Caspian Journal of Environmental Sciences
Online ISSN: 1735-3866
Print ISSN: 1735-3033

Effect of Ibuprofen, Ponstan and Panadol oral suspensions on the gastrointestinal mucosal layer in mice

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ABSTRACT

Antipyretic drugs such as suspensions of mefenamic acid (ponstan), Ibuprofen and paracetamol (acetaminophen) are the most common drugs that wildly used in children to decrease the fever, pain and inflammation. From clinical observations of children using these drugs, they cause gastrointestinal complications and from this, the idea of this research was to find the effect of these drugs on the mucous membrane of the gastrointestinal tract in Swiss albino mice. In the present study, we used 30 mice classified into five groups including G_1 as control group, G_2 received 15 mg/kg/day panadol, G_3, 30 mg/kg/day ibuprofen, G_4, 5 mg/kg/day ponstan and G_5, a combination of panadol and ibuprofen in the same previously- mentioned doses for 7 days respectively. The gastric histological sections of G_2 exhibited normal mucosal; G_4 displayed mild mucosal glandular hyperplasia; while G_3 and G_5 e appeared flat mucosal surface with submucosal hyperplasia of gland mild atypical cells; and G_2 revealed mucosal glandular hyperplasia. The intestine histological sections of G_2 appeared normal intestinal villi with mild inflammatory cells infiltration; G_3 showed dispersed slight shortening of intestinal villi with mild inflammatory cells infiltration; finally, G_4 and G_5 indicated villi hyperplasia with a slight widening of villi with mild inflammatory cells infiltration. NSAIDs are available over-the-counter drugs for adult and in paediatric population and are considered as a safe medicine if used in properly dose in the short-term. The decision to pick an antipyretic should be dictated by safety, efficacy, effectiveness, duration of action and the integrity of the patient gut.

Key words: Antipyretic, Paediatric, Non-selective, Prostaglandins, Anti-inflammatory.
Article type: Research Article.

INTRODUCTION

Fever is one of the important and common symptoms in paediatric diseases (Eefje *et al*. 2015) and known as a combination of physiologic response to a disease. It occurs due to mediated by pyrogenic cytokines and characterized by increase in an essence temperature, generation of acute phase reactants and activation of immune systems (Sahib 2019). Children are more susceptible to fever, may be associated with increased morbidity, such as seizures, brain damage or death (Alexander *et al*. 2018). Physicians usually prefer to describe antipyretics, drug agents, for the feverish child to decrease the temperature and parents anxiety (Chiappini *et al*. 2012). Around the world, the most common drugs used for fever, pain and inflammation are non-steroidal anti-inflammatory (NSAIDs) agents, as Mefenamic acid (Ponstan) and Ibuprofen (Huang *et al*. 2014). They have both anti-inflammatory and analgesic properties (Struct 2016), while paracetamol (acetaminophen) is an analgesic and antipyretic medication and is not classified as a member of the non-steroidal anti-inflammatory drugs (NSAIDs; Charles *et al*. 2018). It is widely used in children because of its high effectiveness and good safety profile (Klotz 2012). Mefenamic acid (Ponstan) is a strong inhibitor of cyclooxygenase, and have an analgesic action. This drug is commonly used in patients who were suffering from arthritis, injuries, rheumatoid, osteoarthritis and dysmenorrhea (Balasubramanian & Sumanth 2010). Ibuprofen is a non-selective inhibitor of cyclooxygenase-1(COX-1) and Cyclooxygenase-2 (COX-2) (Woessner & Castells 2013). In spite of its anti-inflammatory properties, ibuprofen may be weaker than some other NSAIDs. It has a prominent antipyretic and analgesic role

Caspian Journal of Environmental Sciences, Vol. 20 No. 3 pp. 539-544 Received: Dec. 14, 2021 Revised: Feb. 23, 2022 Accepted: April 09, 2022
DOI: 10.22124/CJES.2022.5687

Publisher: University of Guilan, Iran

(Marginean *et al*. 2017). Paracetamol is absorbed in the gastrointestinal tract and reaches to a peak in plasma concentration about 30 minutes. The approximate-time that it needs to get the maximal temperature reduction is 2 hours (Singla *et al.* 2012). While the action mechanism of this drug is not completely understood, it is supposed that the acetaminophen-caused antipyretic effect occurs by central inhibition of the enzyme Cyclooxygenase (COX), although its beneficial effects, poisoning, kidney failure and hepatotoxicity are the gravest adverse effects of paracetamol, which may happen due to acute exposure (Ghanem *et al*. 2016; Bunchorntavakul & Reddy 2013). It has been reported that the combined use of paracetamol and ibuprofen reduces fever very rapidly for the first three hours after the second dose, compared to either paracetamol or ibuprofen alone. However, another study explained that the combination of these two drugs is uncertain to be more effective to improve the comfort in febrile children compared to a single antipyretic agent (monotherapy; Kanabar 2017). It is necessary to determine the reason of fever and then provide effective treatment to give the body a chance to respond against the pathogen that causes the fever, and the decision to pick an antipyretic should be dictated by safety, efficacy, effectiveness, duration of action, and cost (Kunkulol *et al*. 2013). The aim of the present study was to demonstrate the effects of frequent administration of some pyrogenic reducer on the structure of the gastrointestinal mucosa in the healthy adult mice.

MATERIALS AND METHODS

Experimental animals

Thirty (30) adult male albino mice were used in this study. The mice were brought from the animal house of Baghdad Medical College. Most mice with 18-20 g in weight were selected for the study. Experience was performed from 15th to 22st February 2020. The animals were separated into five groups. Each group consisted of six animals maintained in animal house of Science College, Mustansiriyah University, Baghdad. The animals were housed in polypropylene cages under hygienic conditions and maintained at normal room temperature (20-22 ºC). The animals were allowed consuming food and water ad libitum and led the animals adapted in this condition for 7 days until the experiment start. The groups were as the following:

Group 1: control group without any treatment.
Group 2 were given 15 mg/kg/day divided into 4 doses as 0.01 mg dose^{-1} of panadol suspension orally using a stomach cannula every 6 hours for 7 days.
Group 3 were given 30 mg/kg/day divided into 4 doses as 0.0075 mg dose^{-1} ibuprofen suspension orally using a stomach cannula every 6 hours for 7 days.
Group 4 were given 5 mg/kg/day divided into 4 doses as 0.005 mg dose^{-1} of ponstan (mefenamic acid) suspension orally using a stomach cannula every 6 hours for 7days.
Group 5 were given mix of 15 mg/kg/day divided into 4 doses as 0.01 mg dose^{-1} and 30 mg/kg/day divided into 4 doses as 0.0075 mg dose^{-1} of Panadol and ibuprofen suspension respectively via oral route every 6 hours for 7 days.

Experimental technique

The drugs used including panadol syrup 120 mg / 5 mL (GlaxoSmithKline group companies Farmaclair, Herouvile France) at 15 mg/kg/day ibuprofen syrup 100 mg / 5 mL, (Medfarma, UAE) at 30 mg/kg/day and Mefenamic acid -Ponstan- syrup 50 mg / 5 mL (Mission Vivacre Limited – India) at 5 mg/kg/day. The animals were observed in their cages for clinical symptoms daily until the end of the experimental period.

Preparation of histopathological slides

The animals were anesthetized using chloroform and then dissected. The organs such as the stomach, and small intestine were isolated into 10% saline formalin and then subjected to histological procedures and preparation of tissue slides as directed by Banchroft *et al.* (1996).

RESULTS

The study revealed different effects of paediatric antipyretic syrup that use in this study on gastric and intestine mucosal layer. The stomach histological sections of group 2 was treated with 0.01 mg/dose of panadol suspension showing look-like normal mucosal (Fig. B) compared to the control in group 1 (Fig. 1A). Group 3 treated with

0.0075 mg dose^{-1} ibuprofen suspension, exhibited flat mucosal surface with sub mucosal hyperplasia of gland mild atypical cells (Fig. 1C) compared to control that does not exhibit any change in the same layers and cells. Group 4 treated with 0.005 mg/dose of ponstan (mefenamic acid) suspension, displayed normal mucosal but with mild mucosal glandular hyperplasia (Fig. 1D). Group 5 received mix of 0.01 mg dose^{-1} panadol and 0.0075 mg dose^{-1} ibuprofen and exhibited mucosal glandular hyperplasia (Fig. 1E).

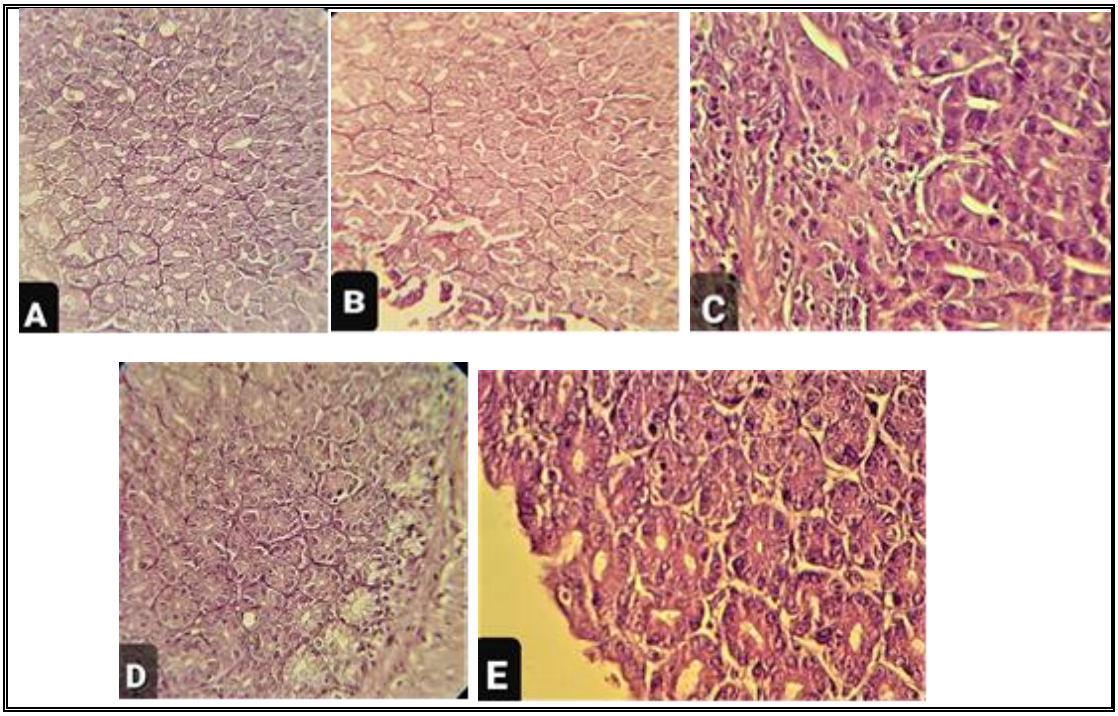

Fig. 1. Histological sections of mouse stomach tissues from non-demonstrated and demonstrated groups. **(A)** Histology of normal control mouse stomach (40 X); **(B)** showing look- like normal mucosal - histopathological changes seen in mouse treated with panadol; **(C)** Section from mouse treated with ibuprofen showing flat mucosal surface with submucosal hyperplasia of gland mild atypical cells , **(D)** section look- like normal mucosal but with mild mucosal glandular hyperplasia ,treated with ponstan; **(E)** showing mucosal glandular hyperplasia section from mouse treated with mix (panadol and ibuprofen).

The histological sections of the mouse intestine treated with all aforementioned doses as follows: Group 2 treated with panadol exhibited normal appearance of intestinal villi with mild inflammatory cells infiltration (Fig. 2 B) compared to control group (Fig. 2A), while group 3 with ibuprofen displayed normal appearance of intestinal villi with mild inflammatory cells infiltration (Fig. 2C). Group 4 with ponstan treatment, showed widening of intestinal villi with inflammatory cells infiltration inside the villi (Fig. 2D). Group 5 treated with mixed panadol and ibuprofen exhibited intestinal villi hyperplasia with slight widening of villi (Fig. 2E).

DISCUSSION

Mucus and the value of pH are a natural barrier to both diffusion and absorption of foreign entities such as drugs, and these drugs or treatments may interact or interfere with the function of the intestinal mucous. Hence, this study was to find out the role of this type of antipyretics on this layer of the GI system. Ibuprofen, ponstan and Panadol are the most commonly-used for treating the pain and fever, and they are an over-the-counter (OTC) drugs (Marhamah *et al*. 2020). As we know the first two drugs belong NSAIDs while panadol belongs to analgesic drugs, so it needs regular evaluation of these drugs. We investigated the histological changes of Panadol, Ibuprofen, ponstan and a combinations of Panadol and Ibuprofen in stomach and intestine tissues of the mice, and as we found, there was an induction of histopathological abnormalities in these tissues, and when we compared this study with other studies, the results were in agreement with Maria et al. (2018) in the sub-mucosal hyperplasia of the gastric and dispersed slight shortening (Maria *et al*. 2018), hyperplasia with a widening of intestinal villi with mild inflammatory cells infiltration in the ibuprofen, ponstan and a combinations of Panadol and Ibuprofen groups while when using panadol group we found normal mucosal layer for gastric and intestine and this results

were in line with Bernard (2004). NSAIDs are classified fundamentally into basic and acidic preparations Ito *et al*. (1992), so Bjarnason (2018), Rostom (2002) and Rao (2000) their colleagues confirmed that NSAIDs cause direct irritation of the gastric mucosa due to acidic activity which breaks the mucosa barrier and diffusion of acid into the mucosa and cause gastric ulcers (Ito *et al*. 1992 Rao *et al*. 2000 : Wallace 2008), and also the inhibition of prostaglandin activity by uses of NSAIDs causes increased gastric acid secretion and decrease the ability of the gastric mucosal defence (Ahluwalia *et al*. 2019). Ibuprofen was found recently even in a short-term use that can induce gastric erosions and ulcers (Kalra *et al*. 2009: Falavigna *et al*. 2020). The demonstration from this abovementioned result that NSAIDs induced gastric histopathological abnormalities. This was confirmed by the single use of Ibuprofen and combination use of Ibuprofen with panadol from the appearance of the same histological changes on the gastric and intestine. This finding was confirmed by Kalra *et al.* (2009) and Sostres *et al.* (2013) demonstrated that these drugs cause erosions, erythema, mucosal haemorrhage, and gastric or/and intestinal ulceration or perforation of lower GI and upper GI and events were frequent in these two places (Kalra *et al*. 2009; Sostres *et al*. 2013). Many studies need to understand the wise use of NSAIDs to prevent serious complications.

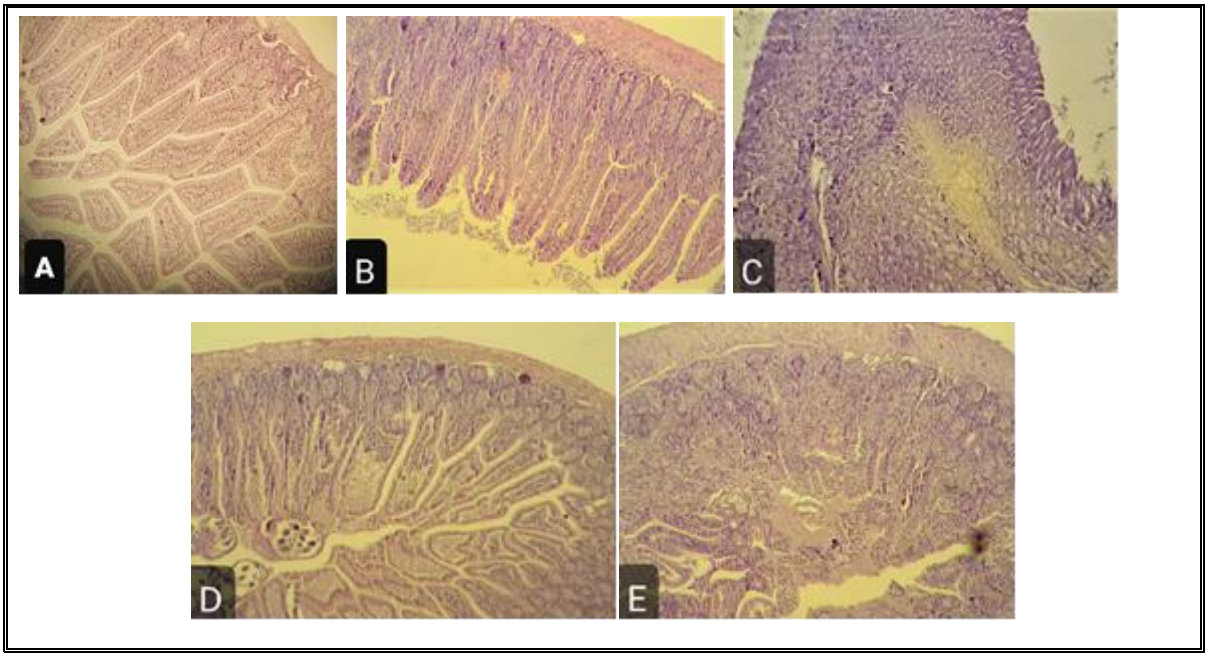

Fig. 2. Histological sections of mouse intestine tissues from treated and non-treated groups. **(A)** histology of normal control mouse intestine (X10) , **(B)** section from group treated with panadol showing look-like normal appearance of intestinal villi with mild inflammatory cells infiltration, **(C)** Section from mouse treated with ibuprofen showing dispersed slight shortening of intestinal villi with mild inflammatory cells infiltration , **(D)** section from group treated with ponstan showing widening of intestinal villi with inflammatory cells infiltration inside the villi, **(E)** section from group treated with mixed panadol and ibuprofen showing intestinal villi hyperplasia with slight widening of villi.

CONCLUSION

NSAIDs are one of the most popular OTC drugs, for both adults and children. It has a good safety profile if used with precaution, as the adverse effect are infrequent. The side effect tend to appear more in patients high dose of NSAIDs for long duration. Specific precaution should be taken for the paediatric age group. Choosing Antipyretics should depend on the safety, efficacy, effectiveness, and duration of action. Also it is better to avoid combination of NSAIDs, as this increase the risk of complication.

REFERENCES

Ahluwalia, A, Jones, MK, N & Tarnawski, AS 2019, Mitochondria in gastric epithelial cells are the key targets for NSAIDs-induced injury and NGF cyto-protection. *Journal of Cellular Biochemistry*, 120: 11651-11659.

Alexander, KCL, Kam, LH & Theresa, NHL 2018, Febrile seizures: An overview. *Drugs Context*, 7: 212536. DOI: 10.7573/dic.212536.

Balasubramanian, S & Sumanth, A 2010, Mefenamic acid – Role as Antipyretic. *Indian paediatrics*. May, 17, Vol. 47: 453.

Bancroft, JD, Stevens, A, & Turner, DR 1996, Theory and practice of histological techniques. 4th Edition, Churchill Livingstone, London, Toronto.

Bernard, B 2004, Gastrointestinal safety of paracetamol: Is there any cause for concern? *Journal of Expert Opinion on Drug Safety*, 3: 269-272.

Bjarnason, I, Scarpignato, C, Erik, H, Michael, O, Kim, DR & Angel, L 2018, Inflammatory drugs, *Gastroenterology*, 154: 500-514.

Bunchorntavakul, C & Reddy, KR 2013, Acetaminophen-related hepatotoxicity. *Clinical Liver Disease*, 7: 587-607.

Charles, NF, Estella TF, Kechia, F, Bathelemy, N & Bonaventure, NO 2018, Overview of non-steroidal anti-inflammatory drugs (NSAIDs) in resource limited countries. *MOJ Toxicology*, 4: 5-13. DOI:10.15406/mojt.2018.04.00081.

Chiappini, E, Parretti, A & Becherucci, P *et al.* 2012, Parental and medical knowledge and management of fever in Italian pre-school children. *BMC Paediatric*. 12: 97, [http://dx.doi.org/10.1186/1471-2431-12-97].

Eefje, GP, de, B, Julie, MML, Dagmar, ASH, Nicole, L, Yvonne, GH, Geert-Jan, D & Jochen, WLC 2015, Work load and management of childhood fever at general practice out-of-hours care: an observational cohort study, BMJ Open. 5(5): e007365. DOI: 10.1136/bmjopen-2014-007365.

Falavigna, M, Stein, PC, Flaten, GE & Di Cagno, MP 2020, Impact of mucin on drug diffusion: development of a straightforward in vitro method for the determination of drug diffusivity in the presence of mucin pharmaceutics, 12(2), 168.

Ghanem, CI, Perez, MJ, Manautou, JE & Mottino, AD 2016, Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity. *Pharmacological Research*, 109: 119-131.

Huang, C, Lu, B, Yi-Hong, F, Zhang, L, Jiang N, Zhang, S & Li- Na, M 2014, Muscovite is protective against non-steroidal anti-inflammatory drug- induced small bowel injury. *World Journal of Gastroenterology*, 9; 21; 20(31).

Ito, Y, Yukinari, T, Yanagawa, A & Nakagawa, T 1992, NSAIDs (non- steroidal anti-inflammatory drugs) for the treatment of rheumatoid arthritis. *Nihon Rinsho Japanese Journal of Clinical Medicine*, 50: 509-514.

Kalra, BS, Chaturvedi, S, Tayal, V & Gupta, U 2009, Evaluation of gastric tolerability, anti-nociceptive and anti-inflammatory activity of combination NSAIDs in rats. *Indian Journal of Dental Research*, 20: 418.

Kanabar, DJ 2017, A clinical and safety review of paracetamol and ibuprofen in children, *Inflammopharmacology*. 25: 1-9.

Klotz, U. 2012, Paracetamol (acetaminophen)-a popular and widely used nonopioid analgesic, *Arzneimittel-Forschung*, 62: 355-359, DOI: 10.1055/s 0032-1321785.

Kunkulol, RR, Sonawane, A, Ashok & KCh 2013, Evaluation of efficacy and tolerability of acetaminophen (paracetamol) and mefenamic acid as antipyretic in patients with febrile illness: A comparative study. *International Journal of Medical Research & Health Sciences*, 2: 23-29.

Marginean, CO, Meliț, LE & Chinceșan, M 2017, Communication skills in paediatrics - the relationship between paediatrician and child. Medicine (Baltimore) 96: e8399.

Marhamah, F, Singgih, Huldani, Harun, A, Bayu, IS, Austin, BC, Aminuddin, PP, Sri R & Andika, PP 2020, A review of nonsteroidal anti- inflammatory drugs (NSAIDs) medications in dentistry: Uses and side effects. *Systematic Reviews in Pharmacy*, 11: 293-298.

Maria, OM, Lorena, EM, Simona, M & Vladuț, S 2018, Ibuprofen, a potential cause of acute haemorrhagic gastritis in children - A case report. *The Journal of Critical Care Medicine (Targu Mures)*. 4: 143-146, DOI: 10.2478/jccm-2018-0022.

Rao, CV, Sairam, K & Goel, RK. 2000, Experimental evaluation of *Bocopa monniera* on rat gastric ulceration and secretion. *Indian Journal of Physiology and Pharmacology*, 44: 435441.

Rostom, A, Dube, C, Wells, GA, Tugwell, P, Welch, V, Jolicoeur, E & Lan A 2002, Prevention of NSAID-induced gastroduodenal ulcers. Cochrane database of systematic reviews. 4 DOI: 10.1002/14651858.CD002296.

Sahib, AEl 2019, Pathogenesis of fever. *Clinical Manual of Fever in Children*, 2: 53-68, DOI: 10.1007/978-3-319-92336-9_3.

Singla, NK, Parulan, C & Samson, R *et al*. 2012, Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. *Pain Practice*, 12: 523-532, DOI:10.1111/j.1533-2500.2012.00556.x.

Sostres, C, Gargallo, CJ & Lanas, A 2013, Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Research & Therapy*, 15 Suppl. 3 (Suppl. 3), S3. https://doi.org/10.1186/ar4175.

Struct, BJ 2016, The structure of ibuprofen bound to cyclooxygenase-2, *Journal of Structural Biology*, 189: 62-66, DOI: 10.1016/ j.jsb.2014.11.005.

Wallace, JL 2008, Prostaglandins, NSAIDs, and gastric mucosal protection: Why doesn't the stomach digest itself? *Physiological Reviews*, 88: 1547-1565.

Woessner, KM & Castells, M 2013, NSAID single–drug–induced reactions. *Immunology and Allergy Clinics of North America*, 33: 237-249.

Bibliographic information of this paper for citing:

Qasim Alkafajy, S,A 2022 Effect of Ibuprofen, Ponstan and Panadol oral suspensions on the gastrointestinal mucosal layer in mice. Caspian Journal of Environmental Sciences, 20: 539-544.