Hindawi
Journal of Chemistry
Volume 2023, Article ID 8384739, 12 pages
https://doi.org/10.1155/2023/8384739

Research Article

Development of Modified-Release Diclofenac Sodium Capsules Using Blends of Pectin-Clay Multiparticulate Hybrid Systems as Release Retardants

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Received 22 August 2023; Revised 26 October 2023; Accepted 21 November 2023; Published 5 December 2023

Academic Editor: Nagesh Gunavanthrao Yernale

A combination of inorganic and organic hybrid systems is of high research interest as they provide novel hybrid systems for the improvement of existing properties, overcoming limitations of the parent materials, and for the optimization of their controlled release potential. This study sorted to develop and pharmaceutically assess the release profile of diclofenac sodium using cocoa pod husk (CPH) blended with different proportions of either talc or bentonite as multiparticulate composite release modifiers. Preformulation investigations of the multiparticulate hybrid systems included pH, swelling index, moisture content, elemental contents, and flow properties. The FTIR was also used to investigate the compatibilities between pectin and bentonite (PB), pectin and talc (PT), and diclofenac and pectin-talc (DPT), as well as diclofenac and pectin-bentonite (DPB). The diclofenac content, uniformity of the weight of capsules, *in vitro* drug release, and the kinetics and mechanism of release of diclofenac from the hybrid systems were also investigated using mathematical models. The pectin yield was 23.3%, with the water-holding capacities of pectin-talc (PT) and pectin-bentonite (PB) hybrid systems being 6.4% and 5.0%, respectively. The swelling indices of PT and PB were 110.0 and 130.0 in 0.1 M HCL at pH 1.2 and 130.0 and 149.0 in phosphate buffer at pH 6.8, respectively. This system was also found to exhibit excellent flow properties, and there were no diclofenac-excipient interactions. All formulated batches passed the pharmacopoeial and nonpharmacopoeial tests. They also demonstrated controlled release properties via different release kinetics and mechanisms. This study shows that the pectin-talc and pectin-bentonite multiparticulate composites could be used as release modifiers in pharmaceutical preparations.

1. Introduction

In pharmaceutical industries, clays such as bentonite and talc are crucial components used as excipients to create composites with other biopolymers for modified-release drug delivery systems [1–3]. A combination of inorganic and organic hybrid systems is of high research interest as they provide novel hybrid systems for the improvement of existing properties, overcoming limitations of the parent materials, and for the optimization of their controlled release potential [4]. Lately, composites of clays and biopolymers have gained attention as intriguing materials for innovative drug-delivery systems [5, 6]. Naturally occurring biopolymers such as gums and pectins are usually preferred over their synthetic counterparts in forming composites due to their biodegradability and less toxicity. Pectin hybrid drug-delivery systems are delivery systems which are of most benefit to local pharmaceutical industries either for the development of target release or modified-release medications. Thus, these systems not only possess the ideal qualities of pharmaceutical excipients but also have versatile use, are readily available locally, and are easily formulated with less sophisticated equipment [3, 5–7].

The therapeutic management of pain and inflammation via the use of diclofenac has resulted in several dosage forms for topical, parenteral, and enteral routes. Conventional and controlled-release diclofenac, which are available for oral administration have reported peptic ulceration, renal depression, gastritis, and other side effects [8]. Most controlled-release diclofenac preparations use synthetic polymers as drug-release retardants or matrix carriers due to their good flexibility, resistivity, sensitivity, and chemical compatibility [9]. However, these synthetic polymers have also been reported to be nonbiodegradable, have poor biocompatibility, and have an expensive processing cost resulting in an overall high cost of the formulation [10]. These modified-release dosage forms exist as interventions in an attempt to minimize gastrointestinal toxicity. Hence, there is a need to investigate the use of natural polymers as alternatives in such diclofenac formulations. CPH pectin is rich in polyphenols which have been demonstrated to elicit anti-inflammatory, antinociceptive, and antioxidant properties [11]. These properties could augment the effect of diclofenac when used in this formulation. In addition, pectin has been reported to resist acidic pH and enzymatic actions in the upper gastrointestinal tract [12]. However, the hydrophilic nature and the high swelling capacity of the CPH pectin in the gastrointestinal tract may lead to premature release of the drug when solely used as a matrix carrier [12]. Nonetheless, a pectin-clay composite would allow for the formation of a new and improved hybrid system with properties which would overcome these setbacks associated with the sole use of pectin as well as modify diclofenac release to suit patient needs [13]. These hybrid systems may, therefore, enhance the drug's therapeutic effects and reduce the frequency of dosing and side effects, leading to improved patient compliance [14]. Furthermore, the gastric protective effect of pectin and clay matrix composites is an added advantage. Thus, pectin, which is a dietary fibre, is useful for strengthening the gastrointestinal mucous layer. Pectin also enhances the immune barrier by stimulating the adhesion of commensal bacteria, which aids in the prevention of inflammatory conditions [15]. Hence, a combination of pectin and clay may form useful composites that have the potential for modified-release drug-delivery systems with enhanced bioavailability and drug-release profiles [13, 16]. This study sought to investigate the kinetics, mechanism, and *in vitro* release profile of diclofenac from pectin-bentonite and pectin-talc diclofenac multiparticulate composite capsules formulated via variation of the multiparticulate composite proportions.

2. Materials and Methods

2.1. Materials. Diclofenac sodium powder (Entrance Pharmaceuticals, Accra, Ghana), cocoa pods (Cocoa Research Institute of Ghana (CRIG), Tafo, Ghana), dicalcium phosphate (Merck, Darmstadt, Germany), talc (UK chemicals limited), and bentonite (UK chemicals limited) were used in this study. Analytical grade chemicals and reagents were employed in this study.

2.2. Pectin Extraction from the Husk of Cocoa Pod (CPH). Ripe, as well as mature, *Theobroma cacao* L. pods were sourced from an experimental plantation of Cocoa Research Institute of Ghana (CRIG) located in Tafo, the Eastern region of Ghana. The whole pod husk of freshly harvested cocoa pods were separated from the seeds and pulp. The husks were minced with the aid of a mechanical blender and prepared for the extraction process. Hot aqueous extraction was undertaken at 50°C as described previously [7]. Ethanol was used in precipitating the extract while the filtration process was carried out twice using a double-folded linen clot. A volume of ethanol which is twice the volume of the extract was used to treat the extract. It was then washed thrice to get rid of any impurities which may be present. The extract was lyophilized (model 7670520, Labconco, USA) under vacuum within 0 mBar–120 mBar at −41°C after the extraction process was repeated until exhaustion. The percentage yield was determined after this process. The lyophilized pectin was packaged with aluminum foil and kept in a ziplock and placed in a desicator. The packaged pectin was then kept at −4°C until utilized [7].

2.3. Preparation of Granules of Pectin-Clay Multiparticulate Composite. A quantity of pectin equivalent to 4 g was accurately weighed into a glass beaker. Ten millilitres of hot water was added and stirred. Two grams of bentonite powder was also weighed and added into the pectin solution and the mixture continuously stirred until a colloidal solution was formed. The formed colloidal solution was dried at 55°C for 3 h in an oven. Granules were prepared from the dry pectin-bentonite (PB) powder mixture . The prepared granules were stored in a desiccator until needed for further analysis. This was repeated for the preparation of pectin-talc (PT) composite granules.

The swelling index, pH, moisture content, compatibility studies, and flow properties of the composite granules were evaluated.

2.4. Evaluation of pH, Swelling Capacity, and Moisture Content of PT and PB Granules. The pH of a solution of 1% $^{w}/_{v}$ PT and PB was determined in triplicate via the use of a calibrated Eutech pH meter (ECPH70042GS, Netherlands). The swelling index was assessed by weighing one gram of the respective pectin-clay composite matrix in a twenty-five millilitre measuring cylinder, and their occupied volumes (V_1) were recorded. An amount of 25 mL of distilled water was added to the test samples and were intermittently shaken for 1 h and were then allowed to stand undisturbed for 3 h. The final volume (V_2) for each was again recorded [17, 18].

The swelling capacity was determined as shown in the following:

$$\left[\frac{V2}{V1} \times 100\right]. \tag{1}$$

To determine the moisture content, 1 g of the respective pectin-clay composite matrix was weighed into three different Petri dishes that had been preweighed after they had been dried at 105°C in an oven to obtain a constant weight. The moisture content was determined as the ratio of the weight of loss of moisture to the weight of the multiparticulate composites expressed as a percentage [17, 18].

2.5. Flow Properties of CPH Pectin-Clay Multiparticulate Granules. The bulk and consolidated (tapped) densities (equations (2) and (3), respectively) were determined by slowly pouring 3 g of the granules into a 50 mL graduated glass measuring cylinder. The volume occupied was noted. This was subsequently tapped 100 times and the final volume was also recorded. The determined apparent (bulk) and consolidated densities were used to evaluate the Hausner ratio (equation (4)) and Carr's index (equation (5)). The fixed-height method was used to determine the angle of repose (equation (6)) of the granules for each formulation. The experiments were carried out in triplicate determinations and their respective mean values were recorded [19].

$$\text{Bulk density} = \frac{\text{weight of pectin and clay matrix}}{\text{bulk volume}}, \tag{2}$$

$$\text{Tapped density} = \frac{\text{weight of pectin and clay matrix}}{\text{tapped volume}}, \tag{3}$$

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}, \tag{4}$$

$$\%\ \text{Compressibility or Carr}'\text{s index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100\%, \tag{5}$$

$$\text{The angle of repose} = \tan x^{-1}\left[\frac{\text{height}}{\text{base radius}}\right]. \tag{6}$$

2.6. Elemental Analysis of Granules of the CPH Pectin-Based Diclofenac Multiparticulate Matrix. Elemental analysis was performed on pellets of hot water solution of the pectin-clay composites which were irradiated with energy-dispersive X-ray fluorescence spectrometer (Spectro X-Lab 2000, Kleve, Germany) [20].

2.7. Preparation of Granules of the Pectin-Clay Diclofenac Composite Multiparticulate Matrix. Modified-release diclofenac pectin-bentonite (DPB) and diclofenac pectin-talc (DPT) hybrid composite capsules containing approximately 50 mg of diclofenac sodium were formulated via the wet granulation technique. The required respective proportions of CPH pectin (Table 1) for each of the developed formulations for DPB capsules were weighed and dispersed in a sufficient volume of freshly boiled distilled water to form a viscous dispersion of granulating fluid. The respective quantities of diclofenac sodium, bentonite, and dicalcium phosphate were weighed and mixed via doubling up for each of the DPB formulations ($F1$–$F3$), as shown in Table 1. A 2360 μm mesh size sieve was used to screen the various powder mixture. The required mixed powders for each formulation were mixed in their respective granulating fluids by geometric dilution. After a damped mass was obtained, it was sieved through a 2000 μm·mesh size sieve. The granules were dried at 40°C for 1 hour 30 minutes in a hot air oven. After complete drying, the granules for each of the DPB formulations were screened through an 841 μm·mesh and stored in a desiccator. The abovementioned process was repeated for formulations of DPT multiparticulate composite capsules ($A1$–$A3$) using ingredients as shown in Table 1.

2.8. Compatibility Studies Using Fourier-Transformed Infrared Spectroscopy (FTIR). The PerkinElmer Fourier infrared spectrophotometer (spectrum 2, sr. no. 94133, UK)

Table 1: Working formula for diclofenac pectin-clay capsules.

Ingredients (mg)	*F*1	*F*2	*F*3	*A*1	*A*2	*A*3	*C*1
Diclofenac sodium	50	50	50	50	50	50	50
CPH pectin	50	50	50	50	50	50	50
Bentonite	10	25	50	0	0	0	0
Talc	0	0	0	10	25	50	0
Dicalcium phosphate	90	75	50	90	75	50	100
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

was used to carry out this investigation on bentonite, talc, pectin-clay multiparticulate composites, and pectin-clay diclofenac multiparticulate composites to investigate excipient-excipient and diclofenac-excipient compatibility studies. A maximum force gauge was used to apply the pressure to the test samples on the diamond crystal. A spectrum was generated in the range of 4000 cm^{-1}–400 cm^{-1} after scanning the sample twenty-four times [21].

2.9. Formulation of Capsules. The conventional punch method was used to hand prepare capsules with 300 mg of granules. The granules were transferred onto the base of the vertically held capsule size "0." The open end of the capsule was repeatedly pressed until the capsule was full. The cap was then reinstalled and the capsule was sealed. An empty capsule shell was employed as a counterbalance when adding the granules or withdrawn until the precise weights were measured [7].

2.9.1. Quality Assessment of Modified-Release Diclofenac Capsules

(1) Uniformity of Weight. An amount of 20 randomly selected capsules from DPB formulation were weighed (SN: AE 436647 Adam Equipment, UK) together and individually as well. Each capsule was completely emptied and the empty shell was weighed and noted. The net weight of the 20 randomly selected capsules was determined as the difference between the total weight of the 20 capsules and the total weight of the 20 emptied capsule shells. The net weight of the individual capsules was also obtained via the subtraction of the weight of the individual emptied capsule shell from its respective capsule weight. This was repeated for DPT capsule formulation [22].

2.9.2. Development of the Calibration Plot for Diclofenac Sodium. One gram of diclofenac sodium powder was weighed into a 10 mL volumetric flask, and 5 mL of distilled water was used to dissolve the content in the flask. The solution was then topped up to volume using distilled water. Solutions of concentrations 400–2100 μg/mL were prepared from the stock solution, and their absorbance was determined using the UV-visible spectrophotometer (Merck, Darmstadt, Germany) at 276 nm. This was used to obtain a calibration plot for diclofenac estimation in the subsequent assay and dissolution studies.

2.9.3. Assay of Formulations. A number of 10 capsules from formulation *F*1 of DPB multiparticulate matrix were randomly selected and their contents were completely emptied into a porcelain mortar. The granules were triturated and an amount equivalent to the average net weight of one capsule was weighed into a volumetric flask measuring 50 mL. The diclofenac sodium was extracted using 50 mL of 50% methanol. The content of diclofenac in a capsule of *F*1 from DPB multiparticulate composite capsules was assessed via the use of the UV-vis spectrophotometer (Merck, Darmstadt, Germany) at the wavelength 276 nm. This determination was repeated three times and the abovementioned step was repeated for the rest of the formulations of DPB and DPT capsules [23].

2.9.4. In Vitro Diclofenac Sodium Release Studies. The US Pharmacopoeia dissolution type I apparatus (Lid8 Dissolution Tester, Vanguard Pharmaceuticals Machinery Inc., USA) was used to carry out this study in a 900 mL of phosphate buffer, with pH 6.8 per vessel which was set at a temperature of 37°C ± 0.5°C with a rotation speed of 100 rpm/min for 5 h. Aliquot of 10 mL of the solution was sampled at 60, 120, 180, 240, and 300 minutes. These were replaced immediately with equal volumes of phosphate buffer of pH 6.8. The sampled solutions were analyzed at 276 nm using UV-vis spectrophotometer (Merck, Darmstadt, Germany) after they have been filtered. The amounts of diclofenac sodium present were subsequently calculated [24]. Triplicate determinations were carried out for each capsule formulation.

2.9.5. Drug Release Kinetics. The obtained data from the *in vitro* diclofenac sodium release studies were integrated into the mathematical kinetic models (zero order, Higuchi, Korsmeyer–Peppas, first order, and Hixson–Crowell) to determine the mechanisms of diclofenac sodium release from the pectin-clay matrices. The model which best describes the kinetics of the release of this drug is the model with the highest correlation coefficient (R^2) [25].

2.9.6. Result Analysis. The GraphPad Prism version 8 (GraphPad Software Inc., San Diego, California, USA) and Microsoft Excel were used to statistically analyze the study results. The results have been presented as the mean ± standard deviation.

3. Results and Discussion

3.1. Characterization of the Pectin-Clay Composite Multiparticulate Matrices. CPH pectin is a 1,4 galacturonic acid polymer which is extracted from cocoa pod husk waste via

valorization [20]. Solvent systems available in the literature for extraction include hydrochloric acid, nitric acid, and aqueous solvents [20, 26]. In this study, hot aqueous extraction was chosen because this system is environmentally friendly, safe, biocompatible, and cost-effective and can be easily processed into formulations with less-sophisticated equipment [27]. Furthermore, the hot aqueous extract of CPH pectin has shown remarkable applications to suit drug-delivery needs [20]. The yield was 23.3% which is above the reported range of 2%–20% [27, 28]. The reported increase in the yield could be as a result of the difference in the extraction conditions.

The pH of $1\%^{w}/_{v}$ solution of both PT and PB composite multiparticulate hybrid systems were 6.1 ± 0.00 and 6.3 ± 0.00, respectively, which are close to neutral pH. The moisture contents were $6.4 \pm 0.5\%$ and $5.0 \pm 0.02\%$, respectively, for DPT and DPB multiparticulate matrices, which was low, suggesting possible protection from microbial degradation and improvement in mechanical properties of the powders [20]. The swelling indices of PT and PB were 110.0 and 130.0, respectively, in 0.1 M HCl at pH 1.2 and 130.0 ± 0.01 and 149.0 ± 1.40, respectively, in phosphate buffer at pH 6.8. The higher swelling index recorded by DPB multiparticulate composite granules is due to the presence of montmorillonite in the bentonite which has swelling and adsorption properties; for instance, in an aqueous medium, anhydrous montmorillonite becomes a hydrated material and changes to gel with increasing water content. This characteristic plays an essential role in modifying the release of drugs from bentonite-based matrix formulations [29]. CPH pectin is also reported to swell to varying extents in various media. According to earlier studies, a medium's pH, ionic strength, and salt content all affect how much CPH pectin swells [30]. The swelling behaviour exhibited by the formulated pectin-clay diclofenac sodium is crucial for diffusion-controlled drug-delivery systems.

3.2. Flow Properties of PB and PT Diclofenac Composite Matrix Granules. The results as shown in Table 2 show that the granules have excellent flow properties due to the values obtained for angle of repose, Hausner ratio, and Carr's index. This implies that during encapsulation, the granules would flow easily from the hopper to uniformly fill the capsule shell [31].

3.3. Elemental Content of the Pectin-Clay Diclofenac Composite. Elemental analysis of both DPT and DPB composite matrices revealed a rich source of calcium, magnesium, potassium, aluminium, manganese, phosphorus, iron, sodium, zinc, and silicon and other elements such as sulphur, nickel, chromium, and cobalt were present in very minute quantities. The results obtained (Table 3) are comparable to other reported studies [26–28]. The presence of these macro- and microminerals serves as a potential source of nutraceuticals for health benefits such as regulation of metabolic processes when consumed [32]. The mineral contents could also impact on the viscosity and swelling capacity of the matrix as reported [20].

Table 2: Flow properties of the CPH pectin-based diclofenac multiparticulate matrix.

Parameters	DPT granules	DPB granules
Angle of repose (°)	29.40 ± 0.50	27.53 ± 0.85
Bulk density (g/mL)	0.67 ± 0.10	0.73 ± 0.00
Tapped density (g/mL)	0.71 ± 0.00	0.77 ± 0.01
Hausner ratio	1.06 ± 0.05	1.05 ± 0.02
Carr's index (%)	5.63 ± 0.20	5.19 ± 0.01
Flow	Excellent	Excellent

3.4. Diclofenac-Excipients Compatibility Studies. To ascertain the physicochemical integrity of diclofenac sodium in the presence of excipients over the shelf life, compatibility studies were undertaken utilizing FTIR data analysis. This is important primarily for the bioavailability of the active pharmaceutical ingredients (APIs) and the safety of the patient. A mixture of materials is said to be compatible if no new functional groups are detected from the FTIR data of the API and excipients before and after formulation [33].

Talc powder showed characteristic sharp peaks at $667\ cm^{-1}$ and $3675\ cm^{-1}$ due to O-H bending and O-H stretching, respectively, and a broad strong peak for Si-O stretching at $991.39\ cm^{-1}$ (Figure 1(a)), which were consistent with the previous report in the literature [34, 35].

In the FTIR data for diclofenac sodium (Figure 1(b)), peaks were detected at $3386.67\ cm^{-1}$ and $1306.89\ cm^{-1}$ for N-H and C-N stretching vibrations, respectively [36]. The broad band observed around $3225.90\ cm^{-1}$ was characteristic of O-H stretching (of carboxylic acid) and its corresponding O-H bending was the narrow peak at $1383.73\ cm^{-1}$. The carboxylic C=O stretching peak was at $1573.83\ cm^{-1}$ while those for aromatic C=C stretching vibrations were found at $1505.43\ cm^{-1}$ and $1551.42\ cm^{-1}$ as previously reported [36].

In bentonite, the major peaks were observed at $3695.55\ cm^{-1}$ and $3619.64\ cm^{-1}$ for O-H stretching due to the silanol group and water, respectively (Figure 1(c)). The O-H bending peak was detected at $1634.72\ cm^{-1}$. The peaks at $996.31\ cm^{-1}$ and $514.88\ cm^{-1}$ were characteristic for Si-O stretching and Si-O bending vibrations, respectively, as suggested in previous reports [37–39].

The spectrum for pectin (Figure 1(d)) revealed a broad band peaking at $3293.90\ cm^{-1}$ for carboxylic acid O-H stretching vibration, and its corresponding O-H bending vibration at $1435.89\ cm^{-1}$ is consistence with the reported literature [20]. Carboxylic acid C=O was detected at $1605.56\ cm^{-1}$. Peaks detected at $1248.01\ cm^{-1}$ and $1030.87\ cm^{-1}$ correspond to C-O stretching vibrations for aliphatic ether and alcohols as characteristic of complex polysaccharides [40, 41].

Two different combinations of diclofenac and pectin with talc or bentonite (labelled P/B/D and P/T/D) were formulated and analyzed by FTIR compatibility studies (Figures 1(e) and 1(f)). The wave numbers for the relevant peaks of P/B/D and P/T/D have been noted in Table 4. Figure 1(g) shows a comparison of the IR spectrum of diclofenac with those of P/B/D and P/T/D. In both cases of P/B/D and P/T/D, there is a broad band that stretches from

Table 3: Elemental content of pectin-clay diclofenac multiparticulate composites.

Elements	Content in the pectin-bentonite diclofenac matrix (mass %)	Content in the pectin-talc diclofenac matrix (mass %)
Mg	0.74 ± 0.04	9.70 ± 0.01
Al	1.60 ± 0.05	0.91 ± 0.02
Si	4.10 ± 0.11	14.10 ± 0.07
P	2.75 ± 0.09	21.60 ± 0.07
S	0.22 ± 0.01	1.12 ± 0.01
K	1.57 ± 0.06	4.16 ± 0.01
Ca	73.40 ± 0.49	37.30 ± 0.14
Cr	–	0.003 ± 7.07
Mn	0.13 ± 0.00	0.04 ± 0.00
Fe	9.34 ± 0.02	0.93 ± 0.01
Co	0.04 ± 0.00	0.01 ± 0.00
Ni	0.01 ± 0.00	0.004 ± 0.00
Cu	0.03 ± 0.00	0.01 ± 0.00
Zn	–	0.02 ± 0.00
Na	0.0008 ± 0.11	10.06 ± 0.08

(–): absent. Values presented as the mean ± SEM ($n = 3$).

3645 cm^{-1} to 2500 cm^{-1}. This band is due to the O-H stretching of carboxylic acid. However, the O-H stretching bands in the combinations are more intense than those for pectin, bentonite, talc, or diclofenac individually and this may be due to intermolecular hydrogen bonding. Moreover, the broad nature of the O-H stretching bands in P/B/D and P/T/D overshadowed the individual O-H stretching bands for pectin, bentonite, talc, and diclofenac.

In the IR stretching vibration region between 2500 cm^{-1} and 1500 cm^{-1}, the absence of any significant peaks for P/B/D and P/T/D relative to the individual components indicates that no new functional groups were formed due to the interaction between diclofenac and excipients.

Furthermore, a comparison of the fingerprint region (1400 cm^{-1} to 400 cm^{-1}) of P/B/D and P/T/D and those of their constituent materials indicated that there were no new functional groups formed. Peaks observed in the fingerprint region can be attributed to the individual materials. For instance, for P/B/D, peaks at 743.90 cm^{-1} and 1030.14 cm^{-1} may be due to C-Cl bending vibration in diclofenac and C-O stretching in pectin, respectively, whereas for P/T/D, 666.98 cm^{-1} and 1009.83 cm^{-1} indicated O-H bending and Si-O stretching vibrations in talc. Altogether, and as clearly illustrated in Figure 1(g), it may be concluded that diclofenac is compatible with the other excipients as no new functional groups were noticed upon FTIR compatibility studies of the formulated granules.

3.5. Quality Assessment of Pectin-Clay Diclofenac Multiparticulate Composites

3.5.1. Calibration Curve for Diclofenac Sodium. The calibration curve helps to estimate the concentration of diclofenac in the developed formulations. Figure 2 shows that it is linear with the R^2 value of 0.9709, which indicates a good relationship between the absorbance and the concentration of diclofenac sodium. This implies that the absorbance values obtained in various determinations could be used to measure the quantity of diclofenac sodium present in the formulations, which is vital for the efficacy of the formulations.

3.5.2. Uniformity of the Weight and Diclofenac Content in Pectin-Clay Diclofenac Formulations. The mean capsule weights of the DPB and DPT formulations are as shown in Table 5. All formulations had a percentage deviation of <7.5%, as shown in Table 5. This implies that the developed pectin-clay diclofenac capsules met the BP standard for the uniformity of the weight test [42]. This is as a result of the uniform particle-size distribution of granules and their recorded excellent flow properties which could have led to the even filling of the capsule shell and uniform granule compression after filling, resulting in the passing of this test [21]. As a result, it can be seen that the formulations contain even doses of diclofenac sodium between the individual capsules.

The content analysis of formulations of both DPB and DPT capsules fell within the acceptable compendia criteria of 85–115%, as shown in Table 5 [22]. Therefore, the different developed pectin-clay matrix capsules contained the right amounts of diclofenac, which are of allowable pharmaceutical quality. This is essential for accuracy in drug administration since the optimal therapeutic outcome is indicative of application of good manufacturing practices (GMPs) in producing quality products.

3.5.3. In Vitro Drug Release. Diclofenac is a biopharmaceutical classification system (BSC) class II drug, characterized by poor water solubility associated with limited and erratic dissolution profiles and variable bioavailability. However, the use of cocoa pod husk pectin in the development of pectin multiparticulate composite capsules could elicit a significant effect on the release of the medicinal agent with reproducible release profiles [43]. Analyses of the dissolution profiles of the multiparticulate composite

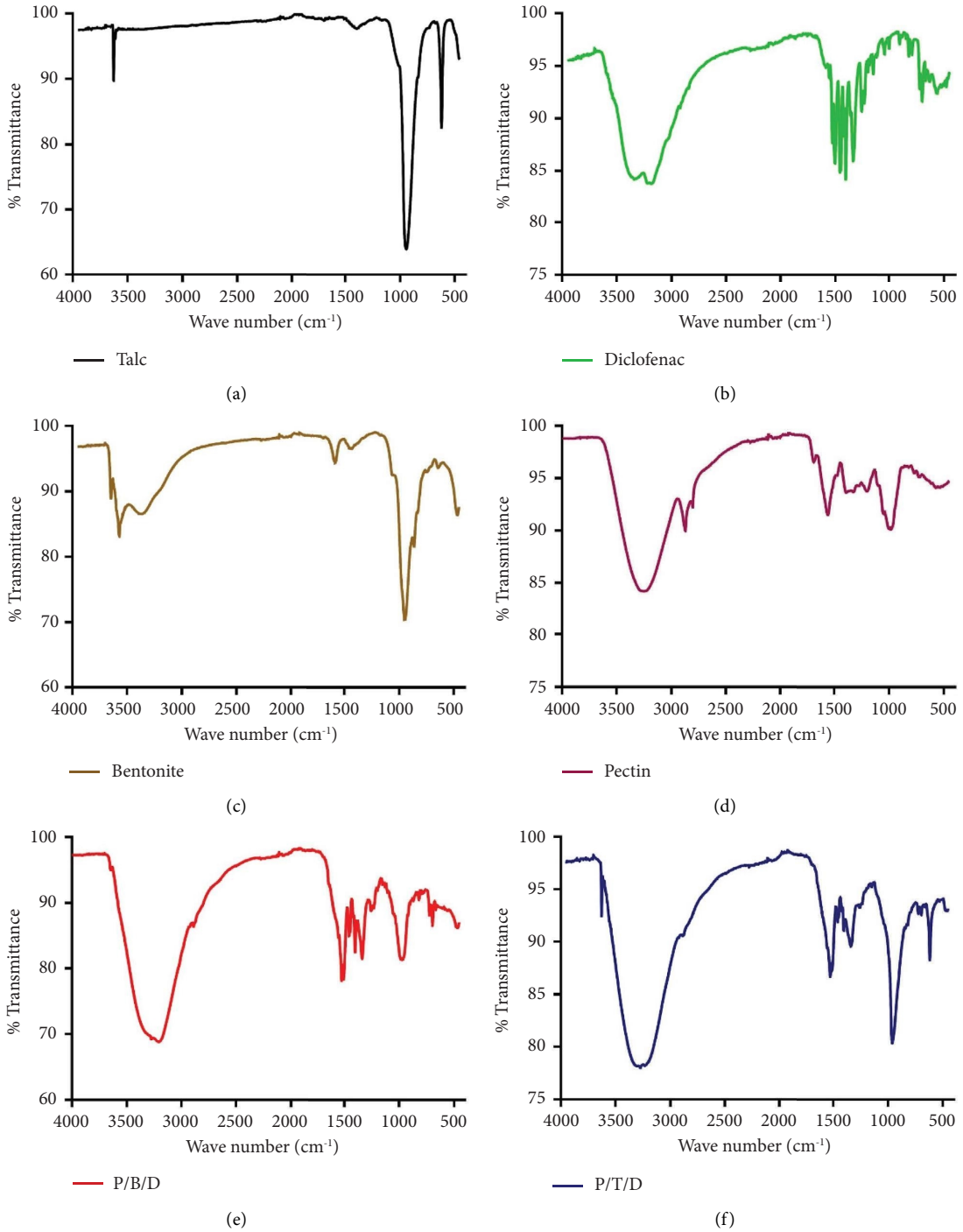
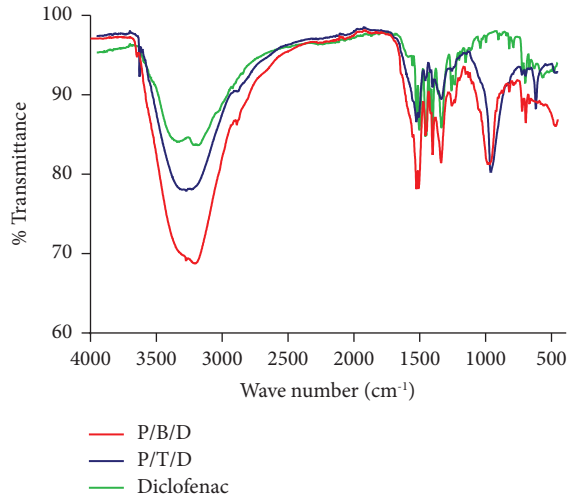


Figure 1: Continued.



(g)

Figure 1: FTIR spectrum of (a) talc powder, (b) diclofenac sodium, (c) bentonite, (d) pectin, (e) pectin, bentonite, and diclofenac combination (P/B/D), and (f) pectin, talc, and diclofenac combination (P/T/D). (g) Overlay comparison of the FTIR spectrum of diclofenac sodium; pectin, bentonite, and diclofenac combination (P/B/D); and pectin, talc, and diclofenac combination (P/T/D).

Table 4: Characteristic FTIR peaks for the various materials and formulations.

Materials	Relevant peaks (cm^{-1})	Type of bond
Talc	667.82	O-H bending
	991.39	Si-O stretching
	3675.47	O-H stretching (with no hydrogen bonding)
Diclofenac	614.90, 747.34	C-Cl bending vibrations
	1383.73	O-H bending
	1452.28, 1470.27	C-H bending
	1306.89	C-N stretching
	1505.43, 1551.42	C=C stretching of aromatic ring
	1573.83	C=O stretching of carboxylic acid
	3225.90	O-H stretching due to carboxylic acid
	3386.67	N-H stretching
Bentonite	514.88	Si-O bending vibrations
	996.31	Si-O stretching
	1634.72	O-H bending vibrations in water
	3619.64	O-H stretching from water
	3695.55	O-H stretching from silanol (Si-OH) groups
Pectin	1030.87	C-O stretching of alcohol
	1248.01	C-O stretching ether bond
	1435.89	O-H bending of carboxylic acid
	1605.56	C=O stretching of carboxylic acid
	2853.15, 2919.19	C-H stretching (aliphatic)
	3293.90	O-H stretching
P/T/D	666.98	O-H bending
	1009.83	Si-O stretching
	1385.91	O-H bending
	1453.21	C-H bending
	1505.65	C=C stretching
	1574.69	C=O stretching
	3323.25	O-H stretching due to carboxylic acid
	3675.92	O-H stretching (with no hydrogen bonding)
P/B/D	743.90	C-Cl bending vibrations
	1030.14	C-O stretching of alcohol
	1304.48	C-N stretching
	1386.53	O-H bending
	1450.81	C-H bending
	1505.74	C=C stretching (aromatic)
	1557.66	C=C stretching (aromatic)
	1574.62	C=O stretching of carboxylic acid
	3252.92	O-H stretching due to carboxylic acid

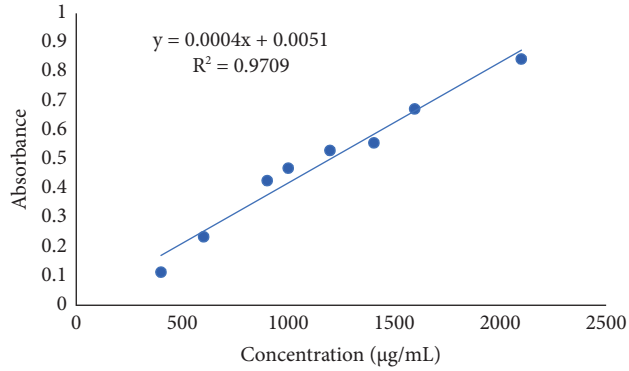


Figure 2: Calibration curve for diclofenac sodium at 276 nm in distilled water.

Table 5: Uniformity of the weight and diclofenac content of pectin-clay diclofenac multiparticulate matrix capsules.

Formulation codes	% Diclofenac content	Total net weight (mg)	Average net weight (mg)	No. of capsules deviating by ± 7.5%	No. of capsules deviating by ± 15%	Inferences
*A*1	103.960 ± 0.04	6024.260	301.213 ± 0.41	Nil	Nil	Pass
*A*2	104.640 ± 0.06	5983.400	299.170 ± 0.09	Nil	Nil	Pass
*A*3	105.230 ± 0.05	6000.110	300.011 ± 0.01	Nil	Nil	Pass
*F*1	97.680 ± 0.03	6250.010	312.501 ± 0.13	Nil	Nil	Pass
*F*2	97.480 ± 0.03	6264.220	313.211 ± 0.01	Nil	Nil	Pass
*F*3	97.370 ± 0.03	6217.140	310.201 ± 0.08	Nil	Nil	Pass
*C*1	97.360 ± 0.03	6244.040	312.201 ± 0.03	Nil	Nil	Pass

Values presented as the mean ± SEM ($n = 3$, % diclofenac content; $n = 20$, uniformity of weight).

capsules are depicted in Figure 1. *C*1 exhibited a controlled release profile, suggesting pectin from cocoa pod alone has control-release properties as reported [44]. When bentonite was employed in the hybrid matrix, the release profile followed a biphasic pattern with an initial slow diclofenac release followed by a rapid release which could be tailored towards therapeutic needs (Figure 3). This property exhibited by the bentonite hybrid system could be associated with montmorillonite, a major component of bentonite, with unique swelling and adsorption properties, that results in entrapment and subsequent drug release [29]. Characteristically, the delayed release was inversely proportional to the quantity of bentonite present in the individual formulations (*F*1–*F*3).

A similar observation was made when talc was replaced with bentonite in the hybrid matrix; however, it was not characterized by biphasic release (Figure 1). The characteristic drug release from the talc composite may be indicative of the slow desorption of diclofenac from the interlamellar space and the matrix surface [4].

3.5.4. Kinetic Models and the Mechanism of Diclofenac Release from Multiparticulate Composite Capsules. Polymeric matrix swelling, material degradation, and diffusion of solutes generally govern the release of drug substance from a polymeric matrix system [25, 44]. The rate of polymeric matrix swelling and its subsequent degradation are affected by variations in physicochemical properties; thus, the release kinetics of polymeric systems will be invaluably affected as these phenomena directly affect the API diffusion rate. To confirm this, the kinetic and mechanism of diclofenac release were fitted into mathematical models. Information on how the best release kinetics of a drug suits any of the kinetic models are statistically given as R^2 values, as shown in Table 6. The results show that formulations *F*2 and *F*1 follow the zero-order release kinetics with R^2 values of 0.8738 and 0.8417, respectively. This implies that the release of diclofenac from these pectin-bentonite diclofenac multiparticulate-composite capsules is independent of the diclofenac concentration in the multiparticulate capsules. As a result, the serum level of diclofenac may remain constant throughout the delivery period. However, the rest of the formulations also followed the Korsemeyer–Peppas release kinetic; thus, the fractional release of diclofenac from the pectin-clay multiparticulate composite is exponentially related to time [44]. Among the formulations which demonstrated the Korsemeyer–Peppas kinetic release of diclofenac, formulation *C*1 was the most optimized formulation due to its recorded highest R^2 value of 0.9989.

The mechanism of diclofenac release from formulation *A*1 was via non-Fickian transport ($0.45 < n < 0.89$), while the rest of the formulations showed a super case II transport mechanism ($n > 0.89$) for the release of diclofenac from pectin-clay multiparticulate-composite capsules [44]. This implies that the release of diclofenac from all the developed

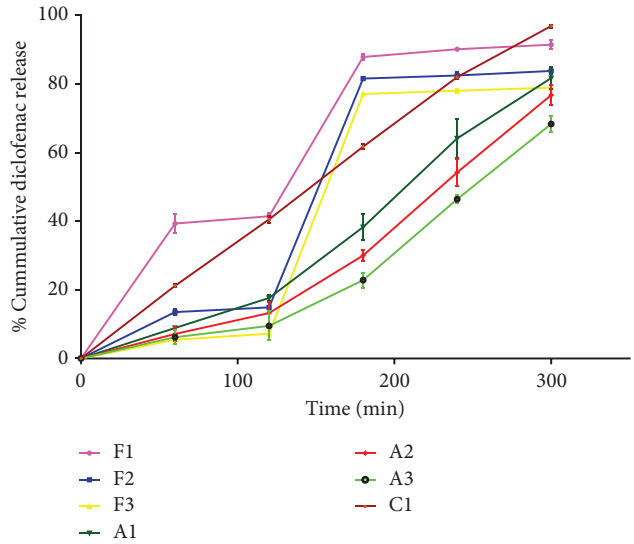


Figure 3: *In vitro* release profile of diclofenac-pectin-clay capsules.

Table 6: Kinetics and mechanism of diclofenac release from pectin-clay multiparticulate composite capsules.

Formulation coded	Zero order	First order	Higuchi	Hixson–Crowell	Korsmeyer–Peppas	
	R^2	R^2	R^2	R^2	R^2	N
*A*1	0.9632	0.9211	0.9408	0.9486	0.9820	0.6171
*A*2	0.9370	0.8879	0.9062	0.9183	0.9683	1.3550
*A*3	0.9085	0.8783	0.8707	0.9010	0.9327	1.9648
*F*1	0.8738	0.8427	0.8166	0.8231	0.8096	1.4352
*F*2	0.8417	0.7987	0.7980	0.7887	0.7986	1.5185
*F*3	0.8113	0.7806	0.7941	0.7757	0.8191	1.5463
*C*1	0.9977	0.8776	0.9919	0.9551	0.9989	1.1273

formulations except for *A*1 was via diffusion and relaxation of the polymer chain in the pectin-clay multiparticulate-composite capsules. This shows that the difference in the physicochemical properties coupled with the different proportions of bentonite and talc affected both the kinetic and release of diclofenac from the multiparticulate composite capsules.

4. Conclusion

The ideal physicochemical properties of the pectin-talc and pectin-bentonite composites coupled with their compatibility with other pharmaceutical excipients and the active pharmaceutical ingredient make them suitable candidates to be used in modified-release formulations. This study had the aim of developing and examining oral modified-release formulations of diclofenac sodium using cocoa pod husk pectin, talc, and bentonite as the natural release modifiers. Upon analyzing the results obtained, it can be concluded that all formulations, containing composites of cocoa pod husk pectin or its combination with talc or bentonite, are capable of exhibiting a modified release of diclofenac sodium. Thus, the formed macroporous structures composed of different entities of pectin and bentonite or pectin and talc offer a novel multifunctional system as a drug-delivery carrier of diclofenac and with desired versatility which could be tailored to meet drug delivery needs, be it sustained release, target release, and controlled release formulations. This could result in the potential of making formulations not only capable of reducing dosing frequency, avoiding dose dumping and consequently minimising adverse effects, but also offers an added advantage of extranutraceutical benefits that also control drug-related adverse effects to ultimately increase patient compliance.

Data Availability

The data used to support the findings of this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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