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Role of Different Types of Polyacrylic Polymers on Decreasing the Ulcerogenic Effect of Certain Non-Steroidal Anti-inflammatory Drugs

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Authors' contributions

This work was carried out in collaboration between both authors. Author EEZED designed the study, wrote the protocol and wrote the first draft of the manuscript. Author HAY managed the literature searches, managed the experimental process. Both authors read and approved the final manuscript.

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ABSTRACT

Flunoxaprofen (FLP) and piroxicam (PIM), acidic non-steroidal anti-inflammatory drugs (NSAIDs), as well as floctafenine (FLN), basic NSAIDs, were coated with anionic and cationic polyacrylic resins adopting the fluidized bed technique. The bioavailability of the uncoated and coated drugs as well as the effect of the coat on the histopathological features of gastric mucosa were determined using male albino rats. Coating the particles largely affected the drug bioavailability as reflected on the peak heights, peak times and AUC_{0-24}. FLP coated with cationic polymer showed increase in the peak height from 140.61 (uncoated drug) to 160.70 µg/ml. Peak time decreased from 4 hrs. to 2 hrs. AUC_{0-24} increased from 2306.51 to 2835.21 µg/ml. hrs. The same parameters of the other two drugs PIM and FLN showed different behaviors according to their physicochemical characteristics as well as the nature of the coating polymer.
Different histopathological changes were observed in animals' stomachs which ranged between: no effect, deficiency of epithelial cells, necrosis, degeneration and hemorrhage. The changes were

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observed in rats administered PIM daily for 30 days as well as those administered FLP and FLN in single doses. Drugs coated with Eudragit-E_{100} showed significant decrease in ulcers obtained with uncoated drugs or drugs coated with the anionic type.

Keywords: Microencapsulation; polyacrylic polymers; non-steroidal anti-inflammatory drugs; Fluidized bed technique.

1. INTRODUCTION

For a long time, non-steroidal anti-inflammatory drugs (NSAIDs), have been used frequently in clinical settings for their antipyretic, analgesic, and anti-inflammatory effects. NSAIDs are thought to demonstrate such effects by the inhibition of cyclooxygenase (COX), resulting in the inhibition of prostaglandin (PG) production at inflammed sites. PG also has important roles in maintaining homeostasis of gastrointestinal mucosa. NSAIDs not only exhibit the expected anti- inflammatory effects but also can cause serious side effects such as gastrointestinal injury [1]. In our aging society, the use of NSAIDs has continued to increase, and their side effects including gastrointestinal mucosal injury have become a clinical problem [2].

Non-steroidal anti-inflammatory drugs (NSAIDs) are groups of the most widely used and responsible drugs that cause recurrence. Beside causing ulcer formation, NSAIDs can also delay in healing of pre-existing ulcers and promote their bleeding [3]. The ability of NSAIDs to promote the bleeding of pre-existing ulcers is most probably related to their inhibitory effects on platelet aggregation. The inhibition of platelet aggregation by NSAIDs occurs as a consequence of the inhibition of thromboxane synthesis. The NSAIDs have been shown to increase basal acid secretions as a result of COX-1 mediated prostaglandin depletion in rats with gastritis, but not in those with intact stomachs. In humans, NSAIDs-induced acute gastric injury has been shown to be greater. Acid plays a key role in the development of acute gastric mucosal lesions in the rat stomachs and that NSAIDs-induced reduction in gastric mucosal blood flow only occurs in the presence of acidic conditions. On the other hand, administration of NSAIDs leads to early release of interleukin-1b (IL-1b) [4], one of the most potent inhibitors of gastric acid secretion, which may be a protective mechanism against NSAIDs induced mucosal injury [5].

Acrylic resins have been used to encapsulate drug particles and to obtain solid dispersions with different physicochemical properties and also to alleviate certain side effects of the parent drugs [6-10].

Eudragit polymers are a series of acrylate and methacrylate polymers available in different ionic forms. Eudragit-L_{100} and Eudragit-E_{100} polymers belong to the class of poly (meth) acrylates polymers that are insoluble but permeable in digestive fluids. These polymers possess alkaline functional groups which lend themselves to pH independent swelling (in the physiological range) and enable sustained release of active ingredient in the formulation [11,12].

The study in this part aimed to assess the effects of encapsulation of Flunoxaprofen (FLP) and Floctafenine (FLN), representing the acidic as well as basic NSAIDs respectively, with either Eudragit -L_{100} or Eudragit -E_{100} on the bioavailability and histological characteristics of gastric mucosa of rats. In addition, the effect of prolonged administration of uncoated and coated Piroxicam (PIM) on rats' stomachs was also examined over a period of 30 days.

2. MATERIALS

Flunoxaprofen (FLP) (Sigma- Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Amriya pharmaceuticals industries, Alexandria, Egypt.

Piroxicam (PIM), (Pfizer, New York, USA) was a gift sample kindly supplied by Sigma pharmaceuticals industries, Quweisna, Egypt.

Floctafenine (FLN), (Sigma-Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Sigma pharmaceuticals industries, Quweisna, Egypt.

Eudragit-L_{100} and Eudragit-E_{100} were purchased from RÖhm Pharma GMBH, Darmstadt (Germany).

All other reagents and chemicals were analytical grades and were used as received.

2.1 Equipment

Fluidized bed spray granulator equipped with an atomizing nozzle and a special set for coating small particles: Glatt AG, CH-Prattelen, Switzerland, Spectrophotometer: Beckman Mod. 24, Beckman Inset. Fullerton, USA. Gas chromatograph: Erba Mom. 2400 V, Italy.

3. METHODS

3.1 Coating of FLP, PIM and FLN with Eudragit –E_{100} and Eudragit -L_{100}

3.1.1 Preparation of the coating solution

Coating solutions in concentration of 5% w/v Eudragit - E_{100} (cationic type), Eudragit - L_{100} (anionic type) in acetone-isopropyl alcohol mixture (1:1) were prepared by dissolving 30 gm of each Eudragit - E_{100} or Eudragit - L_{100} separately in 200 ml solvent mixture [13].

3.1.2 Coating technology

Reviewing the literature about air suspension technique revealed that microencapsulation by this technique reduces processing time and improves the product properties. It was also proven to be more convenient method especially in case of thermo-labile materials.

The process consists simply of supporting 30 gm drug in the vertical container fluidized from below by a stream of air. The exhaust filter was shaken from time to time to keep the entire drug inside the container. After adjusting the atomized compressed air, the solution of 5% w/v of either Eudragit -E_{100} or Eudragit -L_{100} in acetone-isopropyl alcohol mixture (1:1) was sprayed over the bed. The spraying pump was adjusted to be 10 rpm to give a suitable droplet size from the sprayed solution. The temperature was maintained at 35-40°C during the coating process.

The volume of the solution needed to produce the desirable microcapsules was 200 ml. When the microcapsules have been formed, the spray was turned off and the product was left to fluidize inside the apparatus for about 60 minutes for complete drying at the same temperature. The encapsulated particles were stored in a desiccator over anhydrous calcium chloride for 48hrs before any further study. Table 1 shows the operating conditions in coating the chosen NSAIDs.

Table 1. Operating conditions in coating the chosen NSAIDs

Operating conditions in coating the chosen NSAIDs	
Core material	**Chosen NSAIDs**
Inlet air temperature (°C)	(60)
Material temperature (°C)	(35-40)
Out let air temperature (°C)	(33-36)
Air flow rate (m^3 / min.)	(0.75-0.9)
Spray rate (ml / min.)	(6.9)
Spray pressure (atm.)	(1.5-2.0)
Diameter of spray nozzle (mm)	(0.8)
Drying conditions	(40°C, 60 min)
Mesh size (µm)	(80-250)
Charged weight (g)	(30)

4. BIOAVAILABILITY

Uncoated, Eudragit- E_{100} coated as well as Eudragit -L_{100} coated drugs were administered to three groups each of 28 male albino rats weighing 240±10 g. The animals were fasted for 20 h prior to the experiment but had free access to water. Each treatment was suspended in I per cent w/v methylcellulose solution. A dose level of 40 mg/kg was kept constant for all the treatments involving FLP and FLN. Control animals were dosed with an equivalent volume of I per cent methylcellulose solution free from drug. Four animals were scarified at time intervals of 1, 2, 3, 5, 7, 12 and 24 h. Blood samples were collected, immediately centrifuged (5000 rpm for 20 min) and the assay was performed in plasma for FLP according to Prabagar et al. 2009 [14] and for FLN according to the method reported by Gehan et al. 2005 [15].

5. *IN-VIVO* ULCEROGENICITY STUDIES

5.1 Experimental Animals

Male Wistar rats, weighing 180-200 gm, were obtained from National researches center (Cairo, Egypt). Rats were maintained at 22±1°C on a 12h light-dark cycle allowed rat chow and water ad libitum. The allocation of animals to all groups was randomized. *In-vivo* experimental protocols had the approval of the institutional animal ethics committee (IAEC) (IAEC/PROPOSAL/DB-4/2010).

Before the start of the experiments, rats were housed individually in wire mesh cages to avoid coprophagy under controlled environmental conditions. Food was withdrawn for 36h but water was allowed ad libitum [16]. The absence of ulcers in some of the treated groups has revealed that the pre- fasting conditions alone doesn't induce ulcer.

In case of long term drug administration, the same procedure was followed except that the animals were kept on normal diet along the time of 30 days while administering a daily dose level of 1.06 mg/kg [17-19]. The animals subjected to long term administration were kept under constant observation throughout the experiment. The bioavailability was calculated as previously reported [14].

At the end of the experiment, the abdomen was opened. Each stomach was excised, dissected along the greater curvature and contents were emptied by gently rinsing with isotonic saline solution. Each stomach was pinned out on a flat surface with the mucosal surface uppermost [20].

5.2 Macroscopic Examination of Gastric Ulcers

The ulcer incidence, represented as hemorrhagic lesions and gastric ulcers were examined and assessed macroscopically with the help of a 10x binocular magnifier immediately after the animals were sacrificed. To quantify the induced ulcers in each stomach, the scoring systems described in the literature [21,22] was employed. The induced ulcers in these experiments were in the form of small spots punctiform lesions and thus each was given a score between 1 mm and 4 mm. Ulcers of 0.5 mm diameter were given a score of 1 mm whereas ulcers of diameters 1 mm and 2 mm were given scores of 2 mm and 4 mm, respectively. Stomach with no pathology was assigned a score of zero. For each stomach, an ulcer index was calculated as the sum of the total scores of ulcers. Six determinations were made for each drug suspension administered. The average ulcer index is presented as the mean (n=6) ± SD.

5.3 Histopathological Examination of Stomach Sections

For histopathological examination, the stomach was surgically extirpated from each group and opened through vertical incision along the greater curvature and photographs were taken of the inside surface of the stomach. The stomach tissues were then washed in 0.9% saline and a portion of it was kept in 10% buffered formalin for histopathological studies. The sections were then stained with hematoxylin and eosin. The tissue sections were examined under an Olympus BX51 (Olympus Corporation, Tokyo, Japan) microscope and images were captured with a digital camera attached to the microbeads [23].

5.4 Statistical Analysis

One way ANOVA test followed by Tukey posttest was used for comparisons between the treatment and control groups. Data were presented as Mean ± SD. The P values <0.05 was considered as significance level during this study.

Previous work showed that there is no chemical interaction between the adopted drugs and polymers utilizing infrared analysis (IR) and differential scanning calorimetry (DSC) techniques. The *in-vitro* release of drugs from different microbeads was also followed in our previous work [24].

6. RESULTS AND DISCUSSION

6.1 Bioavailability Results

The plasma levels at different time intervals for rats administered coated and uncoated drugs are illustrated in Fig. 1.

From Fig. 1, the rats received the E- coated FLP, FLN or PIM showed serum concentrations higher than those received corresponding uncoated drug as well as drugs coated with Eudragit –L_{100}. Rats received L-coated FLP, FLN or PIM showed blood level time curves with broad peaks occurring at 6, 5 and 4 hours respectively. Table 2 shows the peak height, peak times as well as AUC_{0-24} of FLP, FLN and PIM either uncoated or coated with the cationic and anionic Eudragits.

The higher bioavailabilities obtained with E-coated drugs compared to the L-coated agree with the results obtained by Kenneth et al. 2013 and Moustafine et al. [25,26] who worked on ibuprofen. Although neither the coated nor the uncoated FLP and PIM dissolved in artificial gastric juice, their behavior in the rat stomach seemed variable. The high plasma levels obtained in rats administered cationic resin-coated drugs confirmed the view of buffering

action of the reign. The cationic resin would dissolve in the immediate microenvironment of the drug particles and accordingly increase the pH, and therapy the dissolution rate and gastric absorption of the drug would be increased. On the other hand, the acidic NSAIDs may react with the resign itself to form a soluble salt in situ. The drug particles that escaped absorption in the stomach would be wetted before reaching the comparatively alkaline juice of the small intestine where complete and rapid absorption took place [27].

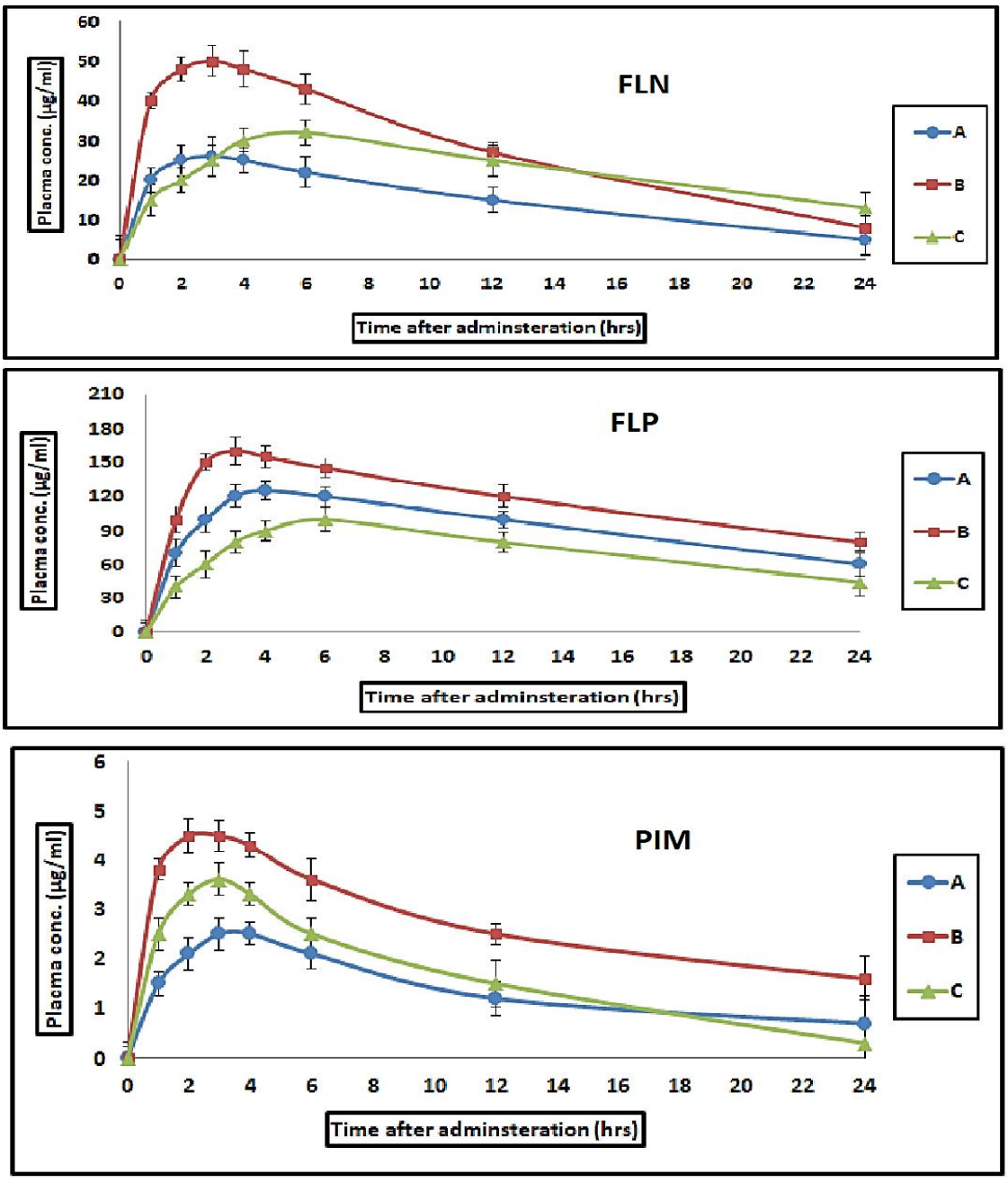

Fig. 1. Blood plasma levels of the chosen drugs after systemic administration to rats: (A) uncoated drug, (B) drug coated with cationic polymer, (C) drug coated with anionic polymer

Table 2. Bioavailability criteria of Flunoxaprofen, Floctafenine and Piroxicam after systemic administration to rats

Drug	Peak height (µg/ml)			Peak time (hrs.)			AUC_{0-24} (µg/ml. hrs.)		
	A	B	C	A	B	C	A	B	C
Flunoxaprofen	140.61±2.17	160.71±3.62	105.32±2.12	4	2	6	2306.51	2835.21	1694.46
Floctafenine	32.7 ± 2.32	50.02 ±1.93	35.11± 2.93	3	2	5	397.59	658.29	559.51
Piroxicam	3.71 ± 0.86	4.82 ± 0.52	3.06 ± 0.79	3	2	4	38.75	62.46	33.15

(A) Uncoated drug, (B) drug coated with cationic polymer, (C) drug coated with anionic polymer
The Results are Average of Four Readings

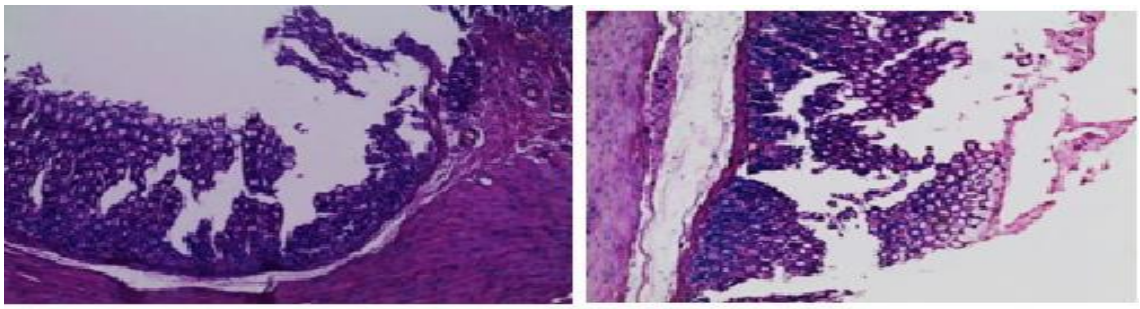

Fig. 2. Gastric mucosa of rats dosed with uncoated drug 40 $mg.kg^{-1}$. Shown are broken and ruptured lining epithelial cells and gastric glands. a- Flunoxaprofen, b- Floctafenine

The low plasma levels and long peak time, seen with the anionic resin-coated drug may be attributed to the insolubility of this resin in the acidic pH. The coated particles would remain undissolved until reaching the small intestine where they dissolve in the alkaline pH. A lag time would be taken for the coat to swell and then dissolve before the drug particles. Complete absorption will take place from the small intestine [28] with the weakly basic FLN, however, the effect of the cationic coating was found to increase the wettability and hence rapid dissolution of the drug in the stomach. Absorption of FLN would therefore start in the small intestine at a faster rate for the E-coated drug compared with either the uncoated or L-coated drug. On the other hand, The L-coated particles will take some time first to swell and dissolve in the relatively alkaline fluid of the small intestine before releasing the drug for absorption. The obtained results of the coated as well as uncoated drugs are parallel to those obtained by Akhgari et al. [29] who worked on indomethacin.

6.2 Histopathological Results

The gastric mucosa of animals administered either uncoated FLP or FLN showed marked ulceration with complete disappearance of mucosal surface (Fig. 2a and 2- b).

In the photographs, severe histological changes, such as deficiency of epithelial cell, necrotic degradation of the mucosa, hyperemia of the capillaries, hemorrhage are distinctly observed. From these results and the gross observations, it could be considered that such severe damage would require a fairly long period for recovery.

The histological changes observed in gastric mucosa of rats administered either FLP or FLN coated with Eudragit-L_{100} were similar to those seen in rats administered the uncoated drugs, but the degree of damage was higher in case of FLP (Fig. 3- a and 3 -b).

The changed appearances observed in rats administered the uncoated drugs and drugs coated with Eudragit-L_{100} are in marked contrast to those of the usual surface cells (Fig. 4- a, 6 -b and 4-c).

Fig. 4. shows photographs taken for rats' stomachs administered FLP and FLN coated with Eudragit-E_{100}. Minor changes, such as necrotic degeneration at the mucosal surface,

deficiency of epithelial cells, were observed, but their degree was slight in comparison with the changes caused by uncoated drugs and drugs coated with Eudragit-L_{100}. From these findings the protective effect of Eudragit-E_{100} on both FLP and FLN is histologically reflected, i.e. the results obtained by method reported by Kazuhide Higuchi et al. [30] which is based on the loss of staining ability by injured epithelial cells as the preliminary diagnostic stage of gastric ulceration. The histological examination of the gastric mucosal tissues revealed that the oral administration of either FLP or FLN coated with cationic polymer, Eudragit-E_{100}, produced comparatively less damage than the same doses of either the uncoated drugs or drugs coated with the anionic polymer, Eudragit-L_{100}.

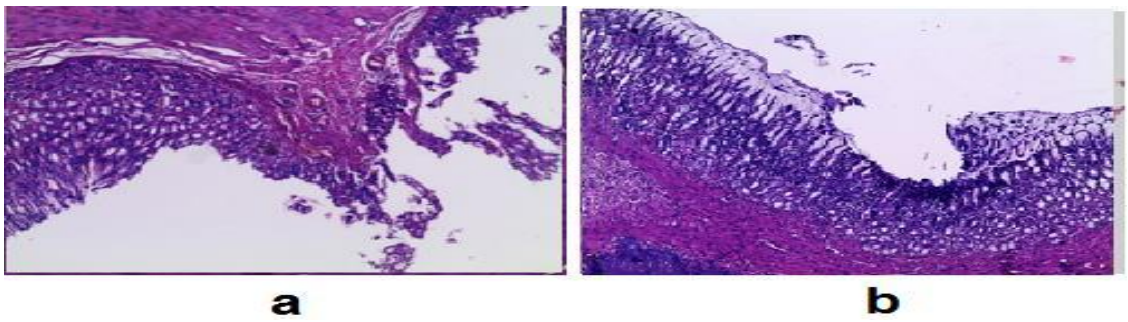

Fig. 3. Gastric mucosa of rats dosed with 40 mg.kg-1 drug coated with anionic polymers. Shown are numerous pale cells that did not pick up the stain and numerous capillaries engorged with blood cells. a- Flunoxaprofen, b- Floctafenine

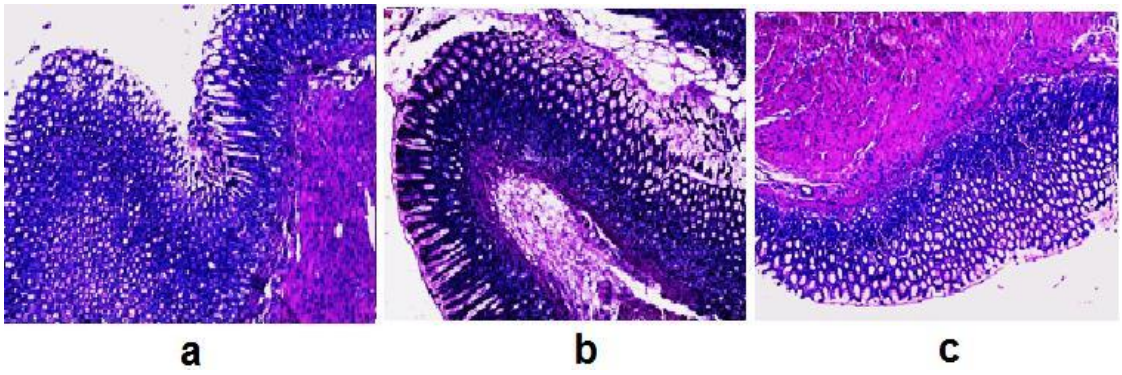

Fig. 4. Gastric mucosa of rats dosed with 40 mg.kg^{-1} drug coated with cationic polymers. Shown are intact normal epithelial lining cells, chief cells and parietal cells. Overall gastric histology appears normal: a- Flunoxaprofen, b- Floctafenine, c- 2 ml of 1% w/v methylcellulose

Table 3. Histopathological findings in the stomachs of rats administered uncoated and coated-Flunoxaprofen, and Floctafenine

Observation	Time after administration (hrs.)	Flunoxaprofen			Floctafenine		
		Uncoated	E-coated	L-coated	Uncoated	E-coated	L-coated
Deficiency of epithelial cells	7	+++	-	+++	+++	-	++
	12	+++	-	+++	+++	-	+++
Necrosis and degeneration	7	+++	-	++	+++	-	++
	12	+++	-	+++	+++	-	+++
Hemorrhage	7	+++	+	++	+++	+	+++
	12	+++	+	+++	+++	+	+++

- *+++ Severe, ++ Moderate, + slight, - no ulcers*
- *Animals administered only methylcellulose showed no ulcers*
- *The results are average of four readings.*

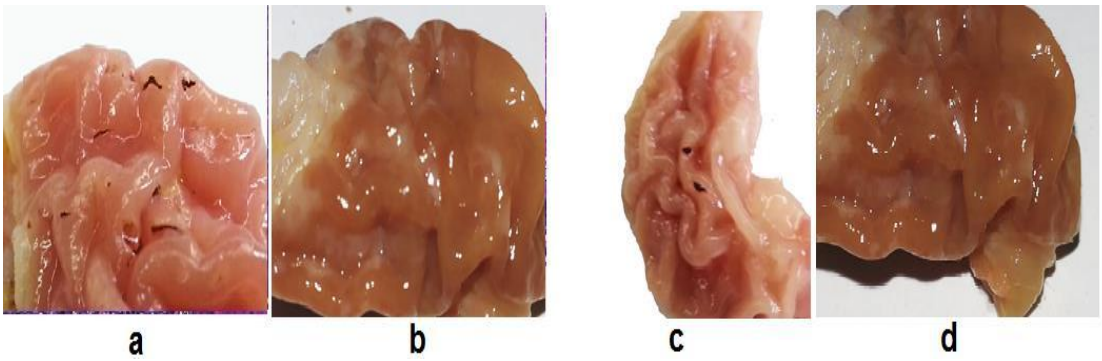

Fig. 5. Stomachs of rats dosed daily with 1.06 mg.kg^{-1} either uncoated or coated piroxicam for 30 days: a- uncoated piroxicam, b- piroxicam coated with cationic polymers, c- piroxicam coated with anionic polymers and d- one per cent methylcellulose only

6.3 Long Term Study

Eight animals, four from each group which administered either uncoated PIM or PIM coated with Eudragit-L_{100} showed severe hemorrhage and death along the experimental time. The responsible cause of death was the gastric injuries as manifested by the microscopic examination of the rats' stomachs. Table 3 shows the ulcer development 30 days after administering coated and uncoated PIM.

Fig. 5. shows stomachs of rats administered coated and uncoated PIM.

7. CONCLUSION

Rats received E-coated FLP, FLN or PIM showed serum concentrations higher than those received corresponding uncoated drug as well as drugs coated with Eudragit-L_{100}. Histopathological examination of the gastric mucosal tissue revealed that oral administration of either FLP or FLN coated with cationic polymer showed less damage than the same doses of either uncoated or coated with anionic polymer.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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