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Keywords: Sida acuta gum, ibuprofen, sustained release, matrix tablet, guar gum.

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Evaluating Hydrocolloids of *Sida Acuta* as Sustained Release Matrix for Ibuprofen Tablet

Sustained Release Ibuprofen Tablet using *Sida Acuta* Gum

Akpabio E I [α], Uwah T O [σ], Effiong D E [ρ] & Godwin J [ω]

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Results: Ibuprofen granules using guar gum (G1) had a flow rate of 5.19 g/s and particle density of 1.22 g/ml while granules containing *Sida acuta* gum (G2) had a flow rate of 5.60 g/s, granule and particle density of 1.23 g/ml. Tablets for both batches complied with official standards in mechanical properties of friability and crushing strength. The release kinetics obtained from the *in vitro* dissolution study showed that Batch G1 released 94.55 % of the ibuprofen while Batch G2 released 96.82 % of it in the 8 hours. Both batches followed zero-order while the mechanism of release was non-Fickian diffusion as the n-diffusion exponent was less than 0.5 for both batches. The t-test showed significant difference in the percentage of drug released by both batches of tablets ($P < 0.05$).

Conclusion: Sida acuta gum was useful as the sustained-release delivery of ibuprofen as the matrix tablets gave out higher content of the therapeutic active ingredient hence could serve as a substitute for synthetic polymer in drug delivery.

Keywords: Sida acuta gum, ibuprofen, sustained release, matrix tablet, guar gum.

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I. Introduction

The non-invasiveness, convenience, and ease of administration that characterize the oral route make it the route of choice in drug use. Solid dosage form drug design and presentation (which uses the oral route) continues to be improved upon to achieve reduced dosage frequency, better patient compliance, and, more importantly, improved therapeutic efficacy. This tripartite intention of drug formulation is achievable when drugs are delivered at non-toxic steady state in the plasma or the tissue level despite changing the *in-vivo* environment[1]. Despite the many synonyms used to explain delivery strategies that maintain plasma steady-state, sustained-release (SR) is one of such nomenclatures that accurately describe drug delivery systems that help to achieve these intentions by continuously releasing the therapeutic actives over an extended period on single dosing, thereby maintaining a prolonged effect. Orals, injectibles, and topicals have been formulated as sustained delivery. Some approaches employed to arrive at sustained release include; encapsulation of slow-release granules, tableted slow release granules, drug complexation technique, coated tablets, ion activated system, and even the tablet matrix system [1,2]

In the matrix system, a therapeutic active is embedded throughout the polymer matrix of insoluble/hydrophilic substance. The release of the drug depends on drug dissolution within the polymer matrix and diffusing out through pores in the matrix. In some formulations, the matrix physically increases in size to form a gel as the drug dissolves in it, thus allowing the drug to exit through the gel's outer surface. Many naturally occurring polymers with unique, desirable drug release retarding characteristics are used in filling the roles of excipients for SR. For the matrix systems, polymers in use include starches, hydrocolloids and cellulose as well as their derivatives. The use of gums in dosage forms and in formulating sustained release are reported in the literature. [3,4,5,6]

Sida acuta (SA) is a weed of tropical, semi-avid, and occasionally sub-tropical and warmer temperate regions. It invades open woodlands, pastures, waterways (i.e., riparian vegetation) plantations, crops, and gardens. The whole plant, although smoked in

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Mexico as a substitute to Marihuana, is reported to being widely used as a traditional medicine in Columbia, especially as an external bath for snake bite [7]. The leaves of the plant are the source of the hydrocolloid used in this research work.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used for treating pain, fever and inflammation. Some of the conditions it covers include dysmenorrhea, migraines, and rheumatoid arthritis. It has been used with some success for treating ankylosing spondylitis, gout, and psoriatic arthritis. It may reduce pain, fever, and inflammation of pericarditis. The need for managing recurrent chronic pain while overcoming frequency of administration, especially for drugs with short half-life, has necessitated the production of analgesics with sustained-release. One of such is the Neurofen® 300mg back pain capsules (an encapsulated slow-release pellet of ibuprofen). This work, therefore, was to design, formulate and evaluate sustained-release ibuprofen matrix tablets using *Sida acuta* hydrocolloid as the matrix former. Guar gum was used as a reference natural polymer.

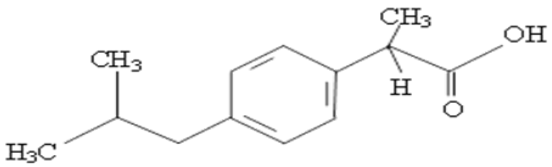


Fig. 1: Chemical structure of Ibuprofen

II. Materials and Methods

Ibuprofen hydrochloride, guar gum (Riedel De Haenac Seelze Hannover) and Microcrystalline cellulose (Guarajat Micro wax Limited, India) were obtained commercially whereas the *Sida acuta* gum was obtained locally from the leaves of the plant (from Faculty of Pharmacy farm, University of Uyo, Nigeria).

a) Study area

The study was carried out in the Undergraduate Pharmaceutics laboratory, instrument room for dosage form evaluation, and the tableting unit, all of the department of Pharmaceutics, Faculty of Pharmacy, University of Uyo, Nigeria from November 2018 - April 2019.

b) Preparation of Sida acuta gum

The leaves of the *Sida acuta* plant were collected, milled into small sizes, and weighed. The milled leaves were macerated in 7 L of hot water containing 0.1% of sodium metabisulphite for 24 h. After that, the macerate was filtered. To the filtrate, an equal volume of acetone was added in order to precipitate the gum. The precipitate was further washed with acetone severally to remove the chlorophyll and then air-dried for 24 h. The dried gum was weighed and evaluated.

c) Evaluation of the gum

The solubility, swelling index, water absorption index, pH, and organoleptic features of the gum were determined as described in previous researches [4,8]

d) Swelling Index

About 1.0 g quantity of SA gum was weighed into a measuring cylinder, and the volume occupied noted. Distilled water (10 mL) was added to it, shaken vigorously, and allowed to stand for 24 h. The supernatant was subsequently decanted but the volume of the sediment noted. The test was carried out in triplicate. The swelling index was calculated using the relation:

$$S = \frac{V2}{V1}$$

Where S = Swelling index

V1 = Gum volume before hydration

V2 = Gum volume after hydration

This test was also carried out for the guar gum.

e) Solubility Test

The solubility of gum was evaluated three solvents: water, ethanol and acetone. A 1g quantity of gum was weighed and placed in a clean test tube to which 10 mL of distilled water was added. The mixture was shaken vigorously and observed for formation of a homogenous phase. This same procedure was also carried out using the other solvents.

f) Water Absorption Index

A 1 g quantity of gum was weighed into a dish of known weight, and spread to cover the base of the dish. Water was filled in a bucket to a certain level to allow the petri dishes be placed, floating on the water in the bucket. The bucket was covered and allowed to stand for 24 hours, after which the petri dishes were, removed, wiped off, and re-weighed. This procedure was repeated for 48 hours, 72 hours and 96 hours, respectively. The percentage increase in weight, taken as the water absorption index was calculated. Determinations were done in triplicates.

g) pH Test

A 1% w/v dispersion of the gum in water was prepared and the pH determined using a bench-top pH meter (Thermo Scientific Orion Versa star). pH determinations were made in triplicate and the mean value, determined.

h) Preparation of Granules

Two batches of granules were prepared. A gum was used in each batch as the matrix-forming agent. The granules were prepared by the wet granulation technique. The ingredients were weighed accurately and properly mixed in a porcelain mortar. The weighed

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powdered mix was formed into a damp mass for granules production using 95% ethanol. The wet mass was screened through a 2 mm stainless steel sieve and the resulting granules dried at 60°C in a hot air oven (P Selecta, Spain) for 1 hour. The dried granules were further screened, using 1mm stainless steel sieve, and stored for further evaluations.

Table 1: The composition of Ibuprofen-Matrix tablet

Ingredients	G1	G2
Ibuprofen (mg)	200	200
Guar gum (%)	20	-
Sida acuta gum (%)	-	20
Magnesium stearate (%)	1	1
Talc (%)	1	1
MCC q.s to	400mg	400mg

i) Evaluation of Granules

The flow rate, angle of repose, bulk density, tapped density, Hausner's quotient, and Carr's compressibility index were determined in line with methods described by Akpabio*et al*.,(2016) [4] using 30 g of the granules.

i. *Granule density and Porosity*

The fluid displacement method was employed for determination. The weight of a 50 ml pycnometer was determined and noted. After that, the pycnometer bottle was filled with xylene and the excess wiped off. The filled bottle was re-weighed and the difference between this new weight and the empty pycnometer bottle was calculated. A 0.5 g quantity of granules was transferred into the pycnometer bottle. The excess xylene displaced by the granules was wiped off, the bottle further re-weighed. The granule density was calculated using the equation below.

$$\text{Granule density } \rho g = \frac{\rho(Ws)}{Ws-(W2-W1)}$$

G Where

ρ = density of xylene, Ws= weight of sample (granules),
W_2 = weight of pycnometer + xylene + sample
W_1 = weight of pycnometer + xylene

$$Granule\ porosity(\varepsilon)\frac{100(1-\rho b)}{\rho g}$$

Where

ρb = bulk density, and ρg = granule density

j) Formulation of Ibuprofen matrix tablets

The dried granules of ibuprofen were further sieved using a 0.25 mm stainless steel sieve to separate the fine granules from the coarse granules. The weight of the fine granules was determined and the percentage fines were calculated. The fine granules were mixed with magnesium stearate in a beaker and the coarse granules were also incorporated in the beaker and mixed properly. Talc was weighed and added to the mixture of granules and magnesium stearate, and the mixture was compressed at 25 KN using a single punch tableting machine (Cadmach Machinery Co. Pvt Ltd, India).

k) Evaluation of Physical Properties of the Tablets

i. *Tablet Diameter and Thickness*

Ten tablets from each of the batches were selected at random and the diameter and thickness of each tablet was determined using the micrometer screw gauge. The average values of the parameters for each batch was then calculated.

ii. *Tablet Weight Uniformity*

Twenty tablets were randomly selected from each batch, weighed individually, and the average weight was determined using an electronic scale (Ohaus Corporation, Australia). The mean and percentage variation was calculated for each batch.

iii. *Tablet Hardness and Friability*

This was done using the hardness tester. Ten tablets were chosen at random from each batch. Each tablet was placed diametrically between the Monsanto hardness tester (Rolex, Chandigarh), and the force needed just to crush the tablet was noted. The mean of the hardness of each batch was determined. Another ten tablets from each batch were obtained dusted, weighed and placed in separate drums of a Roche friabilator (DT-2D). The tablets were tumbled at a speed of 25 revolutions per minute for 4 minutes. The tablets were then removed, dusted and weighed again. The friability of the tablets were expressed as a percentage using the formula below;

$$\text{Friability} = \frac{change\ in\ tablet\ weight}{original\ \ tablet\ \ weight} \times 100$$

iv. *Preparation of Ibuprofen Standard Calibration Curve*

The standard concentration was prepared by dissolving 50 mg of Ibuprofen in 50 mL of 95% ethanol. This stock concentration was serially diluted appropriately using 0.1N HCl. The drug was assayed with a spectrophotometer (U2100 PC Shanghai, China) and a standard curve of absorbance versus concentration was determined.

v. *The in vitro Drug Release Study of Ibuprofen Sustained Release Tablet*

The in vitro dissolution study for the tablets was carried out using the USP basket method at 50 rpm (revolutions per minute) in a 900 mL dissolution medium containing 0.1NHCl maintained at 37 ± 0.5. A 10 mL aliquot were withdrawn and replaced with an equivalent 10 mL of the fresh dissolution medium. The withdrawn aliquot was filtered through a Whatman filter paper, and assayed using the UV Spectrophotometer (U2100 PC Shanghai, China). The assay was done at a wavelength of 264 nm.

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vi. *Tablet Content Uniformity*

Three tablets from each batch were weighed and crushed. The powder was mixed with 20 mL of chloroform for 15 minutes and filtered. The residue was then washed with three 10 mL of chloroform and the combined filtrate was gently evaporated to dryness. The residue from the filtrate was dissolved in 50 mL of methanol (95%). This solution of the residue in methanol was titrated using 0.1M sodium hydroxide solution, and an indicator, phenolphthalein. The content of ibuprofen was calculated with each milliliter of 0.1M sodium hydroxide equivalent to 0.02063 g of Ibuprofen.

III. Results and Discussion

a) Results

i. *Properties of Gums*

The leaves of *Sida acuta* yielded a 3.75% gum and is used at a concentration of 20% as a matrix former in this formulation (table 1). The yield of the gum from the leaves is low. The *Sida acuta* gum is a dark brown gum with a characteristic smell. On standing in an aqueous medium, it gave a swelling power of about 8%, and the dispersed gum in the aqueous medium is slightly acidic. Other physicochemical properties of the gum are given in Table 2. The Ruthenium and Molisch test carried out on *Sida acuta* gum gave results found in Table 3. The results confirmed that what was obtained after preparation from the leaves is the hydrocolloid.

Table 2: Properties of Guar Gum and *Sida acuta* Gum

Parameters	Guar Gum	*Sida acuta*
Organoleptic properties	Off white odorless substance	Dark brown with a characteristic odor
Swelling index	8.64 ± 0.12	8.36 ± 0.15
pH	6.06 ± 0.10	5.88 ± 0.21
Water absorption index	1.28 ± 0.13	1.26 ± 0.17
Solubility		
In water	Soluble to form mucilage	Slightly soluble
In ethanol	Insoluble	Insoluble
In acetone	Insoluble	Insoluble

Table 3: Confirmatory Tests of Gum

Test	Observation	Inference
Ruthenium Test: Small quantity of dried gum powder mounted on a slide with ruthenium red solution and observed under a microscope	Pink color develops in both samples	Gum present
Molisch test : 0.1g of dried gum powder + Molisch's reagent + conc. H_2SO_4 on the side of the test tube	Violet color observed at the function of the two layers in both samples	Carbohydrate present

b) Micromeritics of Granules and Properties of Tablets

The densities, Carr's index, and other micromeritic parameters of both batches of granules are represented in the Table 4 below. The micromeritics of powdered materials is a measure of the flow property and indicates the potential for use in direct compression. The batch of granules formed from the gum had good flow properties with the Hausner's quotient and Carr's index being < 1.2 and 12% respectively. This means granules formed from the gum can be compressed without addition of anti-adherents as excipients. The tablets formed has a friability of less than 1% and a crushing strength of 5Kgf, as seen in Table 5. The release kinetics and mechanism of the drug is seen in Table 6 and Figure 2. It shows that the tablets using *Sida acuta* gum released more than 95% of the drug over the 8 hour period of the study, and followed a zero order release kinetics.

Table 4: Micromeritics and Flow Properties of Granules

Batch/ parameter	Bulk density (g/ml)	Tapped density (g/ml)	Flow rate (g/s)	Carr's index (%)	Hausner's ratio	Angle of repose (°)	Granule porosity (%)	True density (g/ml)
G1	0.31±0.00	0.35±0.01	5.19±0.00	11.43±0.02	1.13±0.01	33.69	74.60±0.38	1.22±0.00
G2	0.30±0.01	0.34±0.00	5.60±0.00	11.76±0.01	1.13±0.01	31.29	75.61±0.02	1.23±0.00

Key: G1= Granules containing guar gum

G2 = Granules containing *Sida acuta* gum

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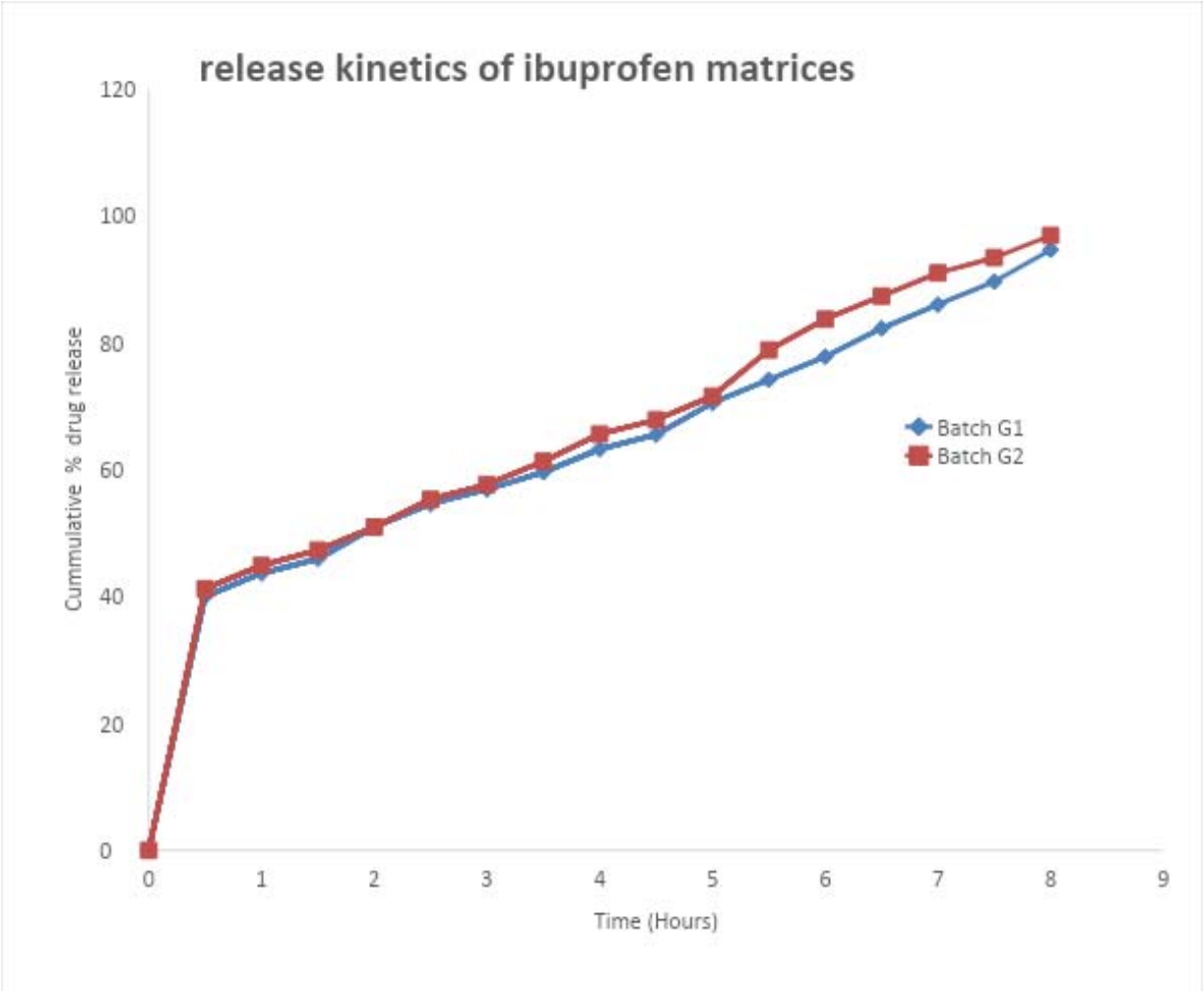
Table 5: Physical Properties of Ibuprofen Sustained Release Tablet

Batch /Parameters	Weight uniformity (g)	Hardness (Kgf)	Diameter (mm)	Thickness (mm)	Friability (%)	Content uniformity (%)
G1	0.40±0.02	5.00±0.01	12.61±0.00	3.26±0.01	0.99±0.00	105±1.00
G2	0.41±0.02	5.05±0.01	12.61±0.01	3.27±0.01	0.84±0.01	103±2.00

Key: G1 Ibuprofen tablets containing guar gum
G2 Ibuprofen tablets containing *Sida acuta* gum

Table 6: Release Kinetics of Ibuprofen Tablets

Batches	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsemeyer/Peppas (R^2)	n(diffusion coefficient)	t_{50} h
G1	0.9961	0.8739	0.9582	0.9225	0.0230	1.90
G2	0.9661	0.8692	0.953	0.9117	0.0110	1.90



Key: G1 is tablet matrix with guar gum
G2 is tablet matrix with *Sida acuta* gum

Fig. 2: Release profile of Ibuprofen matrices using natural gums

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IV. Discussion

The yield of the *Sida acuta* gum from the leaves of the plant is very low as compared to other gums from seeds or exudates from the stem [4, 8]. The result seen from the Ruthenium and Molisch tests for the *Sida acuta* gum is same for guar, indicating confirmation of the obtained gum. The pH of natural polymers is a useful parameter in determining their suitability for pharmaceutical formulations. This is because the solubility and stability of active ingredients are a function of the pH which can be influenced by an excipient's pH. *Sida acuta* being 5.88 in pH is weakly acidic (Table 2) while that may make the gum not suitable for use in drug formulations that might stay longer in the buccal cavity because of a possible mucosa irritation. It can, however, be useful as uncoated tablet matrix without gastric irritation [9].

a) Swelling index and Hydration capacity

The swelling index of the *Sida acuta* gum is relatively high with a value of 8.36% although lesser than that of guar gum. The degree of swelling of a gum reveals its capacity of its individual particles to absorb water molecules and increase in size on hydration. The swelling index value of natural gums together with their simplicity and cheap production process has been reported to be reasons for their suitability for use as release modifying polymers, one way guar gum is used [10,11]. For the flow properties, Guar gum has been reported to have a good flow[12]. There is no statistical difference between the flow of the granules of both gums when tested at $p \leq 0.05$. It means that granules formed from both gums can be directly compressed without anti-adherents as excipients.

b) Mechanical properties of Tablets

The mechanical properties of the tablets show no statistically significant difference (at $p \leq 0.05$) for both gums in the crushing strength, friability, and tensile strength, hence on the basis of obtaining tablets with satisfactory friability and crushing strength, any of the gum could be used interchangeably. However a more sensitive parameter to determine the mechanical strength of tablets, the crushing strength friability ratio (CSFR), reveals that tablets with *Sida acuta* gum as matrix-former were mechanically stronger (CSFR value of 6.01) than those of guar gum (CSFR is at 5.05).

c) Dissolution studies and Release kinetics

The release kinetics of the drug is seen in Figure 2. It shows that both gums sustained the release of the drug over a period of 8 hours giving a cumulative percentage of release to be almost 100% (specifically 96% for *Sida acuta* but 94% for Guar). At the 6h, 77% and 83% of drug was released from tablet batches of G1 and G2 respectively. Similar release kinetics was reported by Jaleh *et al.,* (2006) for natural gums such as guar gum [12]. Thus, both gums qualify as excipients for sustained release. Drug release from a tablet matrix involves concurrent penetration of matrix by the surrounding dissolution medium, drug dissolution and drug leak out through the interstitial channels within the matrix. The interplay of these three processes predicts the drug release kinetics and is usually influenced by the physicochemical properties of the drug and the polymer[13,14]. It is worthy to note that while t_{50} (that is the time for 50% of the drug release) for batches of tablets of both gums was the same (1.9 h), after 5 h, batch of tablet with *Sida acuta* released higher percentage of the active ingredient and maintained it until the 8th h when it returned to the rate of release of the tablet with guar gum. This observation may be explained with the inter particulate arrangement of the gum when well hydrated in an aqueous medium. The higher swelling index value of guar gum whose gel mass retarded the drug release in the matrix core from the 5th h, may likely be responsible. A similar value for t_{50} was reported by Eziuzo *et al.,* (2017)[15] in his kinetic studies of diclofenac matrix tablet using *Sida acuta.*

The data from the dissolution studies of the two batches of drug were subjected to four drug release models and correlation coefficient (the linearity of R^2 values) describes the likely release model. The two batches of tablets released their drug content following the zero order (Table 6). This means the same concentration of the drug is released with time throughout the period of the study irrespective of the amount of the drug that is left in the matrix. Thus, drug release process is constant and independent of initial concentration of drug in the drug delivery matrix [13]. Sustained release matrix tablets of *Sida acuta* and other solid dosage forms using natural gums or their blends have been reported to follow this course of drug release although a controlled release could have different concentration released at different times as intended.[10,12,13, 15]

V. Conclusion

Sida acuta gum modified the release of ibuprofen over a sustained period of 8 h, had good swelling index and favorable micromeritics that can make it qualify for polymer useful in sustained release even as a directly compressible excipient. It is equally valuable in use as a substitute for guar gum although the main challenge is in the yield. This no doubt requires further work to see how it can be improved.

a) Significant statement

This study, therefore, discovers the release modifying potential of *Sida acuta* hydrocolloid comparing favorably well with guar gum, a bio-polymer that can be beneficial for application in sustained release formulations. This study will help the researcher to uncover another source for tablet matrix-former from

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Sida acuta leaves that many researchers were yet to explore. However, with the low yield got, a new process on improving yield of the hydrocolloid may be investigated.

Conflict of Interest: None

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