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# Formulation of sustained release diclofenac sodium tablets using a blend of hydrophobic and hydrophilic polymers

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## ABSTRACT

The limitations of conventional oral dosage forms, particularly those containing drugs with short biological half-lives has led to the development of sustained release formulations. The objective of this study was to develop a sustained release diclofenac sodium tablets using a hydrophobic (Eudragit RS PO) polymer in combination with hydrophilic polymers (*Abelmoschus esculentus* and polyethylene glycol) as release rate control agents. Nine (9) batches of diclofenac sodium granules (B1-B9) were prepared with a combination of Eudragit RS PO, *Abelmoschus esculentus* powder and polyethylene glycol (PEG) at different ratios and compressed into tablets via direct compression. The granules were evaluated for flow properties while the tablets were analyzed for their weight uniformity, dimensions, friability, crushing strength and in-vitro drug release. Drug-excipient interactions study was carried out using Fourier transform infra-red spectroscopy (FTIR). Bulk and tapped densities of the granules ranged 0.41-0.58 and 0.50-0.72 g/cm$^3$, respectively, with Carr's indices (11.9 - 20.8%), Hausner's ratios (1.14 - 1.26) and angles of repose (< 30°). Formulated tablets had uniform weight, friability ≤ 0.50% and crushing strength range of 3.15 - 7.89 kp. Tablet showed variable sustained drug release with highest release of over 70% in 7 h. FTIR study showed no interaction between drug and excipients. Sustained release tablets of diclofenac sodium were successfully prepared with Eudragit RS PO and a combination of *Abelmoschus esculentus* powder and polyethylene glycol (PEG) as release modifiers. Batches B6 and B9 tablets released over 70% of drug within 7 h of dissolution testing.

**Keywords:** Coacervation, diclofenac, polymers, sustained release, tablets.

## 1. INTRODUCTION

Polymers are macromolecules used in the pharmaceutical industry as carriers of active principles in drug formulations or in drug delivery devices (Srivastava et al., 2016). They are covalently bonded monomers used as a backbone in conventional and sustained release formulations (Gheorghita et al., 2021). These polymers are classified as natural or synthetic, hydrophilic (soluble) or

hydrophobic (insoluble) based on their origin and solubility (Schmidt, 2019). In recent years, biodegradable natural and synthetic polymers have received increased interest in their application in novel drug delivery systems (Bhatia, 2016).

These polymers have been extensively used in advanced pharmaceutical dosage form designs for a variety of purposes such as matrix system carriers for drug in oral drug delivery systems (Debotton and Dahan, 2017). These applications in oral dosages are dependent on their hydrophilic and hydrophobic properties (Ali et al., 2014). Polymers such as xanthan gum, sodium alginate, hydroxyl ethyl cellulose (HEC), hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC) and polyethylene oxides are hydrophilic and hence used in enhancing the release rates of drugs (Gupta et al., 2021). While polymers such as cellulose acetate propionate, ethyl cellulose, ammonium methacrylate co-polymer (example includes Eudragit RS PO) and waxes are hydrophobic and are used in delaying drug release (Abd El-Halim et al., 2010; Wasilewska and Winnicka, 2019).

Polymers are major components in the preparation of sustained release solid dosage forms. Their therapeutic advantages over conventional dosage forms makes them preferable. These advantages include; reduced frequency of drug administration, minimal side effects and improved patient compliance (Wen et al., 2015). The preparation of sustained release formulations involves the embedding of drugs in a polymer matrix, where it is release gradually over time in a controlled or timely manner. The use of two or more polymers in the preparation of sustained release formulations have received continual interests from researchers (Tiwari et al., 2003; Ganesh et al., 2008; Islam et al., 2013; Eraga et al., 2017). The combination of hydrophilic and hydrophobic polymers in the same formulation confers certain properties, where one polymer acts as the drug release retardant while the other acts in modifying the drug release (Gupta et al., 2021). This study was set to investigate the control drug release effects of a blend of hydrophilic polymers (natural and synthetic) at different concentrations, from diclofenac sodium matrix tablet formulations prepared with Eudragit RS PO polymer.

## 2. MATERIALS AND METHODS

### Materials

Diclofenac sodium powder (Edo Pharmaceuticals Limited, Benin City, Nigeria), Eudragit RS PO (Rohm Pharma GmbH, Darmstadt, Germany), polyethylene glycol (PEG) (Mol. Wt 4000) (Sigma-Aldrich, Germany), lactose (Sigma Chemicals, St. Louis, USA), ethanol and concentrated hydrochloric acid (BDH Chemicals Ltd, Poole, England), magnesium stearate (A.H.A. International Co. Ltd, China), talc (Chemic Laboratory Reagents & Fine Chemicals, France). *Abelmoschus esculentus* (Okra) pods were purchased locally and processed in our laboratory.

### Methods

#### *Preparation of Abelmoschus esculentus powder*

Fresh *Abelmoschus esculentus* pods were washed thoroughly to remove all adhering extraneous materials. The pods were chopped into small pieces with a kitchen knife and spread over clean trays. The chopped pods were sun dried over a period of two weeks to a constant weight. The dried pieces were milled into fine powder using an electric kitchen blender (Eurosonic, China). The pulverized powder was filtered using 710 μm mesh size sieve (Endecotts Ltd., England). The resulting powder was packed in air-tight containers and stored in a desiccator containing silica until use.

#### *Preparation of granules and tablets*

A preliminary Box Behnken Design (BBD) was developed using Design Expert® 10.0 (Statease, Inc. Minneapolis, USA) with one dependent (Eudragit) and two independent (PEG and *Abelmoschus esculentus* powder) variables to determine the optimal combinations of these variables at the concentrations of intended use. The design resulted in a total of nine (9) possible combinations that were used in the formula for the preparation of the nine batches of the tablet formulations in Table 1.

**Table 1** Formula used in the preparation of the diclofenac granules and tablets

| Ingredients | Quantity (mg/tablet) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | B1 | B2 | B3 | B4 | B5 | B6 | B7 | B8 | B9 |
| Diclofenac sodium | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| Eudragit RS PO | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Polyethylene glycol | 22 | 22 | 22 | 30 | 30 | 30 | 38 | 38 | 38 |
| *Abelmoschus esculentus* powder | 30 | 45 | 60 | 30 | 45 | 60 | 30 | 45 | 60 |
| Lactose | 155 | 140 | 125 | 147 | 132 | 117 | 139 | 124 | 109 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Magnesium stearate | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Talc | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Total | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

Calculated amounts of ingredients needed to prepare about one hundred tablets were weighed for each batch. Using the coacervation method, weighed quantity of Eudragit was solvated in 100 ml of ethanol with the required amounts of diclofenac for 24 h. Thereafter, PEG, *Abelmoschus esculentus* powder, lactose, magnesium stearate and talc were added sequentially to the Eudragit-diclofenac ethanol dispersion with continuous stirring. The wet mass was air dried for complete evaporation of ethanol. The resulting dry granules were passed through a 750 μm sieve and stored in an airtight container pending evaluation.

**Evaluation of granules**

***Bulk and tapped densities***

Ten (10) grams granules were poured through a funnel into a 50 ml measuring cylinder and the volume occupied noted as bulk volume. The weight of granules was divided by the bulk volume and recorded as bulk density. The cylinder was then tapped continuously from a height of 2.5 cm on a padded wooden base until a fixed tapped volume was gotten and recorded. The weight of the granules divided by the fixed tapped volume was recorded as the tapped density.

***Carr's index and Hausner's ratio***

The Carr's index was calculated as the difference between the tapped and bulk densities, divided by the tapped density of the granules and expressed as a percentage, while the Hausner's ratio was derived from the division of the tapped density with the bulk density.

***Angle of repose***

Thirty (30) grams granules were poured into a glass funnel with its opening closed and clamped to a retort stand at 5.0 cm above a clean white paper. The funnel was opened to allow the granules to fall freely under the influence of gravity onto the white paper. The height and radius of the circular base of the heap formed by the granules were measured. The arctangent of the ratio of the height to the base of the granule heap was calculated and recorded as the angle of repose.

**Drug-excipient compatibility**

A batch of the granule was subjected to FTIR spectroscopic analysis to investigate possible interaction between diclofenac sodium and the other ingredients used in the preparation (FTIR-4100 Spectrophotometer, Shimadzu Co., Japan). Five (5) milligram quantity of granules was mixed with sufficient potassium bromide (KBr) powder and compressed into a 200 mg tablet. The tablet was scanned over a range of 4000 to 500 $cm^{-1}$ wavenumbers. The process was repeated using a pure powder sample of diclofenac sodium in place of the prepared granule.

**Compression of granules**

Granules from each batch were compressed into tablets using a single punch tableting machine (Manesty, England) set at 35 KN. Tablets weighing 300 mg were punched out by the machine, collected and stored in a close lid container at room temperature for elastic recovery for 7 days before being analyzed.

**Evaluation of tablets**

***Weight variation***

Twenty (20) tablets randomly selected from a batch was weighed individually using an electronic balance (Mettler, Switzerland). The average weight and standard deviation were calculated.

***Dimensions***

Using a Vernier caliper, the diameter and thickness of six (6) randomly selected tablets from each batch were measured and recorded. Their mean and standard deviation values were calculated.

*Friability*

Ten (10) tablets from a batch were weighed and placed in the drum of a friabilator (PTF 10E, Pharma Test Instruments India Pvt. Limited, India), operated at 25 rpm for 4 min. The tablets were removed, dedusted and weighed. The loss in weight of the tablets was calculated in percentage and recorded as the friability.

*Crushing strength*

The compression force required to crack ten (10) randomly selected tablets of a batch using a mechanical tablet hardness tester (Mosanto Chemical Company, Liverpool) was recorded as the crushing strength. The mean value and standard deviation were calculated.

*Dissolution profile*

Dissolution testing was carried out using a USP Type II Dissolution Apparatus (Caleva Company Limited, England) with 900 ml 0.1 N HCl solution (pH 1.2) at 37 ± 1.0°C and 100 rpm for the first 1.0 h and then switched to 900 ml phosphate buffer solution (pH 7.4) for 6 h. A randomly selected tablet from a batch was placed in the basket assembly of the apparatus and lowered into the dissolution medium. A 5.0 ml sample was removed from the dissolution medium at determined time intervals and the withdrawn volume replenished with same volume of fluid with the same temperature and pH as the dissolution fluid. The withdrawn samples were analyzed at 276 nm using a spectrophotometer (Model 23D, Uniscope, England). The amount of drug released at the intervals of sampling was calculated by imputing the absorbance values of the samples into the equation previously generated from the calibration plot of pure diclofenac sodium.

**Release kinetics**

Drug release data obtained from the dissolution tests were fitted into various kinetic equations to determine the model and mechanism of diclofenac sodium release from the tablets. The models employed were:

$Q = kt$ (zero-order equation) ……. (1)

$In\ (1-Q) = -kt$ (first-order equation) ……. (2)

$Q = kt^{1/2}$ (Higuchi equation) . ……... (3)

$Log\ Q = log\ k + n\ log\ t$ (Korsemeyer - Peppas equation) (4)

Where, Q is the fraction of drug released at time t, k is the release rate constant and n are the diffusional exponent. The correlation coefficient ($r^2$) from the plot of each equation was calculated. The drug release profile was considered to follow a particular rate order or mechanism if the $r^2$ value was ≥ 0.9.

**Statistical analysis**

Experimental results were computed and reported as mean ± standard deviations of triplicate determinations. Statistical differences between mean were computed with ANOVA using Microsoft Excel 2007, with p-values < 0.05 being considered significant.

## 3. RESULTS

**Granule flow properties**

Results from the micromeritic evaluations of the various batches of the diclofenac sodium granules are outlined in Table 2. Values of the bulk and tapped densities of the granules ranged from 0.41-0.58 and 0.50-0.72 g/cm$^3$, respectively. Generally, the granule batches exhibited compressibility indices within 11.90-20.80% and Hausner's ratios ranging from 1.14-1.25, an indication of good to fair flowability of the granules. Angles of repose values of the granule batches were lesser than 25° while the granules' flow rates ranged from 2.42 to 5.34 g/sec.

**Table 2** Micromeritic properties of the batches of diclofenac sodium granules (n=3)

| Batch | Bulk density (g/cm$^3$) | Tapped density (g/cm$^3$) | Carr's index (%) | Hausner's ratio | Angle of repose (º) | Flow rate (g/sec) |
|---|---|---|---|---|---|---|
| B1 | 0.58 (0.03) | 0.67 (0.01) | 13.40 (0.02) | 1.14 (0.11) | 17.24 (0.02) | 3.87 (0.62) |
| B2 | 0.57 (0.02) | 0.72 (0.03) | 20.80 (0.01) | 1.25 (0.10) | 19.30 (0.01) | 2.42 (0.60) |
| B3 | 0.41 (0.04) | 0.50 (0.03) | 18.00 (0.02) | 1.22 (0.08) | 22.80 (0.12) | 2.59 (0.29) |
| B4 | 0.49 (0.02) | 0.58 (0.02) | 15.50 (0.01) | 1.18 (0.09) | 18.40 (0.02) | 4.29 (0.13) |

| | | | | | | |
|---|---|---|---|---|---|---|
| B5 | 0.57 (0.02) | 0.68 (0.02) | 16.20 (0.01) | 1.19 (0.10) | 19.80 (0.01) | 2.46 (0.30) |
| B6 | 0.54 (0.03) | 0.67 (0.01) | 19.40 (0.01) | 1.24 (0.11) | 20.30 (0.01) | 2.45 (0.74) |
| B7 | 0.50 (0.03) | 0.59 (0.03) | 15.31 (0.02) | 1.18 (0.12) | 20.21 (0.02) | 5.20 (0.12) |
| B8 | 0.52 (0.02) | 0.59 (0.03) | 11.90 (0.02) | 1.18 (0.12) | 20.70 (0.12) | 5.34 (0.66) |
| B9 | 0.43 (0.05) | 0.51 (0.01) | 15.70 (0.01) | 1.16 (0.11) | 24.70 (0.01) | 3.45 (0.46) |

Standard deviation in parenthesis

**Drug-excipients interactions**

The FTIR spectra of diclofenac sodium powder (a) and its granule (b) used in the formulation of tablets is shown in Figure 1. Diclofenac sodium exhibited spectral peak characteristics at 3394.72 (-NH stretching), 1568.13 (-C=O carboxyl ion stretching), 1502.55 (C = C ring stretching) and 758.38 $cm^{-1}$ (C-Cl stretching) (Figure 1 (a)). These peaks observed for diclofenac sodium remained unchanged when compared with the spectral data of the granule (Figure 1 (b)). An observation suggesting the absence of chemical interaction and complex formation between diclofenac sodium and the excipients used in the formulations.

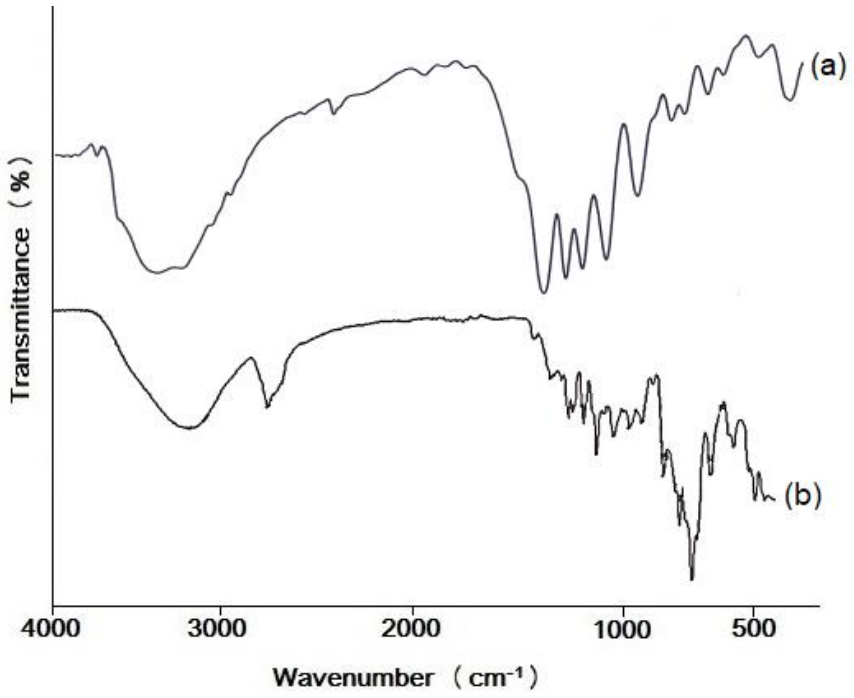


**Figure 1** FTIR spectra of diclofenac sodium (a) and its granule used in tablet formulation (b)

**Tablet properties**

Some of the parameters obtained from the evaluation of tablets formulated from the various batches of granules are shown in Table 3. The tablets exhibited minimal deviations in their weights (302-304 mg) and dimensions while tablet's friability ranging from 0.07-0.50%, decreased with increasing concentrations of *Abelmoschus esculentus* powder in the batch. Crushing strength of the tablets correlated with friability as their values which ranged from 3.15-7.89 kp, increased with decreasing friability values.

**Table 3** Post-compression parameters of the formulated diclofenac sodium tablets (n=3)

| Batch | Weight uniformity (mg) | Dimensions (mm) | | Friability (%) | Crushing strength (kp) |
|---|---|---|---|---|---|
| | | Diameter | Thickness | | |
| B1 | 304.05 (0.02) | 6.35 (0.01) | 2.80 (0.01) | 0.33 (0.01) | 4.60 (0.50) |
| B2 | 303.12 (0.02) | 6.37 (0.01) | 2.81 (0.02) | 0.13 (0.02) | 7.63 (0.43) |
| B3 | 303.25 (0.02) | 6.34 (0.02) | 2.75 (0.02) | 0.20 (0.04) | 5.29 (0.42) |
| B4 | 302.50 (0.03) | 6.36 (0.02) | 2.76 (0.02) | 0.40 (0.03) | 3.63 (0.28) |
| B5 | 304.10 (0.02) | 6.38 (0.02) | 2.77 (0.03) | 0.17 (0.01) | 7.25 (0.50) |

| | | | | | |
|---|---|---|---|---|---|
| B6 | 304.05 (0.01) | 6.34 (0.02) | 2.75 (0.01) | 0.07 (0.02) | 7.89 (0.50) |
| B7 | 304.00 (0.03) | 6.36 (0.01) | 2.76 (0.03) | 0.50 (0.02) | 3.15 (0.70) |
| B8 | 303.05 (0.01) | 6.34 (0.01) | 2.75 (0.03) | 0.30 (0.01) | 4.22 (0.43) |
| B9 | 303.00 (0.02) | 6.35 (0.03) | 2.75 (0.02) | 0.26 (0.01) | 4.84 (0.85) |

Standard deviation in parenthesis

The release profile of the various batches of the diclofenac sodium tablets are shown in Figure 2. Generally, the tablets exhibited an initial variable prompt release within the first 30 min ranging from 10 to 30% drug release depending on the batch and then followed by varying degrees of sustained or prolonged drug release over the next 6.5 h. With the amounts of polyethylene glycol different but constant in batches B1-B3, B4-B6 and B7-B9 tablets, there was increase in drug release with increase in the amount of *Abelmoschus esculentus* powder within the batches. Highest drug release was seen within the batches in B3 (47.0%), B6 (76.7%) and B9 (83.7%) tablets. Overall, only batches B6 and B9 tablets showed over 70% of drug release within the 7 h of dissolution testing. Correlation coefficients ($r^2$ values) generated from the tablet's dissolution data are presented in Table 4. Their values indicated a first order drug release kinetic with a release mechanism most consistent with Higuchi model, suggesting that drug release was essentially by Fickian diffusion.

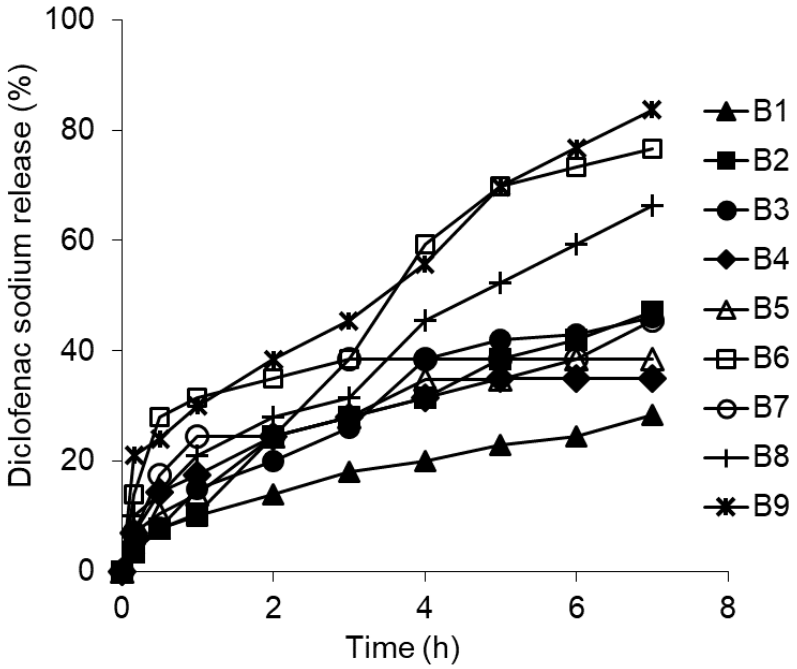


**Figure 2** Dissolution profile of the different batches of diclofenac sodium tablets

**Table 4** Correlation coefficient ($R^2$) of the dissolution studies

| Batch | Correlation coefficient ($R^2$) | | | |
|---|---|---|---|---|
| | Zero order | First order | Higuchi | Korsmeyer-Peppas (n) |
| B1 | 0.9428 | 0.9344 | 0.9498 | 0.7878 (0.6514) |
| B2 | 0.9602 | 0.9826 | 0.9820 | 0.8620 (0.6422) |
| B3 | 0.9486 | 0.9672 | 0.9763 | 0.8570 (0.6409) |
| B4 | 0.8302 | 0.8668 | 0.9693 | 0.9663 (0.6408) |
| B5 | 0.8910 | 0.9201 | 0.9833 | 0.9201 (0.6413) |
| B6 | 0.9220 | 0.9602 | 0.9561 | 0.7156 (0.6094) |
| B7 | 0.7994 | 0.8412 | 0.9367 | 0.9170 (0.6352) |
| B8 | 0.9745 | 0.9845 | 0.9728 | 0.7347 (0.6286) |
| B9 | 0.9525 | 0.9660 | 0.9709 | 0.6408 (0.6043) |

## 4. DISCUSSION

The drug release modulating effect of a blend of hydrophilic polymers (polyethylene glycol and *Abelmoschus esculentus* powder) from diclofenac sodium tablets prepared with Eudragit RS PO was investigated. Batches of granules consisting of varied amounts of the hydrophilic polymers and the Eudragit coacervates of the drug revealed a decrease in powder flow with increase in the amounts of *Abelmoschus esculentus* powder incorporated in the batch, though the blends exhibited good to fair flowability with flow rate > 2.42 g/sec, angle of repose < 24.70º, compressibility index < 20.80% and Hausner's ratio < 1.24. The reduction in flowabilty of the powders with increase in *Abelmoschus esculentus* powder is not in agreement with previous works where the increase led to the formation of spherical and smaller sized granules and improved granules flow properties (Emeje et al., 2007; Onunkwo, 2010; Emeje et al., 2011). Possible reason for the non-consistent result in flow properties may be due to the mucilagenous form of *Abelmoschus esculentus* gum used in their studies as against the dry powder form used here. The liquid gum while acting as a binder impacted cohesive properties on the agglomerates and consequently, granules that were free flowing.

The tablets formulated from the granules passed the weight uniformity and friability tests, in line with the British Pharmacopeia requirements allowing tablet weight deviation of not more than ± 5% of the mean weight and a loss of tablet weight being less than 0.8-1.0% (BP, 2009). But the crushing strength values of the tablets did not all meet the BP specification of 5-8 kp. The lower crushing strength values of the tablets were not expected based on the binding capacity of *Abelmoschus esculentus* but again, the dry powder form used in these formulations coupled with the direct compression of the granules may have been the determinant in the formation of strong bonds between the granule particles and thus conferring a less sturdy mechanical strength to the tablets. Similar low crushing strength values were obtained in an earlier study involving a physical blend of *Abelmoschus esculentus* powder and other ingredients in directly compressed salbutamol tablets (Eraga et al., 2016).

Furthermore, the drug release from the formulated tablets showed that higher amount of the PEG and *Abelmoschus esculentus* powder in their combinations resulted in more drug release. Batches B6 and B9 tablets were the only tablets reaching over 70% drug release in 7 h. This improved drug release may be attributed to the hydrophilic properties of PEG and *Abelmoschus esculentus* powder as reported by previous studies (Emeje et al., 2011; Chandel et al., 2016; Nagpal et al., 2017). These earlier studies proposed a situation whereby the tablet in contact with the dissolution fluid, gradually dissolves the hydrophilic polymers used in its formulation and hence create porous channel that enhances more drug release. Moreover, if the hydrophilic polymers are enmeshed in the matrix network of the hydrophobic polymer, as may be the case with our tablets, then their dissolution may lead to the formation of pores or channels from which the drug leaches out of the tablet matrix network.

Additionally, some researchers have reported improvement in the dissolution and drug release of poor soluble drugs when formulated with a combination of Eudragit RS PO, *Abelmoschus esculentus* powder and PEG while other have explored novel combination of polymers with different dependency on pH, thermos-responsiveness or physiological response in modulating drug release (Khan et al., 2022; Ghasemiyen et al., 2021; Shirazi et al., 2021; Gull et al., 2022). The adjusted coefficient of release kinetic of diclofenac sodium from the tablets aligns with the pseudo-steady Fickian diffusion release approach of the Higuchi model of drug release through insoluble matrix (Siepmann & Peppas, 2011). The pH solubility independent Eudragit RS PO serving as the hydrophobic polymer would have shielded the pH dependent drug from dissolution in the acidic medium but allowing the dissolution of the PEG-*Abelmoschus esculentus* powder combination. But as the tablet reaches an alkaline medium, fluid penetrates it, enhancing drug dissolution and diffusion out of the skeleton of the Eudragit RS PO matrix network (Tang et al., 2018; Damian et al., 2021).

## 5. CONCLUSION

Sustained release tablets of diclofenac sodium were successfully prepared using Eudragit RS PO, polyethylene glycol and *Abelmoschus esculentus* powder as release modulating polymers. The polymers produced tablets with satisfactory mechanical and drug release properties with batches B6 and B9 tablets sustaining over 70% of drug release within 7 h of dissolution testing. Hence, the polymers have proven as an effective combination for the formulation of sustained release tablets with acceptable tablet properties.

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**Authors' Contribution**

SOE designed the study, LNI performed the laboratory experiments while SOE and NDN interpreted the results and prepared the manuscript draft and FEE critically reviewed the manuscript.

**Informed consent**

Not applicable.

**Ethical approval**

Not applicable.

**Conflicts of interests**

The authors declare that there are no conflicts of interests.

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The study has not received any external funding.

**Data and materials availability**

All data associated with this study are present in the paper.

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