WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 6, 2275-2290. Research Article ISSN 2277– 7105

EFFECT OF CERTAIN POLYMERS ON THE ULCEROGENIC ACTIVITY OF A NON-STEROIDAL ANTI-INFLAMMATORY DRUG

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Article Received on
14 April 2015,

Revised on 08 May 2015,
Accepted on 29 May 2015

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ABSTRACT

Diclofenac sodium (DS) is a potent non-steroidal drug with potent analgesic and anti-inflammatory activity. DS is well known to cause gastroduodenal mucosal lesions as an adverse effect. Recently, the serious problem of NSAID-induced small intestinal damage has become a topic of great interest to gastroenterologists. These attributes make diclofenac a good candidate for controlled release dosage form, so as to ensure slow release of the drug in the stomach. The present study reports on the formulation of diclofenac loaded Eudragit RS100, Eudragit RL100, Ethyl cellulose sodium alginate as well as HPMC as a controlled release drug delivery system. Solid dispersion and microencapsulation by ionotropic gelation technique were the techniques of choice in order to coat the drug so as to improve bioavailability and stability and also target a drug at specific sites. The ratio of (1:3) drug to polymer from all polymers used from solid dispersions systems and the best ratio from microbeads were selected to conduct further *in vivo* evaluation, since it was the best ratio which achieved significant reduction in the release of diclofenac at acidic pH of the stomach and maximal release at alkaline pH of the intestine. The obtained *In vivo* results indicate that microencapsulation technique was able to protect the stomach from ulcerogenic effect of diclofenac compared to solid dispersion technique.

KEYWORDS: Diclofenac sodium, Solid dispersion, microbeads, ulcerogenic effect of diclofenac, controlled release system.

1- INTRODUCTION

For a long time, non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, 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 inflamed sites. But PG also has important roles in maintaining homeostasis of gastrointestinal mucosa. Thus, 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 effect of gastrointestinal mucosal injury has become a clinical problem.[2]

NSAIDs affect the entire gastrointestinal system and cause various abdominal symptoms such as epigastric pain, abdominal pain, constipation, and abdominal distension. In some cases, ulceration can occur in the gastrointestinal region without symptoms due to the analgesic effect of NSAIDs. In the small intestine, typical symptoms include a large amount of blood in the stool due to ulceration, anemia of unknown etiology, and symptoms of obstruction due to diaphragm-like stricture. Clinical presentation of diaphragm disease is nonspecific and may include obstructive symptoms, gastrointestinal blood loss, or abdominal pain.[3-5] It is necessary to pay careful attention to these findings and symptoms in users of aspirin and other NSAIDs. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivery a therapeutic substance to the target site in a sustained controlled release fashion. Considerable evidences exist in the literature to demonstrate the effect of formulation on the efficacy of orally administered pharmaceuticals.[6-8]

Acrylic resin and celluloses have been used to encapsulate drug particles and to obtain solid dispersions with different physicochemical properties and to alleviate certain side effects of the parent drug.[9-13]

Sodium alginate is soluble in water and forms a reticulated structure which is cross-linked with divalent calcium chloride to form insoluble meshwork. Alginate's unique property of forming water insoluble calcium alginate gel through ionotropic gelation with calcium ions is

a simple, mild and eco-friendly condition to encapsulate drugs. Another important property of alginate beads is their re-swelling ability. This property is sensitive to the environmental pH 6. Alginate has a property of coating the drug core and also acts as a release rate retardant.[14] The aim of this work in this study was to investigate how gastric lesions induced in rats by diclofenac were influenced by the pharmaceutical properties of the drug. Both solid dispersion preparations and microcapsules having different pharmaceutical properties and pure drug were orally administered to fasten rats and the relationship between pharmaceutical properties of each preparation and the induction of gastric lesions were clarified.

2- MATERIALS AND METHODS

2.1. Materials

Diclofenac sodium (Sigma- Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Amriya pharmaceuticals industries, Alexandria, Egypt. Eudragit RL100 and Eudragit RS 100 were purchased from RÖhm Pharma GMBH, Darmstadt (Germany), Ethyl cellulose was obtained from Sigma- Aldrich Chemi (Germany). Hydroxypropylmethylcellulose (HPMC) and sodium alginate were purchased from RÖhm Pharma GMBH, Darmstadt (Germany). All other reagents were analytical or pharmaceutical grade and used as received.

2.2. Preparation of solid dispersion

Three types of solid dispersion of diclofenac with Eudragit RS100, Eudragit RL100 and Ethyl cellulose (in a ratios of 1:3) drug to polymer were prepared .The method was achieved by dissolving 1500 mg of the polymer in a mixture of ethanol: dichloro methane in a ratio of (1:1) in a glass vessel at 40^{o} C using Vortex Mixer (Maxi mix 11, Thermolyne Corporation, U.S.A.). The mixture was stirred at 400 rpm in a water bath (KOWELL N4, Germany) over 20 min. The mixture of ethanol: dichloro methane in a ratio of (1:1) was used as a solvent for the used polymers. 500 mg of drug was gradually added to the above mixture with stirring until completely dissolved. The rotation speed of the magnetic stirrer was continued until the solvent mixture was removed by evaporation. The dry film obtained was pulverized and passed through No 450µm sieve in order to obtain a homogenous particle size.[15-17] The obtained product was kept in a desiccator over silica gel under reduced pressure until used.

2.3. Preparation of microbeads

Microbeads of diclofenac sodium were prepared by ionotropic gelation technique. In this present work four sets of microbeads were prepared by using sodium alginate alone and combination with coating polymers like HPMC and calcium chloride used as counter ion.

The microbeads were prepared in an environment free from organic solvents by dropping a mixture of colloidal copolymer dispersion, the dispersed drug diclofenac sodium, formed mucilage of sodium alginate in calcium chloride solution, which acted as a counter ion. The droplets instantaneously formed gelled spherical beads due to cross-linking of calcium ion with the sodium ion which remain ionized in the solution.[18]

Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for the microencapsulation of diclofenac sodium core material. Preliminary work on the preparation of microbeads revealed that stirring speed and curing time greatly affected the size of microbeads[19] Smaller particles can be prepared by adjusting stirring rate to 500rpm and curing time for 2h and also depending upon the height of the syringe from the level of counter ion solution, compressed force on the plunger of the syringe. The gelled particles were cured to get sufficiently hardened beads, filtered, washed and dried. The colloidal polymer particles fused into the polymer matrix during drying with the drug being dispersed in the latex.

2.3.1. Preparation of sodium alginate microbeads

Microbeads were prepared. A solution of sodium alginate was prepared in 100ml of deionized water. In 50ml of sodium alginate solution, weighed quantity of diclofenac sodium was dispersed uniformly. Bubble free dispersion was dropped through a syringe with a needle into 100ml aqueous calcium chloride solution and stirred at 500rpm. After stirring for 30minutes, the gelled beads were separated by filtration, washed with distilled water and finely dried at 70^{o}C for 6h in an oven.[20, 21]

2.3.2. Preparation of Alginate-HPMC microbeads

Microbeads were prepared using sodium alginate and HPMC as coating polymers. To 50ml of deionized water, HPMC was added and stirred with an electric stirrer to form mucilage. Sodium alginate was added to form uniform dispersion. Weighed quantity of diclofenac sodium was added and homogenized for 5 min. The resulting dispersion was dropped through a syringe with a needle into 100ml of 5%w/v aqueous calcium chloride solution and stirred at 500rpm. After stirring for 30min the formed beads were separated by filtration, washed with distilled water, dried at 70^{o}C for 6h in an oven.[22]

2.4. *In-vivo* ulcerogenicity studies

2.4.1. Experimental animals

Male Wister rats, weighing 180-200gm, were obtained from National researches center (Cairo, Egypt).

Rats were maintained at 22±1^{o}C on a 12h light-dark cycle allowed rat chow and water ad libitum. Five groups of rats (n=6 animals per groups) were used. 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[23] but water was allowed ad libitum. The absence of ulcers in some of the treated groups has revealed that the pre-fasting conditions alone doesn't induce ulcer. Table (1) showed the experimental design and animal groups.

Table (1): Experimental design and animal groups

Group Number		Treatment
I	(Control group)	Rats were orally administered (p.o.) 1ml distilled water
II	Diclofenac (5mg/kg)	Rats were (p.o.) 1ml of diclofenac solution
III	Diclofenac- Eudragit RS 100 solid dispersion	Rats were (p.o.) 1ml of diclofenac-Eudragit RS 100 solid dispersion
IV	Diclofenac-Eudragit RL 100 solid dispersion	Rats were (p.o.) 1ml of diclofenac- Eudragit RL 100 solid dispersion
V	Diclofenac-Ethyl cellulose solid dispersion	Rats were (p.o.) 1ml of diclofenac-Ethyl cellulose solid dispersion
V1	Diclofenac-sodium alginate microbeads	Rats were (p.o.) 1ml of diclofenac-sodium alginate microbeads
VII	Diclofenac-alginate-HPMC microbeads	Rats were (p.o.) 1ml of diclofenac-alginate-HPMC microbeads

As described in the studies[24-26], on the morning of the experiments each fasted rat was orally administered 1 ml suspension of the assigned drug by oral gavage in a dose equivalent to 5 mg per kg of ketorolac or different ketorolac microcapsules systems. Magnetic stirring was utilized to obtain a well-dispersed of each drug and microcapsules suspension. Six hours later[27], each animal was removed, anaesthetized with ether, and the abdomen was opened. Each stomach was excised, dissected along the greater curvature and contents were empties by gently rinsing with isotonic saline solution. Each stomach was pinned out on a flat surface with the mucosal surface uppermost.

2.4.2. 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[27] 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 and 4.Ulcers of 0.5 mm diameter were given a score of 1 whereas ulcers of diameters 1 and 2mm were given scores of 2 and 4, 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 score of ulcers. Six determinations were made for each drug suspension administered. The average ulcer index is presented as the mean (n=6) ± standard error.

2.4.3. Histopathological examination of stomach sections

For histological 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% salaine 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 it.

2.5. 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.

3- RESULTS

3.1. Effect of diclofenac, its solid dispersion systems as well as its microcapsules on ulcer incidence, number of ulcers per rat and cumulative ulcer length per rat

A summary of gastric ulcer data for this experiment is shown in Table 2. Only gastric glandular ulcers were observed.

Rats of Group I (control group) which administered distilled water shows zero ulcer incidence as, no one develop ulcer from the total rats of this group (all stomachs are of normal type).

For Group II, in which six rats administered 10mg/kg of diclofenac[28], all the rats show ulcer in their stomachs with ulcer incidence of 100%, an average ulcers number per rat of 10 and an average cumulative ulcer length per rat of 38.54mm.

For Group III, six rats administered diclofenac solid dispersion of diclofenac-Eudragit RS100, only two rats show ulcer with ulcer incidence of 33.3%, an average ulcers number per rat of 0.42mm and an average cumulative ulcer length per rat of 0.92mm.

For Group IV, in which six rats administered diclofenac solid dispersion of diclofenac-Eudragit RL 100, only two rats show ulcer with ulcer incidence of 33.3%, an average ulcers number per rat of 0.65mm and an average cumulative ulcer length per rat of 1.25mm.

For Group V, in which six rats administered diclofenac solid dispersion of diclofenac-Ethyl cellulose, only three rat shows ulcer with ulcer incidence of 50, an average ulcers number per rat of 0.94mm and an average cumulative ulcer length per rat of 1.84mm.

The obtained results indicated that diclofenac solid dispersion system significantly reduced ulcer incidence, number of ulcers per rat and cumulative ulcer length per rat ($p < 0.05$) as compared with the data of diclofenac group of the same dose.

For Group VI, six rats administered diclofenac microbeads of diclofenac-sodium alginate, only two rat shows ulcer with ulcer incidence of 33.3, an average ulcers number per rat of 0.34mm and an average cumulative ulcer length per rat of 0.61 mm.

For Group VII, six rats administered diclofenac microbeads of diclofenac-sodium alginate-HPMC, only one rat shows ulcer with ulcer incidence of 16.66, an average ulcers number per rat of 0.24mm and an average cumulative ulcer length per rat of 0.52 mm.

The obtained results indicated that, encapsulating of drug in a carrier and slow diffusion of the drug into the mucosal media could alleviate the problem of gastric ulceration.

Microencapsulation of diclofenac using sodium alginate and HPMC significantly reduced gastric irritations and gastric ulcers compared to the free drug ($p<0.05$).

Table (2): Effect of different formula of diclofenac, its solid dispersion and its microbeads on ulcer incidence, number of ulcers per rat and cumulative ulcer length per rat

Group number	Ulcer incidence	Number of ulcers per rat	Cumulative ulcer length per rat (mm)
Group I	0.0% (0/6)	0.0±0.0	0.0±0.0
Group II	100% (6/6)	12.14±0.21	38.19±0.54
Group III	33.3% (2/6)	0.42±0.37	0.92±0.86
Group IV	33.3% (2/6)	0.65±0.90	1.25±0.34
Group V	50.0% (3/6)	0.94±0.18	1.84±0.22
Group V1	33.3% (2/6)	0.34±0.67	0.61±1.23
Group VII	16.6% (1/6)	0.24±1.08	0.52±0.78

- Rats were treated as previously described in the experimental design.
- All data for number of ulcers per rat is presented as Mean ± S.E. (n=6).

3.1. Effect of diclofenac its solid dispersion systems as well as its micbeads on ulcer index

Based on the severity of mucosal damage, each specimen was assigned a score. The scores were averaged and the mean score tabulated as the ulcer index for the drug suspension administered. Six determinations were made for each suspension (on all six rats from each individual treatment group).[29] Ulcer index of all animal groups is presented in Table 3. From the table, it is evidence that, Group I (control group) of zero ulcer incidence shows ulcer index of zero. Group II (diclofenac 10mg/kg) shows ulcer index of 8.31. Group III (diclofenac solid dispersion of diclofenac -Eudragit RS100) shows ulcer index of 0.42. Group IV (diclofenac solid dispersion of diclofenac -Eudragit RL100) shows ulcer index of 0.71.Group V (diclofenac solid dispersion of diclofenac -Ethyl cellulose shows ulcer index of 0.95.

The obtained results indicated that diclofenac solid dispersion system significantly reduced ulcer index ($p<0.05$) as compared with the data of diclofenac group of the same dose.

Group VI (diclofenac microbeads of diclofenac-sodium alginate) shows ulcer index of 0.34. Group VI (diclofenac microbeads of diclofenac-sodium alginate-HPMC) shows ulcer index of 0.25.

The obtained results indicated that, encapsulating of drug in a carrier and slow diffusion of the drug into the mucosal media could alleviate the problem of gastric ulceration.

Microencapsulation of diclofenac significantly reduced gastric irritations and gastric ulcers compared to the free drug ($p<0.05$).

Table (3): Effect of diclofenac, its solid dispersion systems as well as its microbeads on ulcer index

Treatment	Ulcer Index
Group I (Control group)	0.0
Group II Diclofenac (10mg/kg)	8.31±0.45
Group III diclofenac-Eudragit RS100 solid dispersion	0.42±0.16
Group IV diclofenac-Eudragit RL100 solid dispersion	0.71±0.89
Group V diclofenac-Ethyl cellulose solid dispersion	0.95±0.45
Group V1 diclofenac- sodium alginate microbeads	0.34± 0.75
Group VII diclofenac-sodium alginate-HPMC microbeads	0.25±1.04

3.2. Macroscopic observation

Macroscopic examination of rat stomachs of the control group administered distilled water and rat stomachs which administered ketorolac, their solid dispersion systems and there microcapsules were presented in Figures(1).

Gross study of gastric lumina of the control group showed completely an apparent normal gastric mucosa regarding a normal rauga and mucous covering layer (Fig.1-a).

A rat stomach which administered a dose of (10mg/kg) of diclofenac, showed pin point hemorrhagic area as well as a wide spread hemorrhaging as indicated by the red spots which are blood clots (Fig.1-b).

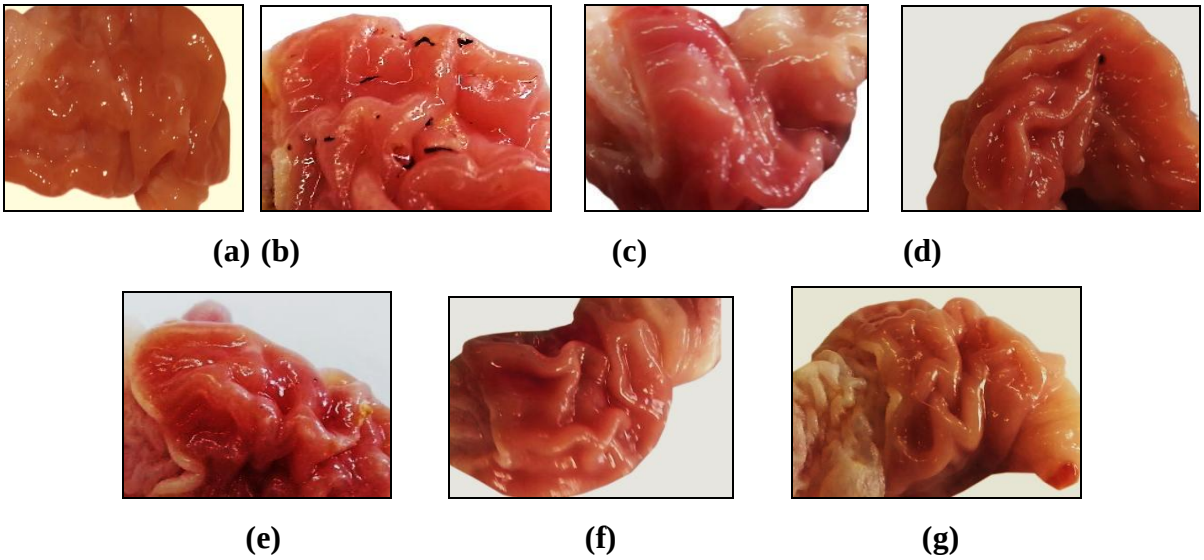
A rat stomach which administered diclofenac -Eudragit RS100 solid dispersion formula, showed a normal gastric mucosa with a small area of congestion covered by a thick layer of mucosa (Fig.1-c).

A rat stomach which administered diclofenac -Eudragit RL100 solid dispersion formula, showed a large area of congestion covered by a thick layer of mucosa (Fig.1-d).

A rat stomach which administered diclofenac-Ethyl cellulose solid dispersion formula, showed a wide spread congestion with a small hemorrhagic area covered by a thick layer of mucosa (Fig.1-e).

A rat stomach which administered diclofenac- sodium alginate, showed a normal gastric mucosa with evoked a focal area of congestion covered by a thick layer of mucus (Fig.1-f).

A rat stomach which administered diclofenac- sodium alginate-HPMC microbeads formula showed an apparently normal gastric mucosa with a little pin pointed hemorrhagic area covered with mucous (Fig.1-g).



(a) (b) (c) (d)

(e) (f) (g)

Figure (1): Representative image showing morphological changes in rat gastric tissues after administration of diclofenac, its solid dispersions as well as its microbeads with different polymers

3.4. Histological examination

Effect of diclofenac, its solid dispersion and its microbeads formula on stomach tissue histopathology is presented in Figures (2).

The histopathological pattern of the mucosal specimens was studied by examining the histology of the treated and control samples.

Histopathological examination of Hx & E stained stomach sections of distilled water administered control rats (n=6), revealed that all the six animals showed completely normal gastric mucosa with excess mucous layer (Fig.2-a).

In diclofenac (10mg/kg) administered rats (n=6), histopathological examination revealed that all the six animals showed pronounced necrotic gastric mucosa with sever dilated congested blood vessels in the lamina properia with severe edema infiltrated by inflammatory cells

(neutrophil infiltration), also superficial mucosal layer showed marked congestion, necrosis (Fig.2- b).

In diclofenac- Eudragit RS100 solid dispersion administered rats (n=6), histopathological examination revealed that stomach tissue of animals showed mild congestion in the lamina properia with minimal widen gastric crypts and excess intercellular mucous secretions (Fig. 2-c).

In diclofenac- Eudragit RL100 solid dispersion administered rats (n=6), histopathological examination revealed that stomach tissue of animals showed superficial focal ulceration with surrounding swallowed degenerated superficial mucosal covering and excess covering mucous layer by inflammatory cells (Fig. 2-d). In diclofenac- Ethyl cellulose solid dispersion administered rats (n=6), histopathological examination revealed that stomach tissue of animals showed mild necrotic gastric mucosa with excess covering mucosal layer with cellular debris and inflammatory infiltration (Fig. 2-e). In diclofenac-sodium alginate microbeads administered rats (n=6), histopathological examination revealed that stomach tissue of animals showed superficial degenerated (swollen cells) infiltrated with inflammatory cells (Fig. 2-f). In diclofenac-sodium alginate-HPMC microbeads administered rats (n=6), histopathological examination revealed that stomach tissue of animals showed superficial swollen (edematous) mucosa covered with apparent thick mucosal layer (Fig. 2-g).

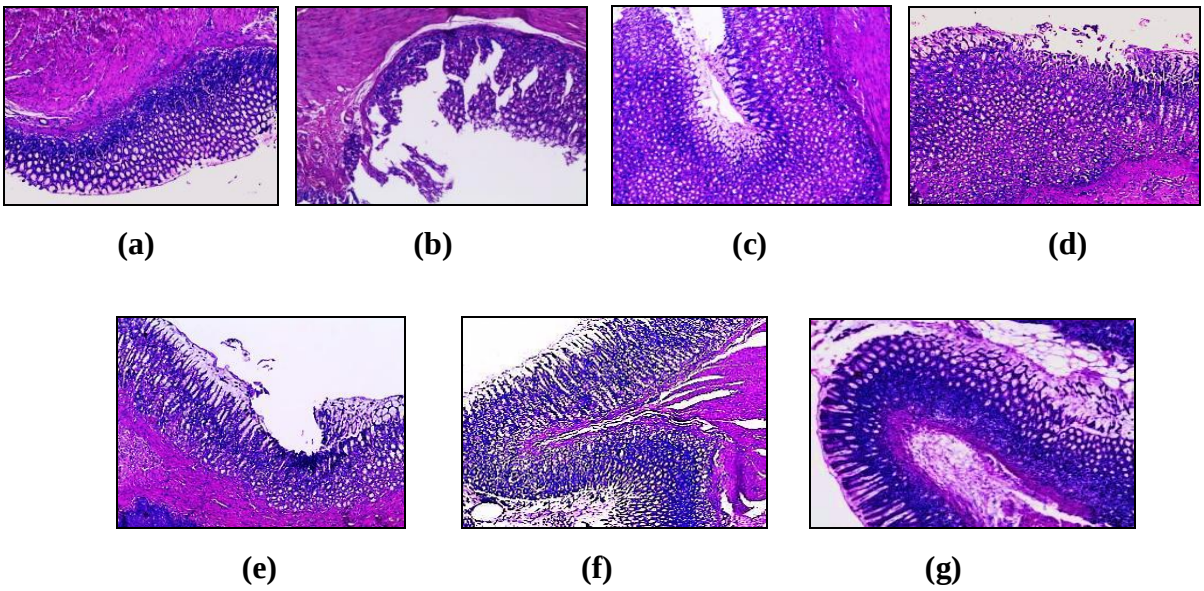


Figure (2): Representative image showing histological observations in rat gastric tissues after administration of diclofenac, its solid dispersions as well as its microbeads with different polymers

4- DISCUSSION

From the obtained results it is clear that, using diclofenac in a dose of (10mg/kg) produces the largest gastric damage. The ulcer index, the number of ulcer per rat, cumulative ulcer length per rat and ulcer incidence were larger compared with other groups either solid dispersion or microbeads ($p< 0.05$).

After administration of a single dose of diclofenac -Eudragit RS 100 solid dispersion formula, significant reduction of 66.7% in ulcerogenic activity as compared to free drug of the same dose in regard to the ulcer index of both groups occurred.

After administration of a single dose of diclofenac -Eudragit RL 100 solid dispersion formula, significant reduction of 66.7% in ulcerogenic activity as compared to free drug of the same dose in regard to the ulcer index of both groups occurred.

After administration of a single dose of diclofenac -Ethyl cellulose solid dispersion formula, significant reduction of 50% in ulcerogenic activity as compared to free drug of the same dose in regard to the ulcer index of both groups occurred.

In case of administration of a single dose of diclofenac-sodium alginate microbeads formula, significant reduction of 66.7% in ulcerogenic activity as compared to free drug of the same dose in regard to the ulcer index of both groups occurred.

In case of administration of a single dose of diclofenac-sodium alginate-HPMC microbeads formula, significant reduction of 83.34% in ulcerogenic activity as compared to free drug of the same dose in regard to the ulcer index of both groups occurred.

The integrity of the gastric mucosa depends on the balance between aggressive (HCl, pepsine) and protective factors (mucus and HCO3-secretion, prostaglandins, mucosal blood flow, nitric oxide).[30].

The treatment is effective depends not only on the blockade of acid secretion, but also on the increased production of factors responsible for protecting the gastric mucosa, thus avoiding damage to the epithelium.[31]

Inhibition of prostaglandin synthesis is well recognized as the central mechanism by which gastrointestinal injury occurs.[32]

This is a result of inhibition of cyclooxygenase enzyme which converts unsaturated fatty acids (which are released during cell injury) such as arachidonic acid to prostaglandins. In the stomach, prostaglandin synthesis is protective as a result of enhanced mucosal blood flow and stimulation of mucous and bicarbonate secretion.[33]

In contrast, in arthritis, prostaglandins mediate pain and some components of inflammation. Recognition of two isoforms of cyclooxygenase, with COX1-predominating in the stomach and an inducible COX-2 expressed at sites of inflammation offer the prospect of separating the beneficial effects of inhibiting prostaglandin synthesis in joints from the harmful effects of inhibiting it in the stomach.[34]

The primary objective of the present investigation was to determine whether the enteric-polymers provide protection against diclofenac -induced damage to gastric mucosa. Results showed that the enteric-polymers used in this study are capable of providing protection to the gastric mucosa against ketorolac -induced gastric injury. In most of our experiments, the diclofenac -induced gastric ulceration was maximally protected by coating with enteric-polymers at the dose of 10mg/kg (fed orally).

The obtained results have been confirmed by the macroscopic and microscopic observations of the gastric mucosa which indicate gastric tissue damage following ketorolac treatment. This mucosal injury was found to be protected when the rats were pretreated with different types of formula of different types of enteric polymers. Maximum protection was observed in case of diclofenac-sodium alginate-HPMC microbeads formula (fed orally).

The histological studies showed that, this is evident from the macroscopic as well as microscopic studies showed a complete protection of the tissue morphology with no ulcers was observed, indicating again the effectiveness of this agent against diclofenac -induced gastric ulceration in rats.

5- CONCLUSION

The obtained results of solid dispersion systems indicated that solid dispersion systems are able to protect the drug in a good manner to some extent. Encapsulating of drug in a carrier and slow diffusion of the drug into the mucosal media could alleviate the problem of gastric ulceration. Microencapsulation of diclofenac using sodium alginate as well as microbeads significantly reduced gastric irritations and gastric ulcers compared to the free drug.

From the obtained results of microbeads, it is clear that the microencapsulation technique is better than solid dispersion technique in coating efficiency as well as in drug release. Microencapsulation technique has a great role in reducing the ulcerogenic as well as the other gastro-toxic side effects of diclofenac. It is clear that the major contribution of the local ulcerogenic effects of diclofenac can be appreciated from the decreased incidence and magnitude of ulcers following the use of enteric coated formulations. It is possible to overcome the problem of gastric damage during the use of diclofenac, by avoiding the exposure of the drug to the ulcer-prone area of the GI tract.

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