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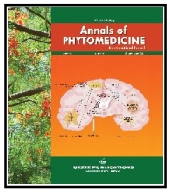

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Enteric coated microgranules of pantoprazole sodium in gastroesophageal reflux disease

Avani Gupta*, Juber Akhtar◆, K.C. Rastogi*, Badruddeen, Mohammad Irfan Khan, Mohammad Ahmad and Sanjay Kumar**
Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India
** Department of Pharmaceutics, Hygia Institute of Pharmaceutical Education and Research, Lucknow-226020, Uttar Pradesh, India*
*** Hygia Institute of Pharmacy, Lucknow-226020, Uttar Pradesh, India*

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Abstract

The gastroesophageal reflux disease (GERD) affected human welfare and economy globally. The major cause of GERD is poor lifestyle and diet. Reflux esophagitis is the endoscopic evidence of damage of the esophageal mucosa which produces heart burn and regurgitation. The aim of the present work was to study the effects of optimized enteric coated microgranules of pantoprazole sodium on gastroesophageal reflux disease (GERD) in animal model. The optimized enteric coated microgranules of pantoprazole sodium were prepared by fluidized bed coater/dryer (FBD) Wurstor technology (bottom spray). The Male Sprague dawley (SD) rats were divided in to four groups (n=6). The normal control group (Group I treated with vehicle), disease control (Group II pretreated with vehicle), Group III pretreated with pantoprazole sodium (40 mg/kg), and Group IV pretreated with enteric coated pantoprazole microgranules (40 mg/kg). All the pretreatments were given 1 h before the GERD induction which was induced in all the groups except Group I. The macroscopic changes in all the rats were observed and scored as 0 to 3 as no macroscopic changes (scored 0), mucosal erythema only (scored as 1), mild mucosal edema or small erosions (scored as 2), moderate edema or erosions (scored as 3). The macroscopic observations of rats (Group III) esophagus treated with pantoprazole sodium showed mild ulcerative lesions (lesion area 12.33 ± 0.26 mm^2) and no inflammation with well mucous membrane, while the esophagus of rats (Group IV) treated with enteric coated pantoprazole microgranules showed mild lesions (lesion area 8.33 ± 0.26 mm^2) and no inflammation in mucous membrane. The normal control group (Group I) rats showed normal esophagus texture; however, diseased control group rats (Group II) demonstrated development of erosion and inflammation. Overall, present work indicated better esophageal protection by enteric coated pantoprazole microgranules as it could ameliorate esophageal damage against GERD.

1. Introduction

Gastroesophageal reflux disease (GERD) directly disturbs the lifestyle and a serious health problem. The global research indicates that gastroesophageal reflux disease trouble about 40% of world population (Bhatia *et al*., 2019). Non-erosive reflux disease is the most common phenotype of GERD. Heartburn and regurgitation are considered classic symptoms but GERD may present with various atypical and extra-esophageal manifestations. Gastric acid plays a principal role in both the normal gastrointestinal physiology and pathophysiology of common disease processes involving the upper gastrointestinal tract (GIT) (Bode *et al*., 2010). GERD is a pathological condition that takes place when acidic gastric contents enter the esophagus, causing symptoms such as heartburn and regurgitation. Gastroesophageal reflux is the passage of gastric content into the esophagus. Resulting typical symptoms are denoted as reflux like dyspepsia (Johnson *et al*., 2017). Reflux esophagitis is the endoscopic or microscopic evidence of damage to the esophageal mucosa. Long-term intra-esophageal pH-monitoring will establish pathologic gastroesophageal reflux when acid exposure time exceeds 5% of the monitoring time. GERD is present when symptoms and/or esophagitis are caused by reflux (Ullal *et al*., 2022). Columnar lined esophagus is a better expression than Barret's esophagus. Symptoms of GERD includes - damage of esophageal mucosa, heart burn, acid regurgitation, *etc*., GERD patient suffers from complication of difficulty in swallowing (dysphgia) resulting from mechanical obstruction and peristaltic dysfunction (Gupta *et al*., 2023). In chronic condition GERD patient suffers from severe erosive esophagitis (Poddar *et.al.,* 2019). The patient feels difficulty and pain during swallowing which results in patient incompliance toward medication of tablets or capsule-especially in geriatrics and pediatric patients (Yadlapati *et al*., 2019). These symptoms of GERD patients had attracted the formulation scientists in improving the formulation methodology for such patient. A healthy esophageal sphincter functions as a valve to keep stomach contents from backing up into the esophagus (Wang *et al*., 2020). When valve function is reduced, stomach acid can enter the esophagus and cause GERD. Patients with GERD have an ineffective valve mechanism between the esophagus and stomach (lower esophageal sphincter), which otherwise prevents stomach contents from backing up into the esophagus. Due to inflammation of the esophageal mucosa, as a result patient with chronic GERD suffered from severe dysphagia

Corresponding author: Dr. Juber Akhtar
Professor, Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India
E-mail: juberakhtar@gmail.com
Tel.: +91-9807002770

and complains uncomfortable and pain during swallowing of solids (Walle *et al*., 2019). This leads to noncompliance of patients toward the treatment where they need to swallow tablets with water and hence, we need a patient friendly dosage form for minimizing the symptoms associated with GERD (Sandhu *et al*., 2018). With the discovery of novel medications in the last five decades, it is now possible to effectively control the quantity of acid produced by the stomach, thereby minimizing symptoms, preventing complications, and finally, ameliorating mortality. The proton pump inhibitors (PPI), are one of the potent inhibitors of gastric acid secretion, and commonly used medications in the world. The PPIs are widely regarded as the pillar of medical therapy for GERD, and they are very effective for curing and healing reflux esophagitis; however, a lack of satisfactory response to the conventional PPI dosage form that is tablets and capsules is often reported, especially in patients with dysphagia in GERD (Schnoll *et al*., 2020). Poor compliance seems to be one of the main causes of treatment. Proton pump inhibitors share the same core structure, but vary in terms of substituents added with the core. Addition of substitutions on the core, it is possible to modify important chemical and physical properties of the compounds due to which pantoprazole is significantly more acid-stable than omeprazole or lansoprazole (Duncan *et al*., 2019). The decision to select one PPI versus another is most likely to be based on the agent acquisition costs, formulations, food drug administration (FDA) labelled indications, and overall safety profiles (Avner *et al*., 2000). Intravenous or parenteral pantoprazole may become the preferred antisecretory agent for patients unable to take oral medications due to dysphagia (Maret-Ouda *et al*., 2020; Shin *et al*., 2013).

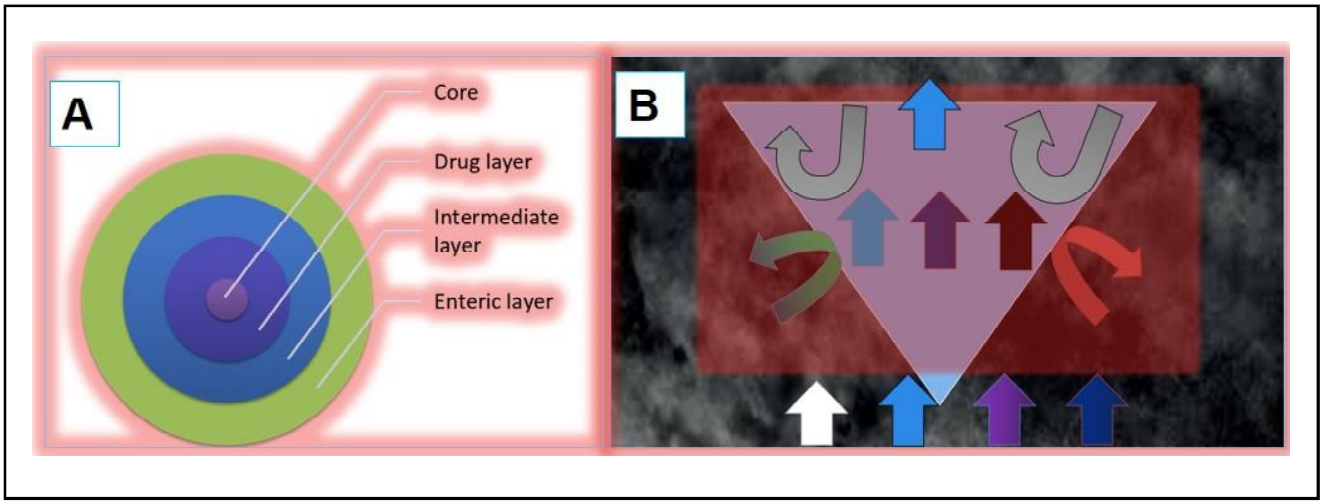


Figure 1: **A. represents enteric coated microgranules with different layers. B. The coatings as performed in fluidized bed coater and or dryer (FBD) Wurstor technology (bottom spray).**

In present work attempts were taken to develop enteric-coated microgranules for a new, patient-friendly formulation, which improves the swallowing while using multiple unit system as shown in Figure 1A. All the coating were performed in FBD employing Wurstor technology (bottom spray) as shown in Figure 1B. The effects of enteric coated microgranules of pantoprazole sodium on gastroesophageal reflux disease (GERD) were also studied in animal model.

2. Materials and Methods

2.1 Procurement of raw material

Pantoprazole sodium obtained as gift sample from Akum Drugs Haridwar, Glyceryl monostearate was purchased from Thomas Baker, Hydroxy Propyl Methyl Cellulose K4M (HPMC K4M) was purchased from Colorcon, Hydroxypropyl cellulose and Triethyl citrate were obtained from Sigma Aldrich. Magnesium stearate was of Thomas Baker. Ecopol S100 and Ecopol L100 D5 received as gift sample from Ideal Cures Limited. Microcrystalline cellulose and Mannitol were obtained from Maple Biotech. Sugar spheres were of MB Sugar and Pharmaceuticals. Talc was obtained from Lobachime. All the ingredients were of analytical grade and generally regarded as safe.

2.2 Animals

All the experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC), of the institute against approval number HIPER/IAEC/103/04/2022. SD rats (200-240 g) were procured from M/S Chakraborty Enterprise Kolkata (Regd. No: 1443/PO/Pt/s/11CPCSEA) and acclimatized under standard conditions of temperature (22 ± 2°C), relative humidity (45-65%) and 12 h light/12 h dark cycles with free access to standard pellet diet and purified water *ad libitum* in institute's animal house (Reg No: 1088/PO/Re/S/07/CPCSEA).

2.3 Enteric coated microgranules of pantoprazole

The enteric coated microgranules of pantoprazole sodium were prepared by fluidized bed coater and or dryer (FBD) Wurstor technology (bottom spray) (Pohlen *et al.,* 2018).

2.4 *In vivo* study

The SD rats were divided in to four goups (n = 6). The Group I served as normal control group, Group II, Group III and Group IV were served as diseased control group, pantoprazole sodium and enteric coated pantoprazole microgranules treated, respectively. The GERD was induced in all the groups except Group I.

GERD was induced by slightly modified method described by Gupta *et al.,* 2017; Rao *et al.,* 2008. The rats were fasted for 12 h under

anesthesia (ketamin 90 mg/kg, i.p.), the abdomen of the animal was opened by a median incision of about 2 cm; then the transitional region between the fore stomach and corpus was ligated very carefully with a 2-0 silk string and constantly the pyloric portion was ligated. A lonGITudinal cardiomyotomy (1 cm length) across the cardiac sphincter was performed to enhance reflux from the stomach into the oesophagus. Immediately the incised regions were sutured and the animal were kept in recover chamber (Medi HEAT, UK) and go back to their home cages. After 6 h, the animals were sacrificed by cervical decapitation and the chest was opened with a median incision and the tissue esophagus and stomach were removed. The tissue organs were opened along the greater curvature of the stomach, and the esophagus was dissected out by extending the dissection line along the major axis. The tissues were washed with physiological saline and were examined for GERD (Khushtar *et al*., 2009).

In each rat, the macroscopic injury of each ulcer was scored by an independent observer according to a scale ranging from 0 to 3 as follows: (0) no macroscopic changes, (1) mucosal erythema only, (2) mild mucosal edema or small erosions, (3) moderate edema or erosions 1 h prior to the induction of GERD, Group I/II, III and IV received vehicle, pantoprazole sodium (40 mg/kg) and enteric coated pantoprazole microgranules (40 mg/kg), respectively. Animals were autopsied after 2 h and esophagitis scored as above.

2.5 Statistical analysis

All the values were expressed as Mean ± SEM (n=6). The data were statistically subjected to analysis of variance (ANOVA) using PASW Statistics, Version 24.0. software (SPSS Inc., Armonk, NY, USA). Tukey's test post hoc analysis was used to determine the significant difference between means. Values were considered significant at $p< 0.05$, otherwise were considered non-significant. GraphPad Prism version 6.00 was used to create the graphs (GraphPad Software, San Diego, CA, USA).

3. Results

3.1 Optimized enteric coated microgranules of pantoprazole

An active compound suspension consisting of pantoprazole sodium, low-substituted hydroxypropyl cellulose (L-HPC) and purified water was prepared. About 40 g of drug is added in 40 ml of water and homogenized. To the above solution 10 ml talc solution 1mg/ml in water was added and finally 150 ml of L-HPC solution prepared separately in water by heating and constant stirring is added to the above solution and homogenized to form a clear solution.

An intermediate suspension consisting of hypromellose, and purified water was prepared. 7% HPMC solution was prepared in water by heating and constant stirring. Table 1 gives the composition of intermediate layer. Sugar spheres were coated consecutively by spraying the active compound suspension and the intermediate suspension in a FBD subsequently granules were dried in the same. An enteric-coating suspension consisting of methacrylic acid copolymer dispersion, ethyl acrylate-methyl methacrylate copolymer dispersion, the glyceryl monostearate emulsion, plasticizer triethyl citrate, talc, and purified water was prepared by stirring. Pantoprazole sodium-coated microgranules were coated by spraying the enteric coating suspension in the FBD. The above granules were then dried in the same.

Table 1: Formulation of enteric coated microgranules of pantoprazole sodium

Core	**Sugar sphere**	**60.0 g**
Active drug layer	Pantoprazole talc low substituted hydroxy propyl cellulose purified water	7.5%, 20%, 5%, 67.5%
	Total spray solution	400 g
	Drug layer microgranules	**150.0 g**
Intermediate layer	Hypromellose talc purified water	8%, 2%, 90%
	Weight gain after coating	153 g
Enteric layer	Ecopol S100 : Ecopol L100 D55	9:1
	Triethyl citrate	1.22%
	Glyceryl monostearate	0.37%
	Polysorbate 80	0.24%
	Talc	0.37%
	Purified water	85.58%
	Total spray solution	100 g

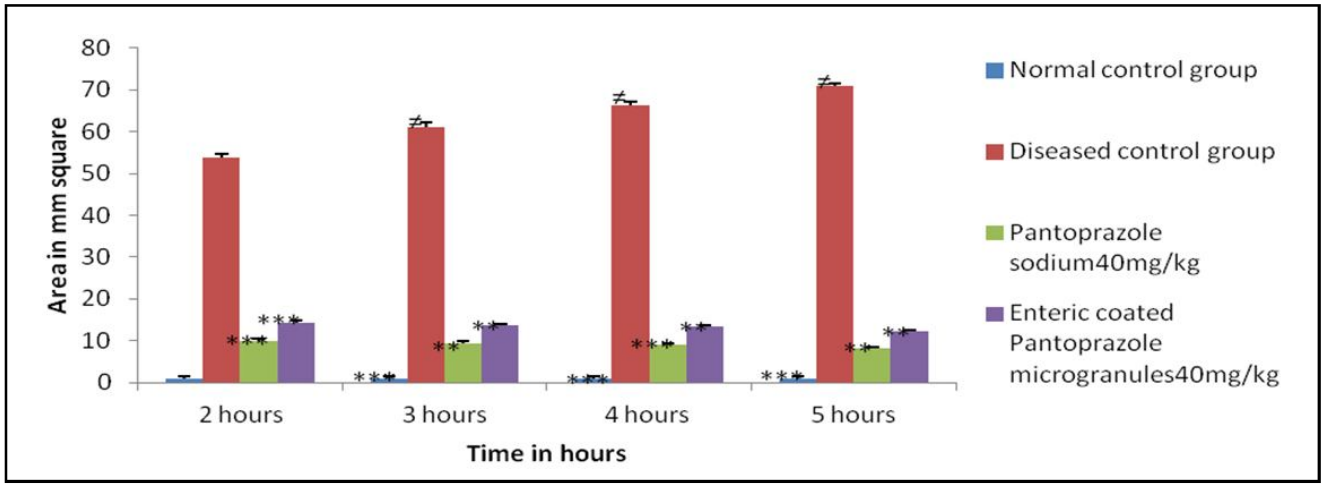
3.2 *In vivo* study

The macroscopic examination of esophagus of normal control group (Group I) not showed any lesion area and normal esophagus epithelium structure while the disease control group (Group II) showed ulcerated esophagus with dark lesions of different size and inflammation. The esophagus of rats in pretreated group (Group III) treated with pantoprazole sodium (40 mg/kg) showed mild ulcerative lesions and no inflammation with well mucous membrane while the esophagus of rats of pretreated group treated with enteric coated pantoprazole microgranules (40 mg/kg) (Group IV) showed no lesions and inflammation in mucous membrane (Figures 3, 4/ Table 2).

Table 2: Representation of comparison of lesion area in different groups of SD rats

Groups	Lesion area mm^2(2h)	Lesion area mm^2 (3h)	Lesion area mm^2 (4h)	Lesion area mm^2 (4h)
Normal control group (Group I)	1 ± 0.58	1 ± 0.58	1 ± 0.58	1 ± 0.58
Diseased control group (Group II)	53.67 ± 0.88$^{\neq\neq\neq}$	61 ± 1.15$^{\neq\neq\neq}$	66.33 ± 0.88$^{\neq\neq\neq}$	71 ± 0.58$^{\neq\neq\neq}$
Pantoprazole sodium (40 mg/kg) (Group III)	14.33 ± 0.45***	13.67 ± 0.26**	13.33 ± 0.26**	12.33 ± 0.26**
Enteric coated pantoprazole microgranules (40 mg/kg) (Group IV)	10 ± 0.45***	9.33 ± 0.51**	9 ± 0.45**	8.33 ± 0.26*

All values were expressed as mean ± SEM (n=6), ≠ p<0.001significant as compared to control group (Group I), *p<0.05, **p<0.01and ***p<0.001significant as compared to diseased control group (Group II).



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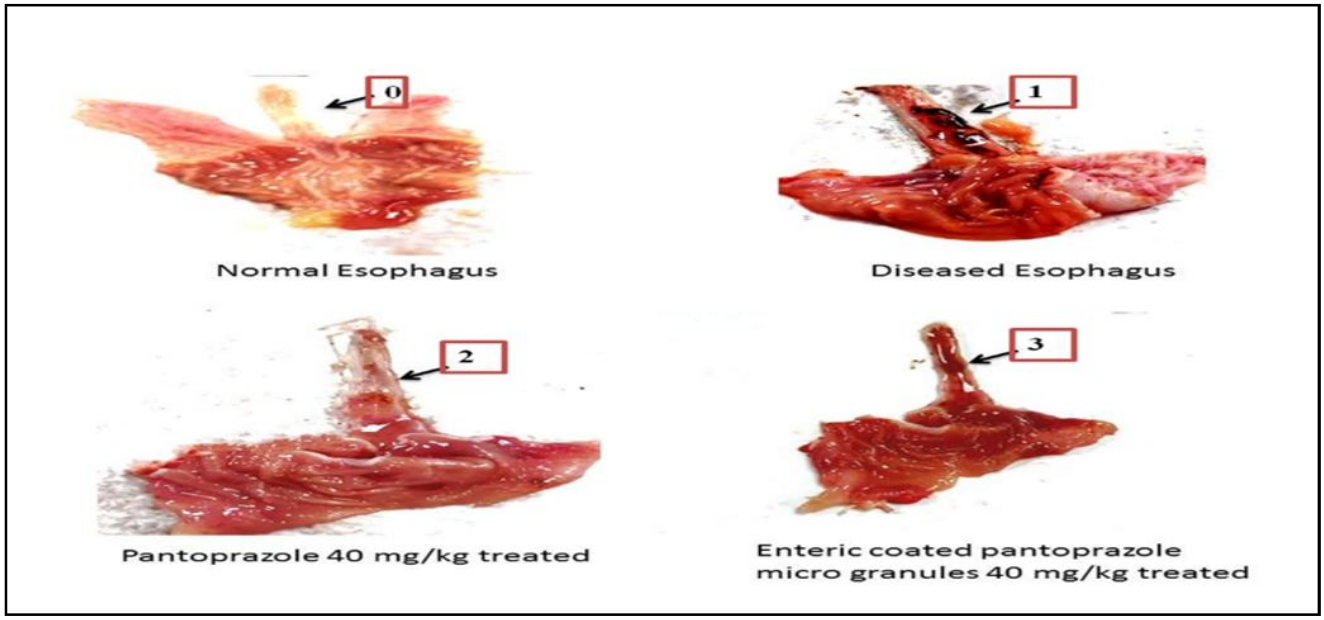

Figure 3: Macroscopic examination of SD rats' esophagus. The normal group (Group I) showed normal esophagus, scored as 0, diseased control rats (Group II) esophagus showed erosion and inflammation, scored as 1, pantoprazole (40 mg/kg) treated group (Group III) showed no erosion but mild inflammation, scored as 2, enteric coated pantoprazole microgranules (40 mg/kg) treated group (Group IV) showed no erosion no inflammation, scored as 3.

3. Discussion

The worldwide spread of gastroesophageal reflux disease (GERD) showing an increasing trend during the past decades. GERD has a major health concern today (Monteiro *et al*., 2020). The prevalence of GERD in India increases from 7.6% to 30%, being less than ten per cent in most population studies, and greater in cohort studies (Besancon *et al.,* 1993). The major factors associated with gastroesophageal reflux disease GERD include widely use of spices and non-vegetarian food (Katz *et al*., 2004). *Helicobacter pylori* bacteria have a negative relation with GERD; *H. pylori* negative patients have higher grade of symptoms of esophagitis and GERD. Among all GERD patients less than 10% of patients have erosive esophagitis in India (Stedman *et al*., 2000). The gastric mucosa is continuously exposed to bacterial infections (*H. pylori*) (Dandu *et al.,* 2022). The imbalance between aggressive forces such as acid, pepsin, and *H. pylori* (Singh *et al.,* 2022) and defensive factors such as bicarbonate secretion, prostaglandins, gastric mucus, and intrinsic resistance of mucosal cell factors causes peptic ulcers (Dashputre and Naikwade, 2011). In patients with mild and occasional symptoms of GERD, histamine H_2 receptor blockers (H2RAs) and antacids may be used, and proton pump inhibitors (PPI) are used in patients with severe symptoms (Sahara *et al.,* 2013). Prokinetics have limited role in management of GERD. Furthermore, GERD also causes an economic burden; the cost of treating diseases in patients with GERD has been assumed to be twofold more costly than comparable individuals without it (Celebi *et al*., 2016). Modified-release of PPIs has longer effective plasma concentration found in rats. This provides a better effect to block the gastric H^+-K^+-ATPase activity, which allows better intragastric pH control (Rohss *et al*., 2004). Pantoprazole is considerably extra acid-stable than omeprazole or lansoprazole. Pantoprazole remains more bioavailable than omeprazole, stable on frequent dosing, and is not exaggerated by food. Pantoprazole does not drastically influence the activity of hepatic cytochrome P450 and consequently not interacted with other co-administered drugs. Unlike other proton pump inhibitors (PPI), pantoprazole does not include multiple metabolic pathways (Gupta *et al*., 2023).

4. Conclusion

The potential effect of enteric coated pantoprazole against GERD was investigated. The enteric coated pantoprazole microgranules exhibited a potent effect on gastroesophageal reflux disease (GERD). The esophagus of rats in pretreated group (Group III) treated with pantoprazole sodium (40 mg/kg) showed mild ulcerative lesions (lesion area 12.33 ± 0.26 mm^2) and no inflammation with well mucous membrane while the esophagus of rats of pretreated group treated with enteric coated pantoprazole microgranules (Group IV) (40 mg/kg) showed mild lesions (lesion area 8.33 ± 0.26 mm^2) and no inflammation observed in mucous membrane. In macroscopic study the normal rat esophagus (Group I) showed normal esophagus texture (scored as 0), GERD positive rat (Group II) showed the development of erosion and inflammation (scored as 1). However, in pantoprazole (40 mg/kg) treated group (Group III), no erosion was seen but mild inflammation was reported (scored as 2), while in enteric coated pantoprazole microgranules treated group (Group IV), no inflammation and erosion were observed in esophagus (scored as 3). Overall, results indicated that the administration of enteric coated pantoprazole microgranules could ameliorate esophageal damage. This study may help to evaluate histology of esophagus of GERD rats.

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Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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