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Original Research Article

Development of a modified hard gelatin capsule for colon-targeted drug delivery of hydrogel-based piroxicam microparticles

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Abstract

Purpose: *To develop modified hard gelatin capsules (MHGCs) for colon-specific delivery of hydrogel-based piroxicam microparticles.*
Methods: *Solvent evaporation technique was adopted for the microencapsulation of piroxicam using liquid paraffin (PL.MPs) and soybean oil (PS.MPs) which were subsequently encapsulated in MHGCs (water-impervious). Anti-inflammatory and in vitro dissolution studies were conducted on the unencapsulated microparticles (MPs). Furthermore, in vitro colon-specific sequential drug release from impervious capsules was carried out for 2 h at pH 1.2 and 3 h in 6.8, and ≥ 5 h in 7.4, to simulate drug release in the stomach, small intestine, and colon environment, respectively. Differential scanning calorimetry (DSC) analysis was also conducted on the formulations.*
Results: *Edema inhibition of PL.MPs and PS.MPs were within the range of 51.0 – 64.0 and 58.0 – 69.0 %, respectively. In vitro colon-specific drug dissolution studies revealed absence, minimal, and highest amounts of drug release from MHGCs in pH 1.2, 6.8 and 7.4 media, respectively. Decreased crystallinity of the microparticles was indicated by a broad endothermic peak.*
Conclusion: *The MHGCs hold promise as a potential alternative delivery system for hydrogel-based piroxicam microparticles designed for colon-targeted drug delivery. However, clinical development studies are required.*

Keywords: *Modified hard gelatin capsules, microparticles, HPMC acetate succinate, anti-inflammation*

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INTRODUCTION

Drug delivery systems are suitably formulated dosage forms for the purpose-driven administration of one or more active pharmaceutical ingredient/s to achieve optimized therapeutic effects [1]. Drug targeting on the other hand involves the deployment of a predesigned drug delivery system to a predetermined specific site in the body where

high drug cargo is offloaded to mostly exact local therapeutic action. Such systems may sometimes be predestined for an organ or restricted disease site in the body. When discriminatory deposition of the drug is destined for the colon, it is called colon destined (targeted) drug delivery. A colon destined drug delivery system (CDDDS) is designed with an inbuilt capacity to maneuver through the gastrointestinal tract (GIT) highway for the preferential deposition of drugs in the colon environment for the treatment of irritable bowel disease, colorectal cancer, colitis, arthritis, diarrhea, and so on [2-4]. Colon targeting is warranted when local deposition of the drug will improve local therapeutic drug activity, decrease toxicity, minimize administered dose, reduce dosing frequency, and avoid first pass effect.

In the present work piroxicam was purposed for colon targeting for the possible treatment of inflammatory conditions of the colon, including cancer pain. An ideal CDDDS is expected to release no drug in the stomach, minimal or no drug in the small intestine, and the remaining amount of drug in the colon.

Four major design approaches to colon targeting have been identified. They include the prodrug approach, pH-dependent polymer approach, timed release approach, and bacteria enzyme degraded polymer approach [5-7]. In our present investigation, we explored a modified type of timed-release approach by rendering the capsule surface impervious [8].

Piroxicam (Px) the model drug used in our study belongs to Class II Biopharmaceutics Classification System and is a non-steroidal anti-inflammatory drug (NSAID) for the treatment of chronic inflammatory conditions and management of cancer pains [9,10]. Its systemic adverse effects and poor solubility-based low bioavailability have motivated the search for a solution. Microencapsulation of piroxicam and local targeting of the colon may improve its solubility and mitigate its adverse effects, respectively. Therefore, this work aimed to encapsulate piroxicam-loaded microparticles in modified impervious hard gelatin capsules for possible *in vitro* colon-destined drug delivery.

EXPERIMENTAL

Materials

The materials employed include piroxicam (Jiangsu Guotai Pharm, China), soybean oil® (Solive, Nigeria Ltd, Nsukka), liquid paraffin (Labolo Chemie, India), HPMC acetate succinate (Shin-Etsu, Chem company, Japan), labrafil® (Gattefosse, France), dialysis membrane (6000-8000 Da). All other chemicals are of analytical grades and used as supplied. Rats were procured from the Department of Veterinary medicine, University of Nigeria, Nsukka.

Formulation of piroxicam hydrogel-based microparticles (Px.MPs)

The Px.MPs were formulated using the emulsion cross-linking technique. A 50 mL methanolic solution of HPMC acetate succinate and Px was prepared at the following drug: polymer ratios 1:1, 1:2, 2:1, 1:3, and 3:1. With the aid of a needle/syringe drop-wise quantities were introduced into a beaker containing 50 mL of liquid paraffin and 1 mL of Labrafil® (emulsifier). The mixture was homogenized (Ultra-Turrax homogenizer, IKA® T25 digital, Germany) at a speed of 8 000 rpm for 5 min. Then the beaker containing the mixture was placed on a magnetic stirrer set at 800 rpm for 30 min at ambient temperature. A 15 mL quantity of acetone was introduced followed by the addition of 1 mL of 4% w/v solution (7:3 of acetone: 0.01N HCl) of glutaraldehyde. Stirring was carried out for 3 h prior to centrifugation (SM800B, Uniscope, England). Thereafter, the microparticle sediments were washed off with petroleum ether, air-dried, and stored in desiccators for further use. These microparticles prepared with liquid paraffin (PL.MPs) were coded as PL1, PL2, PL3, PL4, and PL5 corresponding to the aforementioned ratios. Another set of microparticles was prepared using soybean oil (PS.MPs) at similar ratios as above and recorded as PS1, PS2, PS3, PS4, and PS5.

Modification of hard gelatin capsules

Hard gelatin capsules were modified (chemically treated) using a method previously described with slight modifications [11]. Briefly, the lower halves of the hard gelatin capsules were detached from the caps. A 25 mL of 37 % v/v formaldehyde solution was first transferred into a desiccator followed by the addition of 0.5 g of $KMnO_4$ to generate formaldehyde vapour. The chamber was closed to enable adequate vapour saturation. Subsequently, dismembered hard gelatin capsules (No. 2) were separately placed on a wire mesh inside the desiccator and left for 1, 3, 6, 9, and 12 h prior to oven-drying at 50 ^oC for 30 min to facilitate a complete crosslinking reaction between formaldehyde and gelatin. Thereafter, the capsules were air-dried for 1 h to remove residual formaldehyde and stored in an air-tight container for further use.

The modified hard gelatin capsules (MHGCs) that were allowed to crosslink for 3 and 9 h were selected (optimized batches) and weighed (Mettler, England) for further use. Batch A capsule bodies and caps were treated and perforated at both ends with a 21G needle. Batch B capsule bodies were partially treated with an unperforated cap coated with Eudragit S 100. The pierced ends were subsequently sealed with a drop of 5 % w/v ethanolic dispersion of Eudragit® S 100 while the body and cap joints were smeared with the same dispersion prior to air-drying at 25 ˚C and curing for 24 h.

Characterization of Px.MPs

Differential scanning calorimetry (DSC)

Thermal endothermic peaks and changes in heat capacity of piroxicam, HPMC acetate succinate, and MPs were determined using a DSC (Netzsch DSC 204 F1, Geratebau, GmbH, selb, Germany). A quantity of microparticles (5 – 15 mg) from different batches was introduced into an aluminum pan, hermetically sealed and the thermal characteristics were obtained within the range of 20 - 400 ᵒ C at the scanning rate of 10 K/min. Crystallinity index (C.I) of the MPs was calculated as shown in Eq 1.

C.I = (EM/EC)100 …… (1)

where C.I (crystallinity index); EM (enthalpy of the MPs); EC (enthalpy of the polymer).

Scanning electron microscopy (SEM) and particle size analysis

The field emission SEM (JEOL JSM- 6500F, Tokyo, Japan) was employed to determine the morphological properties of the Px.MPs. The particle sizes were determined using a motic image analyzer (Moticam, Xiamen, China), connected to a binocular microscope (Hund, Wetzler, Germany) at a magnification of X4. Average particle sizes were obtained and polydispersity index (PDI) was computed as the ratio of the standard deviation to the average particle size of the MPs.

Determination of encapsulation efficiency (EE) and drug loading capacity

The piroxicam content of the MPs was determined and the EE (%) was calculated using Eq 2, while the loading capacity (LC) is as shown in Eq 3.

EE (%) = (D/T)100 ……. (2)

LC = (D/Q)100 ……. (3)

where EE (encapsulation efficiency); LC (loading capacity); T (initial amount of drug incorporated); Q (total quantity of the formulation); D (amount of drug encapsulated).

***In vitro* drug release studies**

In vitro dissolution studies for the microparticles were carried out using a dialysis membrane tied at one end. Px.MPs were introduced into it, wetted with about 10 mL of dissolution medium, tied at the other end, and lowered into the beaker containing 500 mL of simulated gastric fluid (SGF). The beaker was assembled on a magnetic stirrer and operated at a speed of 100 rpm, temperature of 37 ± 1 ᵒ C, and dissolution duration of 2 h to simulate the stomach region. After 2 h, SGF was replaced with 500 mL of phosphate buffer (pH, 6.8) for 3 h and then phosphate buffer (pH, 7.4) for 10 h. A 5 mL aliquot was sampled at hourly intervals, replaced with 5 mL of fresh medium, followed by a UV assay (Spectrumlab, 752s, Netherlands) for drug content. Cumulative percent drug release was then plotted against time.

On the other hand, *in vitro* colon-specific sequential drug release from encapsulated microparticles (PL.MPs or PS.MPs) was also carried out with batches A and B capsules treated for 3 and 9 h. Apparatus II dissolution method was adopted and involved the introduction of the capsules into the rotating basket attached to a spindle. A dissolution experiment in 900 mL SGF, pH 1.2 was carried out for 2 h, the medium was discarded and replaced with phosphate buffer (pH 6.8) for 3 h. Thereafter, phosphate buffer (pH 7.4) was introduced into the apparatus after discarding the pH 6.8 medium, and dissolution was further carried out for up to 24 h. During each dissolution run, 5 mL aliquots of each medium sampled at hourly intervals were replaced with the same volume of fresh medium. Triplicate dissolution runs were carried out with the resultant mean cumulative % drug release plotted against time.

***In vivo* anti-inflammatory studies**

This study was approved by the Institutional Animal Care and Use Committee of the University of Nigeria Nsukka, Nigeria (approval no. DOR/UNN/17/00021), which adhered to the European community guidelines for the use of experimental animals (86/609/EEC) [12]. The *in vivo* anti-inflammatory activity of hydrogel-based piroxicam microparticles (Px.MPs) was done with the rat paw edema test. The phlogistic agent

employed in the study was fresh undiluted egg albumin to induce edema, which is one of the cardinal symptoms of inflammation. Adult female Wistar rats (120 - 150 ± 5 g) were divided into six groups of six rats per group (n = 6). The groups included the pure piroxicam group and commercial product group (reference groups), PL.MPs and PS.MPs groups (as test groups that received microparticles). Other groups include the control groups: groups that received no treatment after inflammation, an untreated group that was un-inflamed, and a group that was inflamed but received only dispersion medium (placebo group).

The rats were restricted from food and water for 12 h prior to the commencement of the experiment. The restriction of fluid was to ensure hydration uniformity and to reduce unevenness in edematous reactions [13]. Reference groups and test groups orally received the equivalent of 10 mg of drug/kg of animal dispersed in normal saline 0.9 %. Placebo was given normal saline (1 mL).

Edema was established within half an hour post-treatment by parenteral administration of 0.1 mL fresh undiluted egg albumin into the sub-plantar tissue of the right hind paw of the experimental animals. Baseline was established by recording the volume of the displaced water by the inflamed right hind paw of the rats after the egg albumin administration, while volumes displaced after drug administration at time intervals (0.5 - 8 h) were noted and recorded using a plethysmometer. At each time interval, the average edema was evaluated with respect to the deviation in base volume displacement by the injected paw (*r -s*). Edema inhibition (E) was calculated using the relationship shown in Eq 4.

$$E\ (\%)=1-((r-s)/(x-y))100 \quad \ldots\ldots\ldots\ldots \quad (4)$$

where *E* (edema inhibition); *r* (mean paw volume of treated rats after egg albumin injection); *s* (mean paw volume of treated rats before egg albumin injection); *x* (mean paw volume of control rats after egg albumin injection); *y* (mean paw volume of control rats before egg albumin injection).

Pharmacokinetic studies

Following the same protocols as in the *in vivo* study, pharmacokinetic evaluation was carried out on selected groups of the experimental animals. After drug administration, a 0.5 mL blood sample was collected at predetermined time intervals (0.5 – 8 h) prior to 5-min centrifugation at 4000 rpm followed by UV assay (Spectrumlab, 752s, Netherlands). The mean % drug plasma concentrations were obtained and plotted against time, from where the area under the curve was determined.

Histopathological study

At the end of the *in vivo* anti-inflammatory study, the animals were sacrificed for a necropsy using ether anesthesia. The kidneys and livers of the animals were harvested and appropriately treated prior to imaging using a motic camera fixed onto a light microscope [14].

Statistical analysis

Statistical analysis was done using GraphPad InStat Demo (USA). Values were expressed as mean ± SD (standard deviation). Then, average variation was assessed by a two-tailed student's t-test; $p < 0.05$ was considered statistically significant.

RESULTS

Thermal properties

Thermal properties of piroxicam (Px), HPMC acetate succinate, and PL.MPs are as shown in Figure 1 (A, B, C). The DSC thermograms of Px, HPMC acetate succinate, and PL.MPs depicted endothermic melting point peaks at 202.86 ^{o}C (sharp), 63.76 ^{o}C (very broad), and 182.20 ^{o}C (moderately broad), respectively. The crystallinity of piroxicam in the matrix was observed to decrease with a crystallinity index of 44.23 % and enthalpy from 360.78 to 159.56 J/g.

Particle size analysis and scanning electron microscopy

The SEM of the microparticles showed that batches PL.MPs and PS.MPs consisted of a mixture of spherical, non-spherical, and aggregated particles with rough surfaces and pores (Figure 2) with the particle size range within 2.0 ± 0.33 - 44 ± 0.19 µm and 4.0 ± 0.22 – 141 ± 0.16 µm, respectively.

The polydispersity index (PDI) of the formulations indicates average particle dispersity within the range of 0.067 ± 0.28 – 0.733 ± 0.31 for PL.MPs and 0.564 ± 0.59 – 0.993 ± 0.53 for PS.MPs which are < 1 (less variation) except formulations PL3 (1.291 ± 0.21) and PS1 (1.100 ± 0.22).

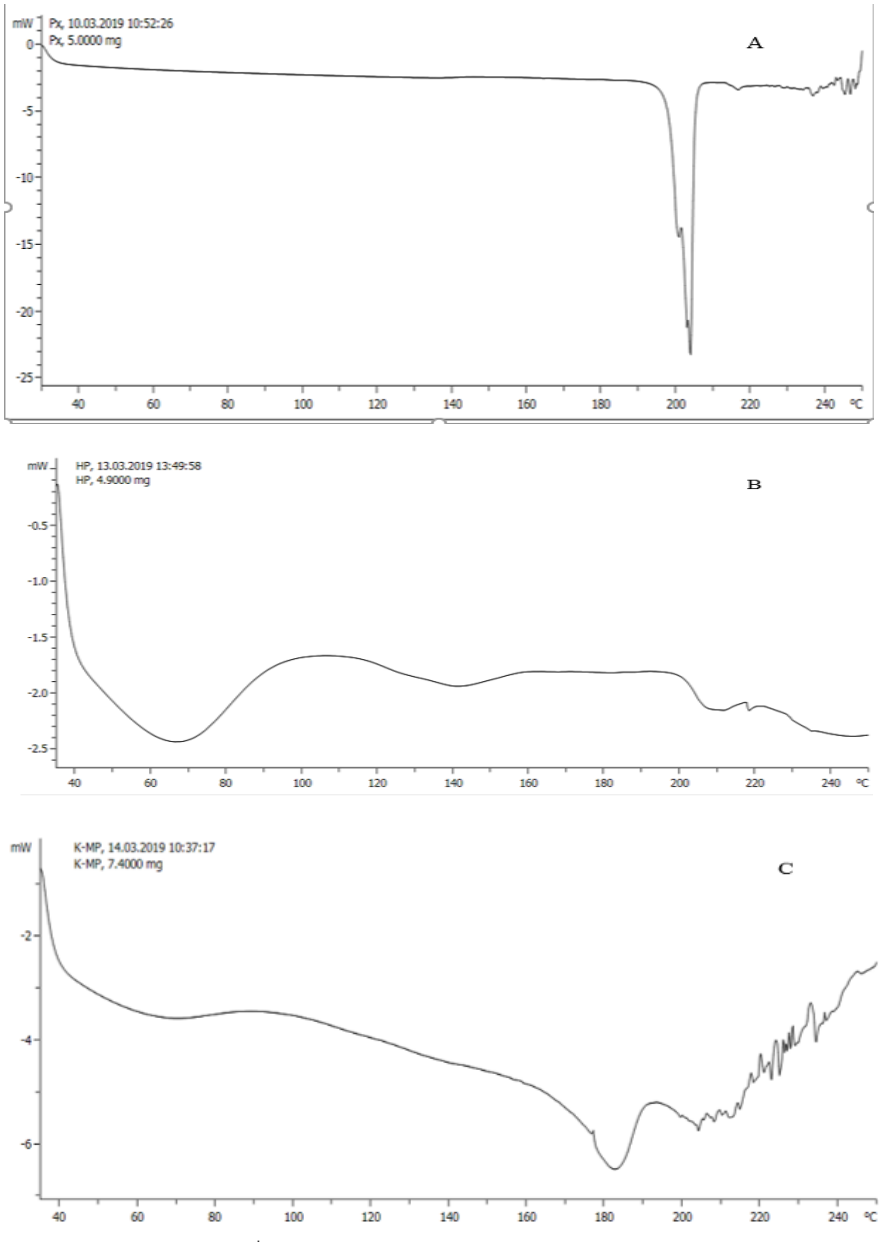

Figure 1: DSC spectra of (A) piroxicam, (B) HPMC acetate succinate, and (C) PL.MPs.

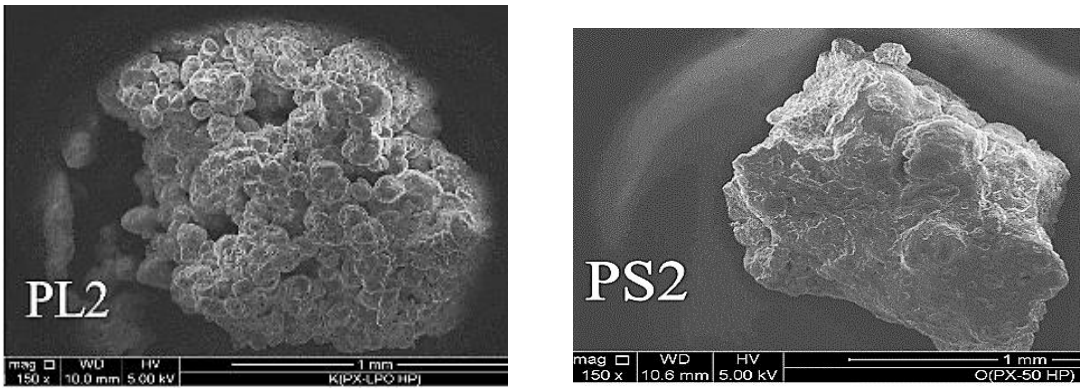

Figure 2: Scanning electron micrographs of microparticles. ***Note:*** PL2 and PS2: (microparticles containing drug: polymer ratio 1:2)

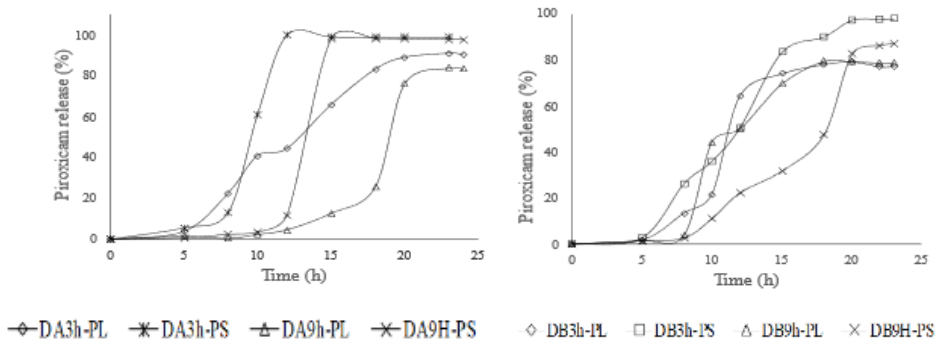

Figure 3: Piroxicam release from batches A and B. ***Key:*** DA 3h-PL (Liquid paraffin MPs, batch A 3 h caps treatment); DA 9 h-PS (Soybean oil MPs, batch A 9 h caps treatment); DB 3h-PL (Liquid paraffin MPs, batch B 3 h caps treatment); DB 9 h-PS (Soybean oil MPs, batch B 9 h caps treatment)

Encapsulation efficiency and loading capacity

The encapsulation efficiencies (EE%) of the MPs formulated in paraffin and soybean oil ranged within 59 ± 0.02 – 85 ± 0.11 % and 53 ± 0.11 - 99 ± 0.01 %, and the LC was within the range of 20 ± 0.13 – 28 ± 0.10 and 17 ± 0.21 - 39 ± 0.6 %, respectively.

In vitro release of piroxicam from microparticles

The % drug release of piroxicam from PL.MPs or PS.MPs using dialysis bag in SGF (pH, 1.2), pH, 6.8, and pH, 7.4 were within 4 - 55%, 4 - 82%, and 31 - 90%, respectively. Batch PS4 had the highest (90%) piroxicam release. On the other hand, there was no drug release from the impervious capsules (MHGCs) in SGF (pH, 1.2) after 2 h. At pH, 6.8, capsule swelling coupled with minimal drug release within the range of 1 - 5% was observed after 3 h (Figure 3). The drug release observed within 24 h at pH 7.4 (simulating colonic environment) ranged between 2 - 99%. Batch A capsules showed more prolonged drug release than batch B. Similarly, capsules that underwent 9 h treatment exposure prolonged drug release than those treated for 3 h. Furthermore, microparticles prepared with liquid paraffin (PL.MPs) prolonged drug release than those prepared with soybean oil (PS.MP) with 3-h treated capsules.

Pharmacokinetics

The plasma drug concentration of PL.MPs, PS.MPs, pure drug, and commercial samples showed the maximum plasma drug concentration of 23.54, 49.31, 18.63, and 19.18 µg/mL in 5, 2, 5, and 2 h, respectively. The PS.MPs had the highest drug plasma concentration. The area under curves (AUCs) values were calculated for PL.MPs and PS.MPs are 188.51 and 456.88 µg/h/mL, respectively. The MPs had the highest AUC ($p < 0.05$) when compared to the reference groups.

Anti-inflammatory activity

The results of the anti-inflammatory studies of the microparticles showed that batch PL.MPs and PS.MPs had edema inhibitions within the range of 51.0 ± 0.12 – 64.0 ± 0.22 and 58.0 ± 0.11 – 69.0 ± 0.10 %, respectively, after 1 h administration. Significant edema reduction ($p < 0.05$) was observed in both MPs when compared to the negative control.

Histopathological features

The histopathological features of the liver and kidney sections of the groups are shown in Figures 4 and 5. The liver section (Figure 4) shows the control groups: C1 (negative reference that received inflammatory agent but no treatment) and placebo (P, that received inflammatory agent and normal saline) with apparent central venous (CV) congestion (white arrows). On the other hand, the group that neither received an inflammatory agent nor treatment control 2 (C2) portrayed normal hepatic lobules with sinusoids (white arrows). Whereas, the kidney of the control groups reveals normal glomerulus (GL) and renal tubules (white arrows) with mild dilatation.

In Figure 5a, the histoarchitecture of the liver in the group that received the commercial sample indicates veinous/sinusoidal congestion, whereas degeneration and necrosis of hepatocytes were obvious in the group that received piroxicam powder. The liver tissue histoarchitecture of the experimental test groups showed mild and insignificant congestion of the central vein. The kidney architecture of the test (Figure 5b) and control groups (Figure 4) reveal renal corpuscles with normal urinary size and tubular

structures with no sign of congestion. However, hypercellularity of the glomerulus (GL) was observed in the kidney section of both hydrogel-based microparticle groups as shown in Figure 5b (PL and PS) which may be a histologic change but not pathological.

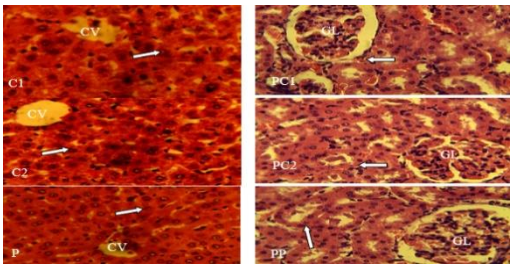

Figure 4: Histoarchitecture of the liver and kidney sections of rat from control groups**.** ***Key:*** C1 (Control 1), C2 (control 2), and P (placebo): (liver sections of the group that received inflammatory agent but untreated, untreated and uninflamed group, and the group that received inflammatory agent and normal saline, respectively); PC1 (control 1), PC2 (control 2) and PP (placebo): (kidney sections of the group that received inflammatory agent but untreated, untreated and uninflamed group and group that received inflammatory agent and normal saline, respectively); GL (glomerulus); CV (central venous); white arrows (indicating cv congestion (liver), renal tubules and the normal architecture of hepatocytes separated by hepatic sinusoids)

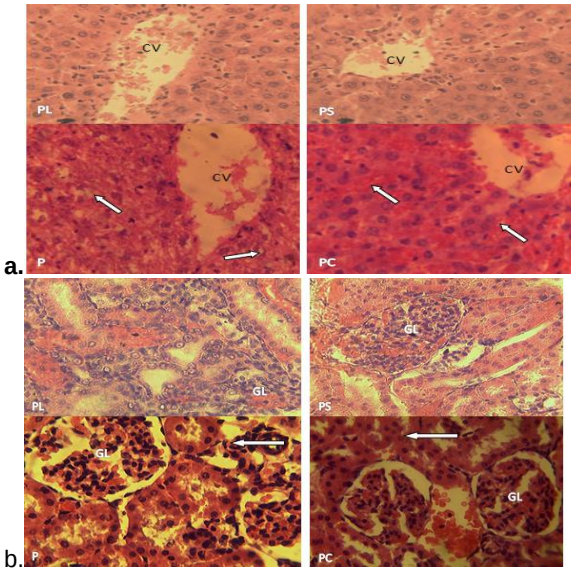

Figure 5: Histoarchitecture of the liver (a) and kidney (b) sections of the Wistar rats. that received microparticles, pure and commercial samples**.** ***Key:*** PL and PS, P and PC (Fig. a, liver architecture of groups that received PL.MPs and PS.MPs, pure and commercial brand piroxicam, respectively); PL and PS, P and PC (Fig. b, kidney architecture of groups that received microparticles batch PL.MPs and batch PS.MPs, pure and commercial brand piroxicam, respectively); GL (glomerulus); CV (central venous)

DISCUSSION

Thermal characteristics of formulations may be affected by excipients characteristics. In this context, the presence of HPMC acetate succinate altered the crystallinity of piroxicam as depicted in the reduced crystallinity and enthalpy of the MPs. This suggests that the excipient and drug combined to produce less crystalline MPs. Typically, lower enthalpy is indicative of diminishing crystallinity and potentiality for retention of drug entrapment over a period of time, while higher enthalpy is suggestive of highly organized crystals bereaved of drug-loading space and destined for drug expulsion [15].

Pores on formulated drugs create paths for fluid ingression. The pores on the MPs are indications of impacted water sorption, swelling, drug entrapment, and drug release pattern of the matrix.

In vitro drug release from microparticles could be influenced by the rate of fluid sorption, swellability, nature of the crystal lattice formed, excipient types and concentrations, and the presence and quantity of pores that facilitate diffusion of drug in the medium [16,17]. In colon-destined drug delivery, the formulation matrix is expected to withhold the drug from being released at the upper gastrointestinal tract (GIT). In SGF (pH 1.2) and pH 6.8, the observed drug release suppression and minimal release respectively from batches A and B are attributed to the impervious nature of the treated capsules and the insolubility of Eudragit S 100 at pH < 7. Eudragit S 100 is only soluble from pH 7; this means that from pH 6.8 and above the polymeric structure begins to breakdown and soften. Complete polymer dissolution took place when the already softened surface interacts with a pH 7.4 dissolution medium. When the treated capsules were introduced into a pH 6.8 medium, the Eudragit S100 seal or plug at the orifice may have begun to soften and allow fluid ingress, hence the minimal drug release observed at this pH.

When the pH 6.8 medium was replaced with a pH 7.4 dissolution medium, the polymeric Eudragit seal on the capsule orifice probably experienced complete dissolution for the orifice to permit liberal fluid sorption which resulted in microparticle hydration, copious drug dissolution, increased diffusion into the dissolution medium, and capsule swelling. Ultimately, the highest amount of drug was released at this pH, which is predictive of preferential drug deposition in the colon if orally ingested. Upon oral administration

of the capsules, it is anticipated that the capsules would witness generous fluid sorption through the eroded dissolved orifice seal and release drug within the jejunum and ileocecal region of the GIT which will continue as it transits into the ascending colon. For the capsules with unperforated but Eudragit S 100-coated caps (batch B), fluid ingress into the capsules must have followed the same process of polymer softening and dissolution at pH 6.8 and 7.4, respectively, and eventual drug release.

The treated (MHGC) capsule bodies resisted aqueous permeation after their exposure to formaldehyde which crosslinked with the amino acid in gelatin. The duration of crosslinking was observed to impact the aqueous resistance of the capsule; thus, capsules treated for 9 h prolonged drug release than those treated for 3 h. Previous worker has earlier made this observation [18].

Successful colon destined drug delivery of our model drug piroxicam is beneficial in a number of ways. Firstly, selective deposition at the colon could provide a therapeutic dose for the local treatment of colorectal cancer or other inflammations. Secondly, first-pass metabolism is evaded through colon targeting. Thirdly, less than the conventional dose of piroxicam would be required to treat the target inflammatory colon disease. Fourthly, the GIT side effect of NSAIDs will be precluded with colon-targeted piroxicam.

CONCLUSION

HPMC-based piroxicam microparticles for controlled drug delivery have been successfully prepared. Chemical modification of hard gelatin capsule is suitable for achieving optimal *in vitro* colon destined release of piroxicam microencapsulated in HPMC.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Prof Godswill C Onunkwo and Prof Sabinus I Ofoefule supervised the work. Prof Nicholas Obitte, Prof Amarauche Chukwu, Prof SI Ofoefule, Dr Calister Ugwu, and Prof Godswill C. Onunkwo variously contributed to the design of the work. Dr Chukwuma O. Agubata, Dr Salome A Chime, and Dr Calister E Ugwu carried out the experimental work. Prof Nicholas C Obitte and Prof Ikechukwu V Onyishi read and edited the manuscript.

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