



## Influence of Cocoa Butter and Coconut Oil Lubricants on Quality Parameters of Effervescent Diclofenac Tablet Formulation

Adedokun MO\*, Olorunsola EO, Nse IA

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Uyo, Uyo, Akwa Ibom State, Nigeria

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### ABSTRACT

Lubrication of effervescent tablet formulations with popular lubricants prior to compression, in many cases, is often accompanied with such challenges as incompatibilities and high cost. Hence, the rising need to search for more effective, more compatible and cheaper natural lubricants for this delivery system to promote patient therapeutic benefits. This work is thus designed to examine the properties of cocoa butter and coconut oil as alternative lubricants in comparison with polyethylene glycol (PEG) at different concentrations in effervescent Diclofenac tablet formulation. Cocoa butter and coconut oil were extracted from the seeds of *Theobroma cacao* and the meat of matured fruits of *Cocos nucifera*, respectively. The physical mixtures of the tablet formulations containing either cocoa butter, coconut oil or polyethylene glycol as lubricants at varying concentrations (0- 4%) were assessed for their density and fluidity properties using angle of repose, Carr's index, Hausner's ratio, bulk and tapped densities as assessment parameters. Direct compression method was used to prepare the tablets at a compression load of 4.5 KgF. The quality parameters of the effervescent tablets – tablet dimensions, weight variation, crushing strength, friability, disintegration and effervescence times - were also evaluated. The flow properties and other parameters were within the prescribed official specifications. Statistically, there was no significant difference between the values of tablet dimensions ( $p > 0.05$ ). While the values of the tablet crushing strength decreased, friability (%), disintegration and effervescence times increased as the lubricant concentration increased for all the batches. Tablets formulated with cocoa butter and coconut oil lubricants at concentrations of 3 - 4 %w/w and 4 %w/w, respectively, exhibited good quality parameters, and, therefore, could serve as alternative lubricants in producing effervescent tablets with acceptable mechanical strength and short effervescence time.

**KEYWORDS:** *Effervescent tablet, lubrication, cocoa butter, coconut oil, polyethylene glycol.*

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### INTRODUCTION

Recently, formulation scientists have increased their effort towards designing delivery systems that would serve as alternatives to oral dosage delivery system which is adjudged the most popular method of drug administration. This is due to the problems such as patients' non-compliance, slow absorption and delayed bioavailability that usually accompany the oral administration [1]. These can be overcome by presenting the drug in liquid form, however, many active pharmaceutical ingredients (APIs) exhibit low level of stability in liquid systems. Thus, effervescent tablet serves as an alternative dosage

form [2-4]. Effervescent tablet formulation is beginning to gain popularity and acceptance as drug delivery system, because of their easy administration and better patient compliance [5]. It is designed to be instantly dissolved in water before administration [6]. The tablet is promptly broken apart by internal release of carbon dioxide (CO<sub>2</sub>) in water by the reaction between acids (typically, tartaric, palmitic and citric) and alkali carbonates or bicarbonates in the presence of water [1,7]. Effervescent tablets are convenient, attractive, and easy to use as pre-measured dosage forms with

\*Corresponding author: mo\_adedokun@yahoo.com; +234 (0) 803 4396 937

faster absorption, enhanced bioavailability [8], improved patient compliance, good stomach tolerance, as well as palatability. The major challenges often encountered in their formulation are technological (especially hygroscopicity) and lubrication. To avoid a premature effervescent reaction in the tablets, materials with low moisture content should be employed as effervescent reaction may begin with small quantity of water present in any of the material constituents [9]. To prepare an acceptable and marketable product, lubrication process has to be carried out with great caution.

An ideal lubricant should reduce friction effectively in small quantities with no adverse effects on the formulation. It should be chemically inert, readily available and reasonably cheap. It should not be affected by process variables and be consistent from batch to batch. However, an ideal lubricant exhibiting all these desirable properties is yet to be discovered [10]. It is thus expedient to evaluate two naturally sourced materials – cocoa butter and coconut oil as novel lubricants in an effervescent tablet formulation.

Cocoa butter (theobroma oil) and coconut oil (copra oil) are edible vegetable lipids obtained from the seeds of Cocoa tree - *Theobroma cacao* (family Sterculiaceae) and endocarp of matured coconut palm - *Cocos nucifera* (family Arecaceae), respectively. These materials had been found to be useful in food and health industries [11, 12]. Alebiowu and Adeagbo [13] had exploited cocoa butter in co-processed form as lubricant in normal release paracetamol tablets. Although, both materials (cocoa butter and coconut oil) had recently been employed as lubricants in conventional paracetamol tablets [14], there seems not to be any reported work on their use in effervescent tablets.

The purpose of this study was therefore to elucidate the effect of the natural lubricants - cocoa butter and coconut oil in designed, formulated and directly compressed effervescent tablets of Diclofenac sodium, a model drug. The tablets' qualities in terms of tablet dimensions, weight variation, hardness, friability, disintegration and effervescence times were then assessed and compared with tablets formulated with polyethylene glycol (PEG) 6000 lubricant.

Diclofenac sodium is a non-steroidal anti-inflammatory drug that is used for symptomatic relief of inflammation, stiffness, osteoarthritis and

joint pain associated with rheumatoid arthritis [15,16]. It is expected that its administration as effervescent tablets would enhance bioavailability which would lead to prompt onset of pharmacological action of the active ingredient and speedy relief to patients in such conditions [9].

## MATERIALS AND METHODS

### Materials

The materials used are Diclofenac sodium, Tartaric acid ((Sigma-Aldrich, USA), Sodium citrate, Sodium bicarbonate, Anhydrous Citric acid, Ascorbic acid (AB Knight and Co., London, UK), Polyvinylpyrrolidone (FSA Lab Supplies, England), Polyethylene glycol (PEG 6000), 95% Ethanol, N-hexane (Sigma – Aldrich Laborchemickalien GMBH, Seelze, Germany). Distilled water was prepared in the laboratory of the Department of Pharmaceutics and Pharmaceutical Technology, University of Uyo, Nigeria. Other materials used are fresh matured cocoa pods and coconut fruits. All other chemicals and reagents used were of laboratory grade.

### METHODS

#### Preparation of lubricant powder

The cocoa pods and coconut fruits obtained from Ikono Local Government Area of Akwa Ibom State were authenticated in the herbarium unit of the Faculty of Pharmacy, University of Uyo, Nigeria. The voucher numbers of authentication are UUPH8 (b) for coconut and UUPH31 (g) for cocoa pods. Extraction of cocoa butter and coconut oil from the plant materials were carried out and stored appropriately as earlier reported in a preliminary investigation [14]. Various characteristics of the prepared lipids – organoleptic properties, specific gravity, acid, saponification, ester and iodine values - were determined. Each of the lipids was then absorbed on adequate quantity of magnesium oxide and stored in a screw-capped bottle [14].

#### Preparation of physical mixtures for effervescent tablet formulation

Direct compression method was employed in the effervescent Diclofenac sodium production. The weight of each tablet was targeted at 1000 mg. The formula for the production of the tablet is as follows:

Ingredients	Proportion (%w/w)
Diclofenac Sodium BP	5.00
Anhydrous Citric acid	11.25
Tartaric acid	22.50
Ascorbic acid	11.25
Sodium Bicarbonate	35.00
Polyvinylpyrrolidone	2.00
Sodium Citrate	X <sub>1</sub>
Lubricant	X <sub>2</sub>

**Note:**

1. The proportions of Sodium citrate employed (X<sub>1</sub>) are 130, 120, 110, 100 and 90 mg for the formulations containing lubricant (PEG 6000, cocoa butter or coconut oil) at 0, 1, 2, 3 and 4 %w/w concentrations (X<sub>2</sub>), respectively.

2. DWL – Diclofenac tablets formulated without lubricant; DPG – Diclofenac tablets formulated with PEG 6000 as lubricant; DCB – Diclofenac tablets formulated with cocoa butter as lubricant  
DCO – Diclofenac tablets formulated with coconut oil as lubricant

A total of 13 batches were produced, a batch was formulated without lubricant (0 %) and four batches each containing 1, 2, 3 and 4 %w/w of polyethylene glycol, cocoa butter and coconut oil, respectively. Appropriate quantities of acids in the formulations; Ascorbic acid, anhydrous citric acid and tartaric acid as indicated in Table 1 were weighed and triturated in geometric dilution for 3 minutes in a porcelain mortar. All basic compounds: sodium bicarbonate, sodium citrate and diclofenac sodium were also weighed and triturated together in another mortar. The acidic and the basic portions were separately dried in an electric oven (P-selecta, 0384635, China) and then mixed together thoroughly in dry air atmosphere. The resultant mixture of each batch which was directly compressible was stored in air tight container.

**Evaluation of physical mixtures for effervescent tablet formulation**

Some density and various fluidity parameters – bulk and tapped densities, flow rate, angle of repose, Hausner’s ratio and Carr’s compressibility index were determined using methods employed by various workers [14,17,18].

**Direct compression of the granules**

To the mix, appropriate quantity polyvinyl pyrrolidone (PVP) as indicated in Table 1 was added and triturated properly. This contained no lubricant and was coded DWL0 (that is, Diclofenac sodium tablets containing no lubricant (0 %w/w)). Also, either polyethylene glycol 6000 (control lubricant), processed cocoa butter or coconut powder (1 – 4 %w/w) was added to the batches of powder mix (four batches for each lubricant). The mixture was compressed directly on single punch tableting machine (Manesty F3, SSF-3) to a target weight of 1000mg at a compression load of 4.5 KgF. The tablets were packaged in Aluminium foil then placed in air-tight containers over silica gel. The diameter and the thickness of each tablet were determined in triplicates using micrometer screw gauge and the mean values were recorded.

**Effervescent tablet evaluation**

**Weight Variation**

Twenty tablets were each selected randomly from the thirteen batches and were weighed individually and the average weight for each of the thirteen batches was determined. The deviation of each tablet from average weight was calculated, the percent deviation and standard deviation were computed.

**Table 1: Formulae for Effervescent Diclofenac Sodium Tablets (1000 mg)**

INGREDIENTS (MG)	DWL0	DPG1	DPG2	DPG3	DPG4	DCB1	DCB2	DCB3	DCB4	DCO1	DCO2	DCO3	DCO4
Diclofenac Na	50	50	50	50	50	50	50	50	50	50	50	50	50
Anhydrous citric acid	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5
Tartaric acid	225	225	225	225	225	225	225	225	225	225	225	225	225
Ascorbic acid	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5	112.5
Sodium bicarbonate	350	350	350	350	350	350	350	350	350	350	350	350	350
Polyethylene glycol (PEG) 6000	0	10(1%)	20(2%)	30(3%)	40(4%)	-	-	-	-	-	-	-	-
Cocoa butter	0	-	-	-	-	10(1%)	20(2%)	30(3%)	40(4%)	-	-	-	-
Coconut oil	0	-	-	-	-	-	-	-	-	10(1%)	20(2%)	30(3%)	40(4%)
Sodium citrate	130	120	110	100	90	120	110	100	90	120	110	100	90
Polyvinylpyrrolidone (PVP)	20	20	20	20	20	20	20	20	20	20	20	20	20
TOTAL	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000

### Friability test

Ten tablets from each of the thirteen batches were de-dusted, weighed and put in the drum of a Roche friabilator (DT – 2D). The tablets were then tumbled for 4 minutes at a speed of 25 revolutions per minute. They were removed, de-dusted and reweighed. The friability was computed as percentage weight loss:

$$\% \text{ friability, } F = \frac{\text{Weight loss} \times 100\%}{\text{Original weight}}$$

### Tablet crushing strength test

Each of ten tablets from each batch was held diametrically in the jaws of Monsanto hardness tester and the force required to crush the tablet was recorded. The mean crushing strength and the standard deviation were computed.

### Disintegration time test

The disintegration time of the tablets was determined using the British Pharmacopoeia disintegration apparatus containing distilled water at  $37 \pm 2^\circ\text{C}$ . Six tablets each from the thirteen batches were placed individually in each of the cylinder of the disintegration apparatus and the time taken for the fragments of the six tablets to pass through the screen was recorded [19].

### Determination of effervescence time and pH

A tablet was placed in a beaker containing 200 ml of water at  $25 \pm 0.5^\circ\text{C}$  and, with the aid of a stopwatch; the time taken to obtain a clear solution was recorded as effervescence time (regardless of some foaming observed) [20]. The pH of the resultant solution was determined on a pH meter (Kent Industrial Measurements, England).

### Statistical analysis

Two-way Analysis of Variance (ANOVA) on a computer software GraphPad Prism® 4 (GraphPad Software Inc., San Diego, USA) was used for statistical analysis of the tablet properties determined for the effervescent tablets. Post-hoc (Turkey-Kramer multiple comparison) test was employed in comparing the differences between the samples. At 95% confidence interval, probability, *p* values less than 0.05 were considered significant.

## RESULTS AND DISCUSSION

The results of the preliminary investigations carried out on cocoa butter and coconut oil - percentage yield of the lipids, organoleptic properties, solubility,

specific gravity, acid, saponification, ester, iodine and pH values of the cocoa butter and coconut oil were as earlier reported [14].

The values of bulk and tapped densities, flow rate, angle of repose, Hausner's and Carr's compressibility indices determined for all the formulations are presented in Table 2. These parameters are the compendial methods for evaluation of powder flow and adequate knowledge about them is crucial during mixing, packaging and transportation [21]. Powder flow from the hopper into the dies of the tablet press often determine the tablet's weight, hardness and content uniformity and is thus a principal requirement in tableting. During tablets manufacturing, the flow of powder/granules from the hopper into dies often determine the weight, hardness and content uniformity [22, 23].

Generally, tablets produced using different concentrations of PEG, cocoa butter and coconut oil as lubricants complied with the standard for tablet uniformity, that is, not more than 2 tablets should vary by more than 5% deviation for tablets containing an average weight of 250 mg or more [22]. However, batches formulated with low concentrations (below 3 %*w/w*) encountered difficulty during ejection thereby causing picking and sticking in the die cavity which led to some weight variation. This was most prominent in the batch formulated without lubricant.

Expectedly, the tablet diameter values are averagely the same for all the tablets in all the batches since they were compressed in the same 12.50 mm die. The plots of mean tablet thickness (Figure 1) and the values of the parameter presented in Table 3 indicate that the higher the lubricant concentration, the higher the tablet thickness. This is probably because as the concentration increases, inter-particulate bonds become weaker between the diclofenac particles; hence the tablets formed upon compression would be less compact.

The crushing strength values obtained for all the batches as presented in Table 3 complied with the minimum standard of not less than 4 KgF considered acceptable for normal release uncoated tablets [15,23]. This is an indication that they possess acceptable resistance to breakage and chipping. It should be noted that crushing strength of pharmaceutical tablets is often influenced by the type and quantity of lubricant employed [22]. It was observed that low concentration of lubricant led to

picking and chipping of the tablets though with high crushing strength, high concentration yielded structurally weak tablets thereby decreasing their

crushing strength as seen in Table 3 and in the typical plots of tablet crushing strength against concentration of the lubricants (Figure 2).

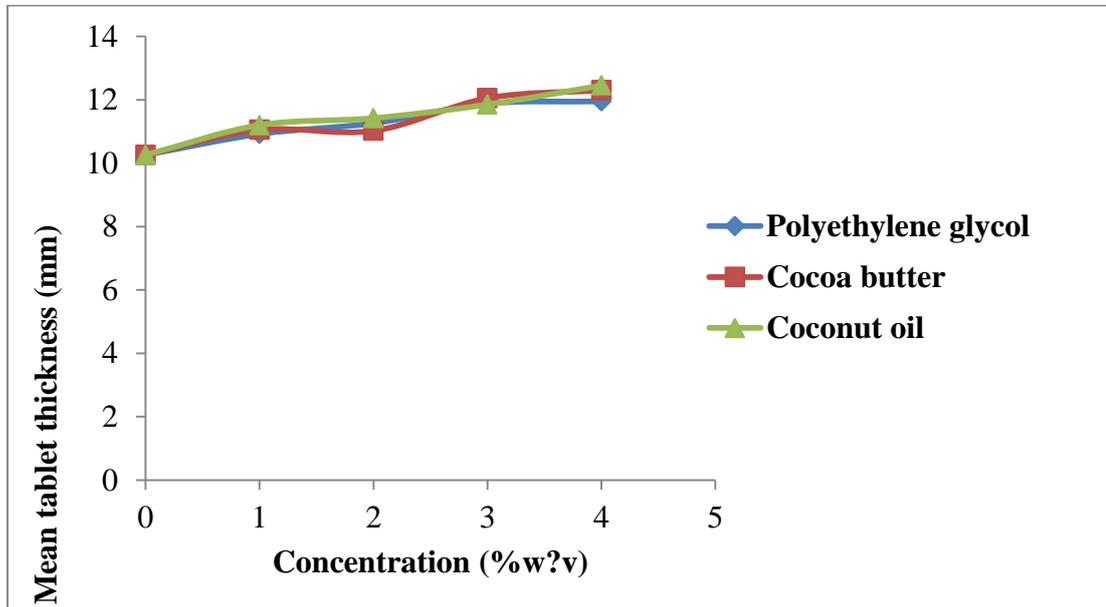


Figure 1: Plots of mean tablet thickness against concentration (%w/w) for effervescent Diclofenac tablets formulated with polyethylene glycol, cocoa butter and coconut oil lubricants

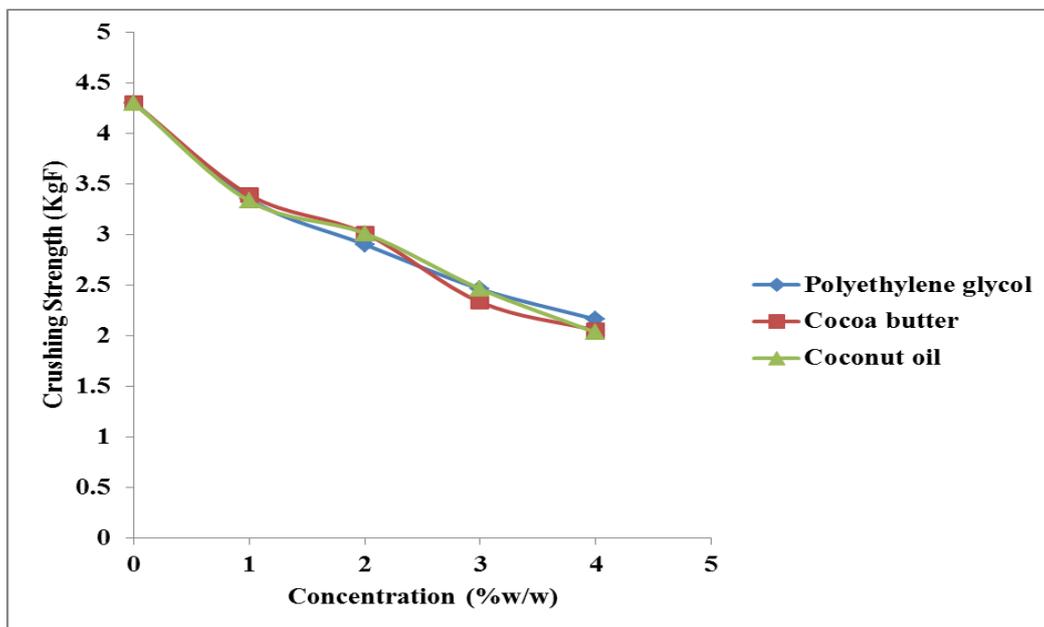


Figure 2: Plots of tablet average crushing strength against concentration (% w/w) for effervescent Diclofenac tablets formulated with polyethylene glycol, cocoa butter and coconut oil lubricants

**Table 2: Density and flow properties of effervescent Diclofenac physical mixtures formulated with cocoa butter, coconut oil and PEG lubricants**

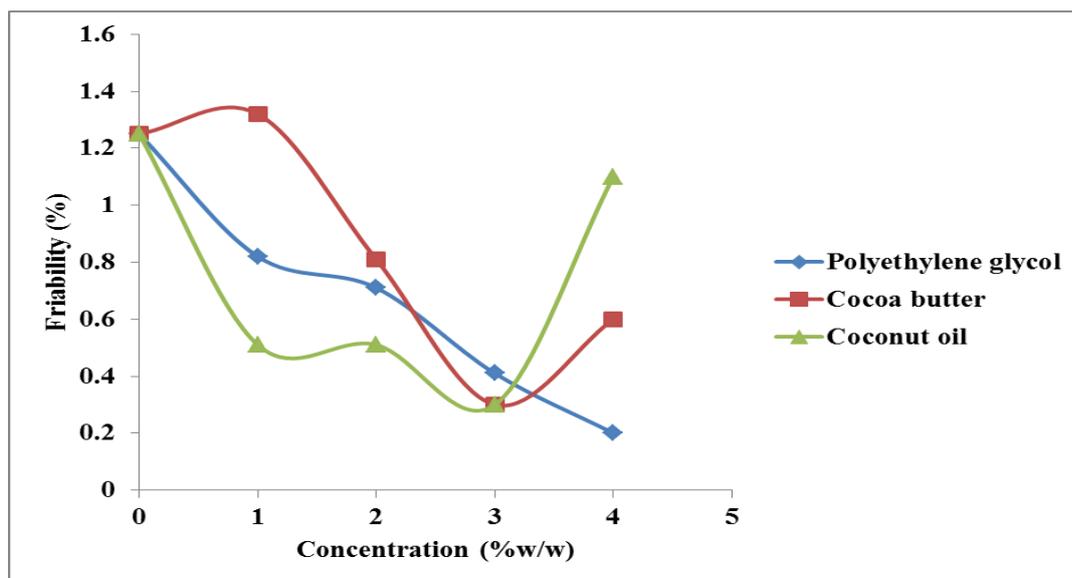
Batches	Bulk density (g/cm <sup>3</sup> )	Tapped Density (g/cm <sup>3</sup> )	Flow rate (g/sec)	Angle repose (°)	Hausner's quotient	Carr's index (%)
DWL	0.859	0.987	21.21	24.1	1.15	12.97
DPG1	0.851	0.983	21.04	27.6	1.16	13.43
DPG2	0.848	0.973	20.69	29.2	1.15	12.85
DPG3	0.865	0.981	20.20	23.1	1.13	11.82
DPG4	0.858	0.980	20.66	25.1	1.14	12.45
DCB1	0.852	0.987	19.83	23.8	1.16	13.68
DCB2	0.854	0.995	20.81	23.9	1.17	14.17
DCB3	0.869	0.973	20.82	23.6	1.12	10.68
DCB4	0.859	0.982	20.33	23.0	1.14	12.53
DCO1	0.859	0.981	20.45	24.5	1.14	12.44
DCO2	0.851	0.961	20.79	26.0	1.13	11.35
DCO3	0.856	0.974	20.44	26.0	1.14	12.11
DCO4	0.859	0.971	20.11	25.4	1.13	11.53

Friability values, which measure the tendency of tablets to resist surface abrasion [22] were shown in Table 3 to generally fall within 0.8-1% which is frequently quoted in literature as the acceptable range for pharmaceutical tablets and granules [24] indicating that the tablets possess good ability to resist surface abrasion. However, in direct compression formulations, values of up to 2% and above have been reported [23]. Generally, at low concentrations of the natural lubricants (up to 3 %<sub>w/w</sub>), there was a decrease in friability values as the concentration increased after which an increase was observed as shown in the representative plots in Figure 3. This may be due to as a result of forces of attraction in the tablet mass [13].

Values of disintegration time (the period of time required under specified conditions for a number of tablets to disintegrate into particles) for the formulated tablets are presented in Table 3. The official compendia stipulates disintegration time for different types of tablets and effervescent tablets must disintegrate in 200 ml of non-agitated water at 15-25 °C within 5 minutes [15,23]. All the tablets passed the disintegration time test for effervescent tablets. Generally, an increase in the disintegration time was observed as lubricant concentration increased for all the formulations (Figure 4). It had been reported that high levels of lubricant may result in prolonged disintegration and dissolution [22].

**Table 3: Quality parameters of effervescent Diclofenac tablets formulated with cocoa butter, coconut oil and PEG lubricants**

Batches	Average tablet diameter (mm)	Average tablet thickness (mm)	Weight Variation (g) Mean ± SD	Crushing strength (KgF) Mean ± SD	Friability (%) mean ± SD	Disintegration time (secs) mean ± SD	Effervescence time (sec) mean ± SD	pH value
DWL	12.55±0.60	10.26±0.48	0.964±0.014	4.30±0.20	1.25±0.05	25.25±0.45	33.50±1.02	6.2
DPG1	12.53±0.62	10.92±0.58	0.980±0.007	3.35 ±0.15	0.82±0.03	28.37±0.53	42.70±1.55	6.1
DPG2	12.50±0.61	11.26±0.48	0.984±0.008	2.90±0.12	0.71±0.03	43.86±0.55	45.66±2.15	6/1
DPG3	12.50±0.59	11.88±0.52	0.993±0.008	2.46±0.11	0.41±0.02	56.21±1.00	48.30±2.04	6.0
DPG4	12.52±0.55	11.95±0.52	1.011±0.016	2.16±0.14	0.20±0.02	94.83±2.45	65.70±1.56	6.9
DCB1	12.51±0.61	11.05±0.62	0.963±0.003	3.39±0.11	1.01±0.06	29.53±1.22	24.90±0.35	6.1
DCB2	12.51±0.56	11.02±0.50	0.972±0.005	3.01±0.13	0.81±0.03	47.55±1.67	28.90±0.50	5.9
DCB3	12.55±0.56	12.05±0.45	0.993±0.003	2.33±0.14	0.30±0.01	44.21±1.05	38.21±0.45	6.0
DCB4	12.54±0.63	12.30±0.60	1.001±0.007	2.05±0.13	0.60±0.03	76.73±3.00	85.34±2.55	6.0
DCO1	12.53±0.59	11.20±0.45	0.964±0.004	3.33±0.19	0.51±0.03	44.08±2.05	45.10±0.83	6.1
DCO2	12.54±0.55	11.42±0.50	0.976±0.031	3.01±0.16	0.51±0.02	56.91±2.01	64.66±2.00	5.9
DCO3	12.57±0.70	11.85±0.55	0.973±0.007	2.46±0.18	0.30±0.02	65.13±1.89	67.33±2.11	5.9
DCO4	12.51±0.61	12.45±0.65	0.995±0.005	2.03±0.12	1.10±0.04	105.06±5.00	104.33±4.05	6.0



**Figure 3: Plots of tablet average friability against concentration (% w/w) for effervescent Diclofenac tablets formulated with polyethylene glycol, cocoa butter and coconut oil lubricant**

The effervescence time of all the formulations were less than 3 minutes and all were in the range stipulated in the official compendia [23]. All of the formulations as seen in Table 3 exhibited complete effervescence within 25 to 104 seconds. Also the effervescence time was observed to be increasing with increasing concentration of lubricant as seen in Figure 5. Foaming was however observed in the course of effervescent time test specifically in the batches formulated with cocoa butter and coconut oil as lubricant because of their hydrophobicity although prompt dispersion exhibited is desirable. The pH values obtained for the dispersed tablets indicated slight acidity, close to the pH condition of the stomach where diclofenac is absorbed and will thus aid its absorption. Also, the values were generally similar which is a pointer to a high level of uniformity of the formulations [18, 24]

Statistically, there was no significant difference between the values of tablet weight variation as well as crushing strength for all the formulations ( $p > 0.05$ ). The values of other parameters – friability, disintegration and effervescence time, were significantly different among the lubricants.

### CONCLUSION

From the study, the two experimental lubricants – cocoa butter and coconut oil – appeared to be better than the commercial PEG in effervescent tablets in view of the better tablet quality properties that their formulations exhibited in many cases. Generally, the rank order of the performance of the three lubricants is: cocoa butter > coconut oil > PEG. The challenge of lubrication of effervescent tablet

can thus be overcome by utilizing cocoa butter and coconut oil as suitable alternatives to the more expensive lubricants like polyethylene glycol.

### AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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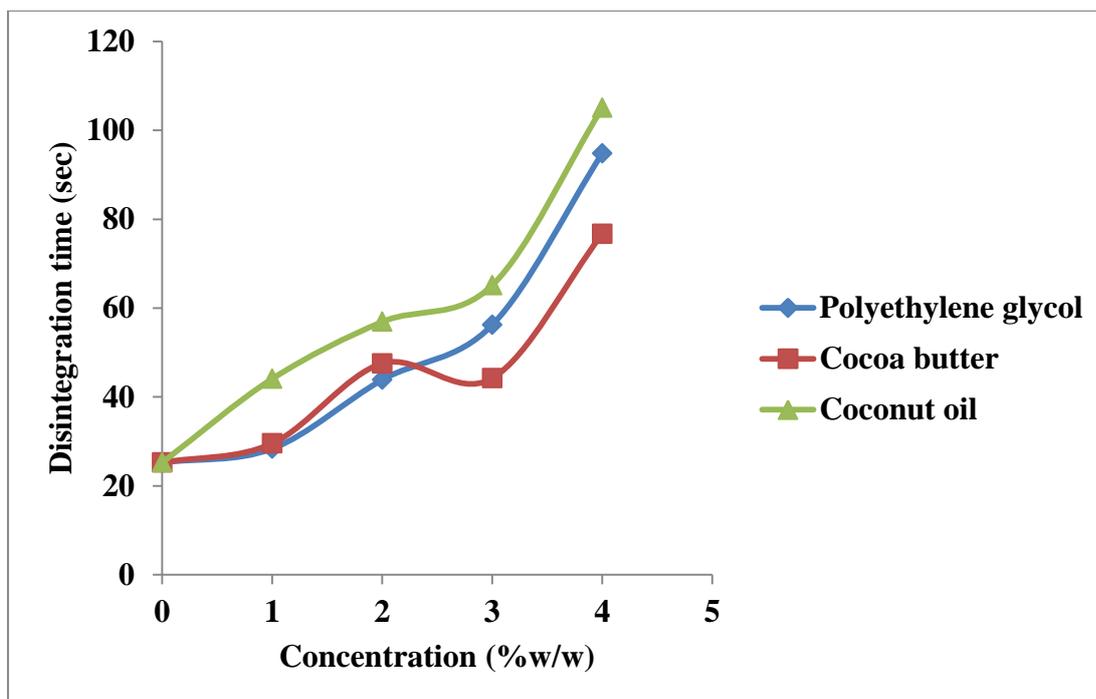


Figure 4: Plots of average disintegration time against concentration (% w/w) for effervescent Diclofenac tablets formulated with polyethylene glycol, cocoa butter and coconut oil lubricant

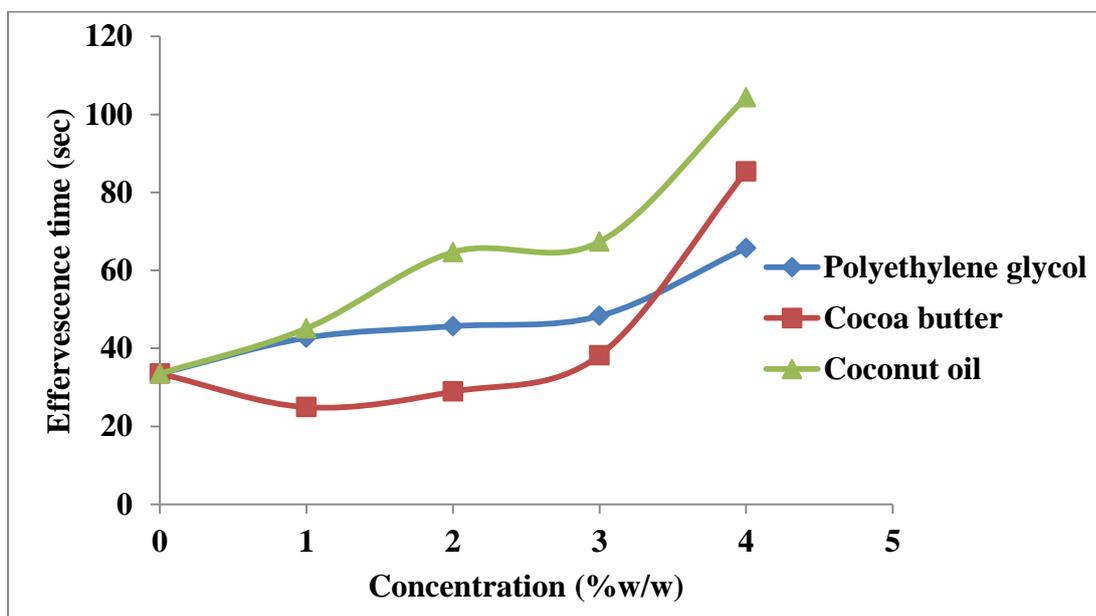


Figure 5: Plots of tablet average effervescence time against concentration (% w/w) for effervescent Diclofenac tablets formulated with polyethylene glycol, cocoa butter and coconut oil lubricants

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