ABSTRACT

Objective: The aim of this research work was to comparatively study various proportions of a natural hydrocolloid-Raphia africana, and polyvinylpyrrolidone (PVP) as release sustaining agents in diclofenac sodium tablet formulation.

Methods: The purified hydrocolloid (R. africana) was characterized by evaluating its organoleptic, physicochemical and flow properties. Diclofenac-polymer ratios of 1:0, 1:0.2, 1:0.4, 1:0.6, and 1:0.8 were employed to produce different granule batches using wet granulation method (that is, the drug was formulated with 0.5, 10, 15 and 20 % w/w of either R. africana hydrocolloid or PVP, and coded DPP-00, DRA-05, DRA-10, DRA-15, DRA-20, DPP-05, DPP-10, DPP-15 and DPP-20, respectively). Flow properties of granules were studied by determining bulk density, tapped density, Carr’s index, and Hausner’s ratio for all the formulations. Compressed tablets were evaluated using various parameters as weight variation, friability, hardness, tablet thickness and diameter, content uniformity and in vitro dissolution evaluated in phosphate buffer (pH 7.3).

Results: Flowability, mechanical and release parameters determined were within pharmacopoeial limits. Generally, the values of bulk and tapped densities increase as binder concentrations increase for both PVP and R. africana hydrocolloid. The values were significantly different across the batches (p < 0.05). Hardness values obtained varied significantly (p < 0.05) and were between 5 and 12 KgF which imply that most of the tablet batches are harder than normal depending on the proportion of the polymer used. All the batches exhibited friability within the standard limit without significant difference in values (p > 0.05), indicating that tablet formulated with the experimental binders would not undergo surface abrasion. All the formulations exhibited zero order kinetics except batches DPP-10 and DPP-15 which showed Higuchi mechanism. Formulation batches DRA-05 and DRA-10 showed maximum drug release of 98% and 95% respectively after 6 h. A prolonged drug release was observed on increasing polymer ratio. Significantly higher release rates (p < 0.05) were observed in the tablets formulated with PVP than those containing R. africana gum. All the batches followed non-fickian diffusion release mechanism.

Conclusion: From the study, purified R. africana hydrocolloid generally appeared to perform better than PVP as sustained release agent.

Keywords: R. africana hydrocolloid, Diclofenac sodium, Sustained release, Zero order kinetics

INTRODUCTION

The sustained release pharmaceutical delivery system is formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration [1]. This duration is in hours for oral dosage forms and varies from days to months in the case of parenteral products. According to some researchers, the basic rationale of sustained release drug delivery system development is to optimize the bio-pharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug so as to achieve and maintain a constant drug blood level such that its utility is maximized, side effects are reduced and the cure of the disease is achieved [2-4]. Employment of prolonged release formulation as supposed to conventional immediate release ones has been a widely accepted approach as it would afford the patient better compliance and enhanced bioavailability [5, 6].

Recently, polymers of plant origin have attracted tremendous interest due to their wide application as pharmaceutical adjuvants such as diluents, binders, disintegrants, thickeners, protective colloids as well as gelling agents. These natural hydrocolloids and mucilage are preferred to the synthetic ones because they are non-prohibitive, bio-compatible, and readily available than the latter. Moreover, the natural excipients are relatively non-toxic, non-irritant, possesses soothing effects and more readily available than the synthetic and semi-synthetic ones [7]. For instance, the choice of a suitable binder for a tablet formulation requires extensive knowledge of the binder properties for enhancing the strength of the tablet and also the interaction between the various materials constituting a tablet [8].

Raphia palm which belongs to the large family, Areaceae, is a genus of about twenty species native to tropical regions of Africa and especially Madagascar with one species (R. teadigra) also occurring in Central and South Africa. They grow up to 16 m tall with basically clustered stems and long leaves, and are remarkable for their compound pinnate leaves, the longest in the plant kingdom. The plants are either monocarpic, flowering once and then drying after the seeds are mature, or hypoxanthic, with individual stems dying after fruiting but the root system remaining alive and sending up new stems [9, 10].

Diclofenac is the most widely used of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of rheumatic disorders. The name diclofenac is derived from its chemical name: 2-(2, 6-dichlorophenyl) phenylacetic acid [11]. The drug has been shown to inhibit the lipoxygenase pathways thereby reducing the formation of the leukotriene. As part of its mode of action, diclofenac may also inhibit phospholipase A2 [12]. It is characterized by rapid systemic clearance, and thus warrants the use of sustained release formulation for prolonged action and to improve efficacy [13]. Also, the various experimental reports such as solubility, pH and half-life indicated diclofenac as a good candidate for a sustained release formulation. A thorough literature search showed that R. africana hydrocolloid, though possesses good binding properties in conventional tablets [14], its activity as a release sustaining agent has not been evaluated. Thus, this study was primarily designed to formulate sustained release diclofenac sodium tablet with R. africana hydrocolloid as a binder and assess its dosage sustainability, using such parameters as weight variation, friability, hardness, tablet thickness and diameter, content uniformity and dissolution test.

MATERIALS AND METHODS

Materials

The materials used are diclofenac sodium powder (Sigma-Aldrich, USA), polyvinylpyrrolidone (PVP) (FSA Lab Supplies, England), talc
powder, lactose, maize starch (BDH Chemicals Ltd, Poole, UK), magnesium stearate (Sigma-Aldrich, USA). Raphia gum was extracted and purified in the Pharmaceutical Technology Laboratory, University of Uyo, Nigeria. All other materials employed were of the Analar grade.

Methods

Gum extraction

Raphia gum was obtained from the incised trunk of R. africana palm at a village in Uyo Local Government Area of Akwa Ibom State, Nigeria. The plant was authenticated in the herbarium facility of the Faculty of Pharmacy, University of Uyo, Nigeria and the voucher number of authentication is UUPPH 8(eii). The gum was purified using an established procedure [10, 15, 16]. The raw Raphia gum was hydrated in 0.5: 95.5 (v/v) chloroform water mixture for 5 d with intermittent stirring, extraneous materials were removed by straining through a piece of calico cloth. The gum was precipitated from solution using absolute ethanol. The precipitated gum was filtered, washed with diethyl ether and then dried in hot air oven at 40 °C for 18 h. The dried gum was pulverized using a laboratory blender (Neelam Industries, India). The extracted gum was screened to obtain fines (<180 µm) and the percentage yield of the gum then computed.

Physicochemical properties

Moisture content and pH

The moisture content of the purified gum was determined by employing an Ohaus moisture balance (Ohaus Scale Corporation, USA). The pH of the supernatant liquid obtained after shaking a 2 g quantity of the gum powder with 100 ml of distilled water for 5 min was determined using a pH meter (Kent Industrial Measurements, England).

Swelling index

The swelling index of the gum sample was determined by the method employed by some workers [17, 18]. A quantity (1 g) of the powdered and dried sample was poured into 15 ml plastic centrifuge tubes and the volume occupied was recorded (V1). Ten milliliters (10 ml) of distilled water was added and the sample was mixed using mortar and pestle to obtain a homogenous mix. Then an appropriate amount of the binder (Raphia gum) was dispersed in a 5 ml plastic centrifuge tube and the volume occupied was recorded (V2). The dispersion was mixed with a vortex mixer (Vortex Gennie Scientific, USA) for 2 min and then allowed to stand for 10 min and thereafter immediately centrifuged at 1000 rpm for 10 min on a centrifuge (GallenKamp, England). The supernatant was decanted and the volume of sediment obtained (V3). The swelling index was then calculated as follows:

\[ \text{Swelling index} = \frac{V_3}{V_1} \frac{100}{1} \]  
\[ \theta = \frac{\tan^{-1} \frac{B}{R}}{R} \]  
\[ \text{Swelling index} = \frac{V_3}{V_1} \frac{100}{1} \]  

Water absorption capacity (WAC)

To 2.5 g of gum sample in a weighed 50 ml centrifuge tube, 30 ml of distilled water was added. This was then agitated on a vortex mixer (Vortex Gennie Scientific, USA) for 2 min and then allowed to stand for 10 min and thereafter immediately centrifuged at 1000 rpm for 10 min on a centrifuge (GallenKamp, England). The supernatant was decanted and the volume of sediment obtained (V3). The swelling index was then calculated as follows:

\[ \text{WAC} = \frac{(V_0 - V_2)}{V_0} \times 100 \]  

Evaluation of flow and density properties of purified gum

Angle of repose

The fixed funnel and free-standing cone method [20-22] was employed to determine the static angle of repose of the purified gum. A glass funnel was clamped on a retort stand with its tip 2 cm above a plain white sheet of paper, placed on a flat horizontal surface. A 30 g quantity of the powder was carefully poured through the funnel until the apex of the cone-shaped heap thus formed by the powder just reached the tip of the funnel. The height of the sample (H) was obtained using a cathetometer. The diameter (D) of the static base was divided by two to obtain the radius R. Angle of repose (θ) for the gum was then calculated using the equation:

\[ \text{Hausner’s index} = \frac{D}{B} \frac{100}{1} \]  
\[ \text{Hausner’s index} = \frac{D}{B} \frac{100}{1} \]  

Evaluation of flow and density properties of diclofenac sodium granules

Preparation of diclofenac granules

Diclofenac sodium granule preparation was carried out based on the following formula:

\[ \text{Diclofenac sodium-100 mg Polymer-x % Magnesium stearate-1 % Talc-1% Corn starch-5% Lactose-g s} \]

Preparation of tablets

Carefully weighed magnesium stearate (0.2 g) and talc (0.2 g) were mixed with each batch of granule in a sample bottle and then transferred into a banker. Each tablet of 400 mg was compressed using a single punch tabletting machine (SSF-3) (Cadmach machinery CO. PVT. Ltd, India) at a compression pressure of 35 kN. Each batch of tablets produced was then stored in an airtight container for further analysis.
The thickness of ten tablets from the different batches were determined using a micrometre screw gauge (0.25x0.01 mm). The average values were then computed for each batch [23].

**Weight uniformity**

Twenty tablets were obtained from each of the batches and weighed individually with an electronic analytical weighing balance (Ohaus Scale Corporation, USA). The mean weight and standard derivation were determined for each tablet batch to establish whether or not it conforms to the official weight uniformity standards [23, 24].

**Hardness test**

Tablet hardness was determined using the Monsanto hardness tester, India (MHT-20). Ten tablets from each batch were used. Each tablet was placed diametrically between the jaws of the tester and the force needed to just crush the tablet was noted. The mean of the hardness was also determined [23, 25].

**Friability test**

Ten tablets from each batch were obtained, de-dusted, weighed and placed in separate drums of a Roche friabilator (DT-2D). The tablets were tumbled for 4 min at a speed of 25 revolutions per minute. The tablets were then removed, de-dusted and weighed again. The friability of the tablets was expressed as a percentage using the formula below [23, 25].

\[
\text{Friability} = \frac{\text{weight loss}}{\text{original weight}} \times 100\% \quad \text{……….. (6)}
\]

**Tablet dissolution and release kinetics studies**

In vitro dissolution test for the tablets was carried out using the United States Pharmacopoeia basket method in the tablet dissolution test apparatus [26]. The tablet was placed in a wire mesh basket suspended in a dissolution medium of 900 ml of dissolution medium containing 2.1 %w/v of citric acid and pH phosphate buffer maintained at 37±1°C in a water bath. The wire mesh basket was rotated at a speed of 50 rpm. The experiment was allowed to run for 6 h and 10 ml aliquot withdrawn at 30 min intervals filtered through Whatman filter paper No.2 and assayed spectrophotometrically using the UV 2100 spectrophotometer. The assayed was done at a wavelength of 276 nm where diclofenac experiences peak absorption. An equal volume of fresh medium was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. The concentration of the active ingredient was then obtained from the standard Beer Lambert’s plot.

The data obtained from the dissolution studies were fitted into the release kinetics of Zero order, First order, Hücchi and Korsmeyer equations using the model dependent methods [27, 28].

**Content uniformity test**

Ten tablets were selected randomly from each batch and powdered. A quantity of this powder corresponding to 100 mg of diclofenac sodium was dissolved in 100 ml of 7.3 pH phosphate buffer stirred for 60 min and filtered. A quantity of 1 ml of the filtrate was diluted to 100 ml with the phosphate buffer. The absorbance of this solution was measured at 276 nm and content of diclofenac sodium was estimated [26, 29].

All the determinations were made in quadruplicates and the values presented were the average values (±standard deviations).

**Statistical evaluation**

All determinations were carried out in quadruplicates (n = 4). Values of parameters were presented as means±SD. Statistical evaluation was performed by employing a two-way Analysis of Variance (ANOVA) on a computer software GraphPad Prism® 4 (GraphPad Software Inc., San Diego, USA). Post-hoc (Turkey-Kramer multiple comparison) tests was used in comparing the individual differences between the samples. At 95 % confidence interval, probability (p) values less than 0.05 were considered statistically significant.

**RESULTS AND DISCUSSION**

The pure gum obtained from *R. africana* exudates was 30.4 %w/w. From the result obtained from the evaluation of gum powder flow (table 2), it was found that the flow rate, Carr’s index, Hausner’s ratio and angle of repose had values that comply with the official standard for good powder flowability.

### Table 2: Flow properties of purified *R. africana* hydrocolloid

| Parameters             | *R. africana* hydrocolloid |
|------------------------|-----------------------------|
| Angle of repose (°)    | 39.60±1.90                  |
| Flow rate (g/sec)      | 1.90±0.10                   |
| Bulk density (g/ml)    | 0.68±0.02                   |
| Tapped density (g/ml)  | 0.88±0.04                   |
| Carr’s index (%)       | 22.72±1.11                  |
| Hausner’s ratio        | 1.29±0.06                   |

Data presented are as mean values±SD, n = 4

The values of physicochemical properties (moisture content, pH, swelling index, water absorption capacity and moisture sorption capacity) determined for the hydrocolloid are presented in table [3]. The values indicate not only that the performance of the experimental hydrocolloid as excipient would be enhanced; it is also suggestive of its compatibility with other components of the formulation [10, 14].
imply that most of the tablet batches are harder than normal. This
range from 4-6 kgF but 5-8 kgF for sustained release tablets [7, 26, 30].
range from 5 -12 kgF which Official hardness values for conventional immediate release tablets
test indicate that the tablets possess significant dose uniformity. It can also be
influenced by the different density of granules and the speed of
its weight. This may depend on the die size of the tablet machine as
during dissolution test. If a tablet is too hard, it may be difficult to
dissolve during dissolution test and soft tablet cannot withstand the
pressure force applied to it. The nature of the polymer used as
binder influences the hardness of tablets. Hardness influences compaction and tablets with high compaction have a high ability to
retard solvent penetration into the tablet core.

The pre-compression evaluation of flowability and densification of the
formulated granules equally depict good flow (as shown in table 4). The higher the concentrations of either PVP or R. africana
hydrocolloid, the higher were the values of bulk and tapped
densities. Generally, as the size of granules increases, the orifice
would be blocked and the flow retarded.

| Batches | Angle of repose | Flow rate (g/s) | Bulk density (g/cm³) | Tapped density (g/cm³) | Hausner’s ratio | Carr’s index |
|---------|----------------|----------------|---------------------|-----------------------|----------------|--------------|
| DWB-00  | 2.18±0.10      | 5.35±0.20      | 0.51±0.01           | 0.57±0.01             | 1.14±0.01      | 10.88±1.01   |
| DRA-05  | 2.65±0.09      | 6.35±0.21      | 0.56±0.02           | 0.63±0.02             | 1.10±0.02      | 13.70±1.01   |
| DRA-10  | 25.27±1.22     | 6.05±0.21      | 0.63±0.03           | 0.73±0.06             | 1.15±0.03      | 15.43±2.00   |
| DRA-15  | 25.6±2.02      | 1.21±0.09      | 0.64±0.05           | 0.68±0.08             | 1.06±0.02      | 6.66±0.88    |
| DRA-20  | 25.64±1.26     | 6.11±0.09      | 0.54±0.022          | 0.597±0.019           | 1.09±0.045     | 9.54±0.90    |
| DPP-05  | 25.94±1.25     | 6.04±0.18      | 0.54±0.022          | 0.553±0.015           | 1.14±0.019     | 14.25±2.01   |
| DPP-10  | 30.39±2.41     | 6.46±0.02      | 0.48±0.012          | 0.600±0.022           | 1.09±0.033     | 9.89±1.04    |
| DPP-15  | 29.55±2.50     | 5.20±0.03      | 0.54±0.020          | 0.723±0.020           | 0.86±0.017     | 16.05±1.08   |
| DPP-20  | 25.90±2.52     | 7.14±0.02      | 0.62±0.022          | 0.723±0.020           | 0.600±0.022    | 16.05±1.08   |

| Batch | Weight variation (g) | Hardness (kgF) | Friability (%) | Diameter (mm) | Thickness (mm) | Drug content (%) |
|-------|----------------------|----------------|---------------|---------------|----------------|------------------|
| DWB-00| 0.40±0.02            | 4.45±0.39      | 1.11±0.01     | 12.51±0.02    | 2.56±0.04      | 82.67±9.5       |
| DRA-05| 0.40±0.01            | 8.20±0.24      | 0.43±0.01     | 12.50±0.02    | 2.57±0.01      | 80.00±8.5       |
| DRA-10| 0.40±0.01            | 9.30±0.21      | 0.45±0.02     | 12.53±0.02    | 2.58±0.12      | 77.33±2.4       |
| DRA-15| 0.40±0.01            | 10.25±0.24     | 0.20±0.01     | 12.55±0.01    | 2.58±0.04      | 73.50±8.4       |
| DRA-20| 0.40±0.02            | 5.85±0.23      | 0.23±0.01     | 12.50±0.02    | 2.54±0.01      | 72.85±2.6       |
| DPP-05| 0.40±0.01            | 6.85±0.23      | 0.45±0.01     | 12.50±0.05    | 2.53±0.02      | 83.00±7.7       |
| DPP-10| 0.41±0.03            | 6.85±0.23      | 0.22±0.01     | 12.50±0.02    | 2.52±0.01      | 80.00±5.5       |
| DPP-15| 0.40±0.01            | 5.85±0.23      | 0.22±0.01     | 12.55±0.01    | 2.52±0.01      | 76.32±7.8       |
| DPP-20| 0.40±0.01            | 10.65±0.23     | 0.45±0.01     | 12.55±0.01    | 2.53±0.02      | 75.15±5.9       |

Data presented as mean values±SD, n = 4.
From the results obtained for dissolution test, plots were made of percentage diclofenac released against time for all the tablets containing *R. africana* hydrocolloid and PVP as binders. Typical plots for tablets formulated with 5 %w/w and 20 %w/w of the binders are presented in fig. (1). Values obtained when data from dissolution studies were fitted into the equations of Zero order, First order, Higuchi and Korsmeyer are as shown in the table (6). Batches DWB-00, DRA-05, DRA-10, DRA-15, DRA-20, DPP-05, and DPP-20 showed zero order kinetics meaning that diffusion in these batches was independent of the initial concentration of drug in the dissolving medium. Two batches of the formulations containing synthetic polymer-DPP-10 and DPP-15 showed Higuchi kinetics. Therefore *R. africana* gum is a good choice for sustained release formulations, thus confirming the findings of Bhosale and co-workers that natural hydrocolloids are effective alternative binders to synthetic ones in the formulation of sustained release tablets [29]. The release rates shown by tablets containing PVP were significantly higher (p <0.05) than those exhibited by those containing *R. africana* hydrocolloid. The mechanism of release for all the batches followed non-fickian diffusion.

Batches formulated with polyvinylpyrrolidone (PVP) showed higher release than those formulated with *R. africana* gum. This may be due to slow hydration of matrix and its property to form a gel layer which retards the drug release from the tablet. Highest release of the polymer (*Raffia* gum) was obtained in batch DRA-05 with 98 % and DRA-10 with 95 % release. The highest release for the synthetic binder (PVP) was obtained in batches DPP-05, at 110 %, 103 % and 96 %, respectively.

The results obtained indicate that the batches complied with the standard requirements for uniformity of active ingredients. This implies that the tablets contain a relatively uniform amount of active ingredient (diclofenac). As a result, the tablets would exhibit uniform potency which characterizes a positive content uniformity test result.

**CONCLUSION**

From the study, the use of Raphia gum as a binder in formulating sustained release diclofenac tablet was satisfactory based on compliance with official standards. All the formulations containing the natural gum exhibit sustained release with formulation DRA-20 containing 20 % of the gum found to release the drug in a slow, controlled manner with maximum drug release of 83 % after 6 h. This implies that the percentage of drug release decreases with increasing polymer content. The rate of release for the synthetic polymer (PVP) was much higher than for the natural polymer (Raphia gum) thereby making Raphia gum a better candidate for sustained release formulation. The kinetics of drug release from the tablets followed zero order with non-fickian diffusion mechanism.

**ACKNOWLEDGEMENT**

The authors appreciate the technical staff of Departments of Pharmaceutics and Pharmaceutical Technology, and Pharmacognosy and Natural Medicine, University of Uyo, Nigeria.

**AUTHORS’ CONTRIBUTION**

The first author conceived and designed the work, supervised the laboratory aspect, assembled, analysed and interpreted the data and wrote the final manuscript. The second author carried out the laboratory work and collected the raw data.

**CONFLICTS OF INTERESTS**

Declared none
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