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A REVIEW ON: FORMULATION AND EVALUATION OF DICLOFENAC SODIUM CAPSULE

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ABSTRACT

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.

KEYWORDS: Diclofenac sodium, cocoa pod husk, pectin-talc hybrid, pectin-bentonite composite, controlled drug release.

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.

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:

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]

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 (*F*1–*F*3), 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 (*A*1–*A*3) using ingredients as shown in Table 1.

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

Ingredients (mg)	F1	F2	F3	A1	A2	A3	C1
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

2.8. Compatibility Studies Using Fourier-Transformed Infrared Spectroscopy (FTIR)

The PerkinElmer Fourier infrared spectrophotometer (spectrum 2, sr. no. 94133, UK) 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 F1 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.

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 ± 0.5% and 5.0 ± 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.

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.

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