native millet starch showed the characteristic peaks seen in the pure diclofenac sodium thermogram, an indication of a less likelihood of interactions between them. But the thermogram of granules prepared with the modified millet starch when compared with that of pure diclofenac sodium showed an extended broader trough at 122 °C and ending in a short spike at 150 °C. This extended broader trough may not necessarily mean that an interaction has taken place but the presence of impurities in the diclofenac sodium granules analyzed.

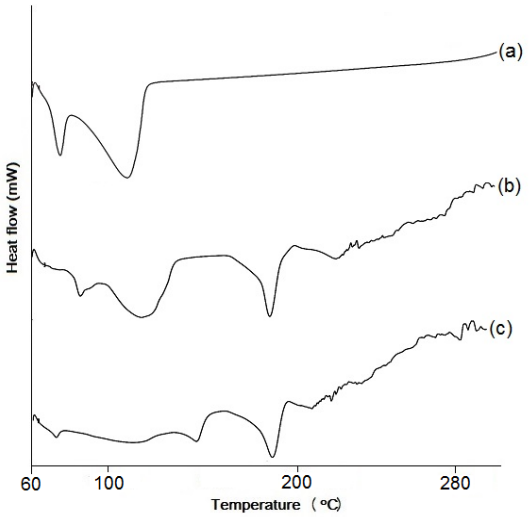

Figure 1: DSC thermograms of pure diclofenac sodium powder (a) and the granules prepared with native (b) and acid modified (c) millet starches

FTIR: The FTIR spectrum of pure diclofenac sodium powder showed characteristic peaks at 758.38, 1502.55, 1568.13 and 3394.72 cm^{-1} (Figure 2 (a)). These peaks observed for diclofenac remained unchanged when compared with the spectral data of the granules (Figure 2 (b & c)). This observation ruled out the possibility of chemical interaction and complex formation between diclofenac sodium and excipients during the mixing and slugging processes.

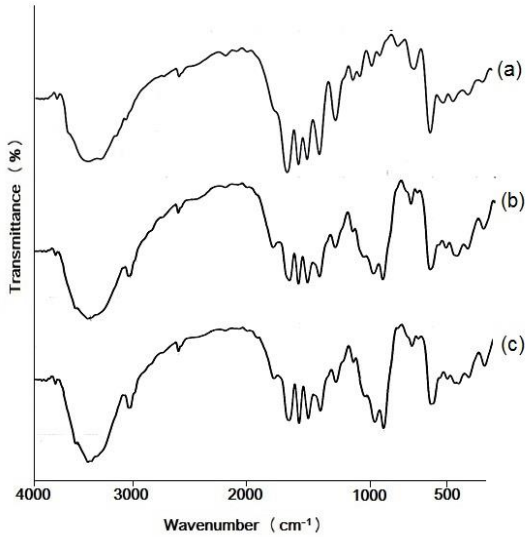

Figure 2: FTIR spectra of pure diclofenac sodium powder (a) and the granules prepared with native (b) and acid modified (c) millet starches

Post-compression parameters

Results from the evaluations carried out on the different batches of the formulated diclofenac sodium tablets are shown in Table 3.

Tablet dimensions and weight uniformity

Results from the tablets dimensions shows that the tablets met the BP specification of not more than a 5 % maximum deviation from the mean diameter value of a tablet [16].

Table 3: Post-compression parameters of the formulated diclofenac sodium tablets

Batch	Weight (mg)	Dimensions (mm)		Friability (%)	Crushing strength (kp)	Disintegration time (sec)	Wetting time (sec)
		Diameter	Thickness				
A	120 (2.00)	6.30 (0.01)	2.48 (0.02)	0.84 (0.10)	6.3 (0.50)	160 (6.50)	105 (3.00)
B	119 (1.10)	6.29 (0.02)	2.45 (0.03)	0.84 (0.08)	6.0 (0.78)	75 (3.50)	62 (4.00)
C	121 (1.20)	6.31 (0.02)	2.51 (0.01)	0.84 (0.03)	6.5 (0.70)	450 (8.50)	180 (5.00)
D	119 (1.00)	6.29 (0.04)	2.45 (0.02)	0.90 (0.01)	6.2 (0.79)	300 (7.00)	140 (4.50)
E	117 (1.00)	6.28 (0.12)	2.45 (0.02)	0.80 (0.05)	4.8 (0.30)	185 (5.40)	110 (4.00)
F	118 (2.20)	6.28 (0.10)	2.45 (0.04)	0.82 (0.05)	4.3 (0.55)	82 (2.00)	73 (2.00)

Standard deviation in parenthesis

The standard deviations (SD) of the tablet diameter values ranged from 0.01 - 0.12. There was also no significant difference ($p > 0.05$) in their values among the batches of tablets. The weights of the diclofenac sodium tablets ranged from 117 - 121 mg and show a non-significant difference ($p > 0.05$) in the tablet weights within and among the batches. These values also met

the British Pharmacopoeia requirement, which stipulates that not more than two of the individual weights should deviate from the average weight by more than ±5 % and none should deviate by more than ±10 % [17]. The variations in the tablet weights were not more than ±5 % of the calculated mean weight.

Friability and crushing strength

These parameters are very important for a fast disintegrating tablet, as they refer to the mechanical strength of the tablet. All the batches of tablets gave acceptable friability values below 1.0 %. The British Pharmacopoeia specifies a range of 0.8 - 1.0 % loss in weight of the tested tablets without capping, lamination or breaking up in the course of the test [17]. Friability relates to the crushing strength or hardness of the tablet and even though it is not an official test, it predicts the tendency of tablets to powder, chip or fragment during transportation and handling [18]. The average crushing strength values of the tablets was between 4.3 - 6.5 kp with the highest values observed in Batch C tablets. The hardness of the tablets was found to be acceptable, as a crushing strength above 4 kp is considered satisfactory for tablets [19].

Disintegration and wetting times

All the tablets formulated disintegrated within 15 min (Table 3) as specified in the British Pharmacopeia for uncoated tablets [17]. The tablets formulated with the native millet starch exhibited the longest times. The disintegration times decreased with increase in the concentration of the disintegrants. As fast disintegrating tablets, only Batches B and F tablets showed excellent disintegrating property by disintegrating within 3 min [20]. The wetting times of tablets has a direct correlation to the rate of fluid absorption by the tablet. This rate of fluid absorption is influenced by the type of disintegrant and the disintegrant's mode of action, i.e. whether the disintegrant effects tablet disintegration when in contact with fluid by capillary (wicking) or swelling effect. Generally, the shorter the tablet's wetting time, the shorter the disintegration time. The wetting times of the formulated tablets correlated with their disintegration times ($r^2 = 0.97$) as the tablet with the shortest wetting time also gave the shortest disintegration time.

Dissolution studies

The drug release profiles of the diclofenac tablet formulations are presented in Figure 3. All the tablets exhibited rapid drug release with over 80 % of drug released within 30 min, except the Batch C tablets prepared with 2.5 %w/w of the native millet starch. Dissolution depends on wetting and disintegration times; hence they are critical to the dissolution profiles of fast disintegrating tablets. There was a direct relationship between wetting time, disintegration time and the drug release profiles of the formulated tablets.

The Batch B tablets with the shortest wetting and disintegration times gave the highest drug release while the Batch C tablets with the longest wetting and disintegration times gave the lowest release. This slow release of the Batch C tablets may be attributed to a delay in the swelling of the primary particles of the native millet starch due to poor water uptake by the starch particles leading to a retarded release of the drug. This observation is in line with a study involving super-disintegrants that works primarily via swelling, where it was found that poor water uptake by swelling disintegrants leads to longer wetting and disintegration times [21].

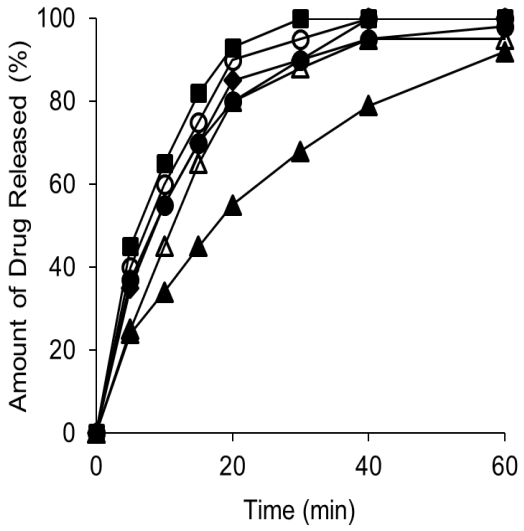

Figure 3: Dissolution profiles of the different batches of diclofenac sodium tablets. (A (◆), B (■), C (▲), D (Δ), E (●), F (○))

Conclusion

It was observed that acid modified millet starch caused a shorter disintegration time and a better dissolution profile when compared with native millet starch in diclofenac sodium tablets. This

shows that acid modification imparts better disintegration and dissolution properties to the starch. The acid modified millet starch can also be used as a cheaper alternative disintegrant to sodium starch glycolate because of their comparable disintegration times and dissolution profiles. This investigation also confirmed the linear relationship between wetting times and disintegration times of compressed tablets.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. SOE supervised the laboratory works, collected and analyzed the data and also prepared the manuscript, VNN carried out the laboratory works while MAI conceived and designed the study.

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