RESEARCH ARTICLE

Evaluation of Immediate Release Tri-Layer Tablets for Analgesic and Antiulcer Properties in Experimental Animals

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ABSTRACT

Using animals as a test subject, we aimed to determine whether tri-layer tablets filled with ibuprofen and ranitidine had any effect on pain or ulcers. The effectiveness against ulcers caused by acetic acid and cold stress was tested. Six rats made up each of the four groups that were randomly assigned. As a control, I was given a solvent and placed in the group. The second group served as the control, while groups III and IV were used to evaluate 100 mg and 200 mg tri-layer tablets, respectively. The oral gavage method was used to administer all medications. It was shown that the number of writhing was 5.12 in the T2 group compared to the control group, indicating a decrease in the medication-treated groups. The heated technique demonstrated the substantial analgesic activity of the medication under examination. After 120 minutes, the drug-treated groups had a latency time that was 9.8 seconds longer than the control group. Treatment with the experimental medicine lowered the ulcer index in an ulcer model generated by acetic acid. T2 had a value that was 0.43 lower than the control group. T2 group showed a significant reduction in ulcer index to 0.33 in ulcers generated by cold restraint stress. This study provides support for the use of multilayered tablets in the treatment of pain and ulcer disorders, since it demonstrated the analgesic and antiulcer benefits of the test medicine in animal models. More studies to determine the exact mechanism are necessary.

Keywords: Pain, Ulcer, Ranitidine, Ibuprofen, Acetic acid, Peptic acid.

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INTRODUCTION

To enhance therapy efficacy and clinical efficiency, various solid formulations for oral controlled release, including matrix tablets, have been created. More and more oral sustained drug delivery systems are now designed with multilayer tablets [1]. An active matrix core plus a barrier or barriers added during the tableting process make up these systems. By decreasing the drug-release surface area and, by extension, the liquid penetration, the barriers prolong the core's interaction with the dissolving medium[2]. The medications in these formulations are released into the bloodstream at a steady and regular rate, which allows them to remain at therapeutically effective concentrations for a long time.[3] These systems can expand, solidify, wear away, and eventually dissolve in the gut, all depending on the properties of the materials used.

The primary factor influencing the control of total release is the composition of each layer. A wide variety of dissolving profiles can be achieved by using multilayer technologies to create tablets with varying release characteristics.[4] Subramanian notes that layered tablets offer greater versatility in obtaining varied drug release patterns, including zero order, bimodal, pulsatile, and delayed release, in addition to a variety of other benefits.[5] A small number of papers have addressed two-layer tablets, whereas the majority have concentrated on the three-layer approach. For long-term medication distribution in the mouth, multilayer tablets are becoming more important.[6,7]

Ibuprofen, an NSAID, has been used for over 30 years as an effective and safe way to reduce pain and fever without a prescription.[8] Ibuprofen has been thoroughly studied for its effectiveness and is available in over 80 countries. The recommended dosage of over-the-counter ibuprofen is 200 or 400 mg, with the option to take it again every four to 6 hours as needed, with a daily maximum of 1200 mg.[9,10] The plasma drug concentration reaches its peak within three hours of taking a single dose of regular-release ibuprofen, and its absorption is quick. Analgesics that offer sustained plasma drug levels for a long period may be beneficial in situations where pain that lasts longer is present or expected, like osteoarthritis, back pain, dysmenorrhea, or pain after surgery.[11] Ulcers of the stomach are among the most dangerous and potentially fatal diseases. Ulcers develop on the inside of the stomach, near the tiny pyloric hole.[12,13] Therefore, the purpose of this study was to try to create analgesic and antiulcer tri-Layer instant-release

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tablets containing ibuprofen and ranitidine. The combined effects of the increased concentration and prolonged duration of action at the target location can increase the therapeutic efficacy of medications in this formulation. The enhanced therapeutic efficacy of the revised formulation was assessed by testing its in-vivo analgesic and antiulcer activity.

MATERIALS AND METHODS

Drugs and Excipients

Ibuprofen and ranitidine were purchased from Discovery Fine Chemicals (Dorset, UK), whereas PG Starch 1500, CCS (Ac-di-sol) and hypromellose E 15 LV were donated by FMC BioPolymer Europe (Brussels, Belgium).

Method of preparation - Ibuprofen and ranitidine Tri-layer tablet

Similarly, three-layer tablets were made utilizing a direct compression process and flat-faced holes with a diameter of 10 mm.[14] Layers of ibuprofen, placebo, and ranitidine were carefully and sequentially added to the die using measured amounts of each mixture. Beginning with the ibuprofen layer at the base of the die and compressed to around 100 kg, the next layer was the placebo, also compressed to about 100 kg, and lastly, the ranitidine, also compressed to about 100 kg. It was then coated onto the tablet. The average core weight of tri-layered Tablets (mg) 1000 for ibuprofen, 100 for placebo and 200 for ranitidine. Thickness (mm) was 9.00 ± 0.3, hardness (N) was 110 ± 25, core tablet weight was 1300.000 ± 2% mg and coated tablet weight was 1325 mg.

Experimental Animals

We got albino Wistar rats (150–175g) from the main animal house, and they may be male or female. In their room-temperature cages, the animals were subjected to a 12-hour light/dark cycle and provided with water and normal laboratory pellets as needed. Before starting the experiment, they were given a week to get used to the lab environment.

Acute Toxicity Test

The experimental medication passed an acute toxicity test in accordance with OECD standards. One starved mouse was administered a limited dose of 2000 mg/kg on the first day, and four more mice were treated in a sequential manner according to the first animal's outcome. The animals were closely monitored for any signs of toxicity, such as loss of weight, diarrhea, tremors, lethargy, or paralysis, every four hours during the first 24 hours and then daily for fourteen days. Acute toxicity testing led to the selection of three dose levels. The acute toxicity research included three different doses: 200 mg as a middle dosage, 100 mg as a low dose, and 400 mg as a high dose, which is equivalent to ten times the intermediate dose.

Animal Grouping and Dosing

Six rats made up each of the four groups that were randomly assigned. I was the group's control. The second group served as the control, while groups III and IV were used to evaluate 100 mg and 200 mg tri-layer tablets, respectively. The oral gavage method was used to administer all medications.

Analgesic Activity of the Test Drug

Writhing test induced by acetic acid

Researchers conducted this test to see whether the medicine had any analgesic effects on the periphery. There were five sets of six rats each group, and the rats might be of either sex. One group received a vehicle (control), while the other three groups received varying doses of the test drug. One group also received a conventional medicine, such as aspirin, at a dosage of 150 mg/kg, one hour prior to the administration of acetic acid. A total of sixty minutes after administration of 0.6% acetic acid (10 mL/kg, i.p.), the number of screams inducing a response was recorded to evaluate the drug's analgesic effectiveness.[15] The animals were administered an injection of acetic acid and then placed individually in inverted flasks. For 20 minutes, their belly muscular contractions and hind limb stretching were recorded collectively.

$$\%\ \text{inhibition of paw edema} = \text{mean writhing count}\frac{(\text{control group} - \text{treated group})}{\text{mean writhing count of control}} * 100$$

Hot plate method

The central analgesic potential of the medication was evaluated in this test. The test involved placing each mouse in a cylindrical open-ended chamber with a floor made of a metal plate kept at 55 ± 1°C. Paw licking and jumping, two components of behavior that may be quantified by reaction times, are both regarded as supra-spinally integrated responses, and they are both produced by this plate. Normal treatment, a vehicle, and two drug doses were given to animals. To prevent paw lesions, they were placed on a hot plate for 15 seconds after one hour. Each animal's reaction time was recorded. Response time was measured by licking the paw or jumping off the hot plate. In one study, reaction times were recorded at 0, 30, 60, 90, and 120 minutes.[16]

Antiulcer Activity

Acetic acid-induced ulcer

The rats were given free access to water during the 24 hour fast that preceded the experiment. Through a laparotomy, we were able to gain access to the anterior wall, which was then injected with 20% acetic acid (50 µL) to cause a gastric ulcer. Because of the ulcerated surface, the stomach was saline-bathed before Merisilk no. 2 and catgut chromic number 2/0 were applied for closure. Immediately after washing, the stomach was reinserted into the rectum and the rectum's entry point was sealed. For 15 days, the animals were given the test medicine and ranitidine, the standard therapy for ulcer treatment, at a dosage of 50 mg/kg p.o. On the sixteenth day following the cervical dislocation and stomach evacuation procedures, the rats were slaughtered along with the ulcer scoring parameters and ulcer index. Group 1, which was given test samples, was one of five groups of animals. Each of groups 1 and 2 received 200 mg/kg of test samples C; Group 3 got 200 mg/kg of test

samples C; Group 4 got 50 mg/kg of ranitidine; and Group 5 got 5 ml/kg of normal saline.

Stress-induced cold restraint ulcers

Researchers examined the effects of hypothermic restraint stress on stomach ulcers in rats. Rats were given 100 and 200 mg/kg of test medicine, 50 mg/kg of ranitidine, and saline as a control after being starved for 24 hours. Stomach ulcers were generated by immobilizing rats in a sealed cylinder cage with a refrigerator set to 2 to 4°C. After three hours, the rats were killed via cervical dislocation, and their stomachs were then cleaned and their contents were removed. The first group received 200 mg/kg of test sample A, the second 200 mg/kg of test sample B, the third 200 mg/kg of test sample C, the fourth 50 mg/kg of ranitidine, and the fifth 5 mL/kg of normal saline as a control.

Statistical analysis

The mean ± SEM was used to express the raw data collected from the experiment. A one-way ANOVA was used to statistically assess the results and compare them among the groups. The results were significant different at $*p < 0.05$ in comparison to the control group.

RESULT AND DISCUSSION

Analgesic Activity

To evaluate the drug's peripheral analgesic effectiveness, the acetic acid-induced writhing test was utilized and the effects are shown in Table 1. This is a quick and dependable method for measuring the effects of plants on pain. The test is highly sensitive and can identify compounds with anti-nociceptive effects at doses that might not be detectable using other methods, such as the hot plate test. However, it is not a pain test that specifically targets sedatives or muscle relaxants; it generates false positive results when testing for sedatives or other pharmacological agents due to its involvement in various nociceptive mechanisms, including biogenic amine release, substance P, bradykinins, and pro-inflammatory cytokines like TNF-α and IL-1β.

Hot Plate Method

A substantial analgesic effect ($p < 0.05$) was observed at 120 minutes in the hot plate method with 100 and 200 mg dosages of the medication compared to the control and at 60 and 90 minutes with 150 mg/kg of aspirin compared to the control (Figure 1). The effects of the medications were similar when compared to the test and standard, as shown in Table 2. It is usual practice to test medications with a central mechanism analgesic using the hot plate technique, which involves measuring the pain sensitivity of rats toward heat.

Table 1: Effect of test drug on acetic acid-induced writhing in rats

Group	*Number of writhing*	*% of inhibition*
Control (Distilled water)	27.1 ± 1.23	-
Aspirin (150 mg) (10 mL/kg)	4.4 ± 0.12*	83.76
T1 (100 mg drug)	9.11 ± 0.93*	66.38
T2 (200 mg drug)	5.12 ± 0.33*	81.10

Table 2: Effect of test drug on hot plate method

Group	*Latency (sec) ± SEM*				
	0 minute	*30 minutes*	*60 minutes*	*90 minutes*	*120 minutes*
Control (Distilled water)	6.7 ± 0.33	3.5 ± 0.25	7.5 ± 0.44	5.6 ± 0.33	5.4 ± 0.44
Aspirin (150 mg) (10 mL/kg)	6.7 ± 0.94	6.8 ± 0.41	8.4 ± 0.44	10.2 ± 0.94*	9.3 ± 1.03*
T1 (100 mg drug)	6.4 ± 0.24	8.2 ± 0.34	7.5 ± 0.32	8.2 ± 1.30*	9.5 ± 0.94
T2 (200 mg drug)	6.3 ± 0.94	6.4 ± 0.44	8.3 ± 0.93	10.3 ± 0.88*	9.8 ± 1.02*

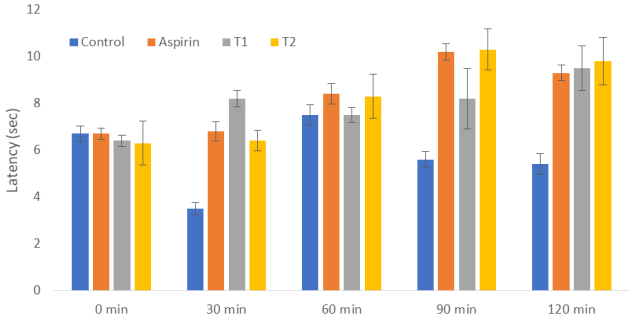

Figure 1: Analgesic activity of test drug in hot plate method

Antiulcer Activity

Acetic acid-induced ulcer model

Test drugs were effective after 14 days of ulcer healed dramatically because of the treatment. It was determined that the ulcer-healing effect at the standard drug was 0.35 ± 0.07 when treated with ranitidine. Test drug T2 demonstrated significantly higher ulcer healing activity (0.43 ± 0.07) in comparison to the control. In a study measuring the drug's ability to cure ulcers, the dose of 200 mg/kg was effective. The outcomes are presented in Table 3.

An imbalance involving aggressive forces and stomach protection is the cause of gastric ulcers.[17] Factors cause hypersecretion of HCl or gastric offensives such as pepsin. Additionally, ethanol causes stomach ulcers via a variety of complex mechanisms, including enhancing offensive factors like gastrin release or acid production or impairing defensive gastric factors like mucus dissolving.[18] The experimental study's findings may or may not be relevant to man's therapy.

Table 3: Ulcer index after administration of test drugs in acetic acid-induced ulcer

Treatment group	*Ulcer index*
Control 5 mL/kg normal saline)	1.44 ± 0.27
Ranitidine 50 mg/kg)	0.35 ± 0.07*
T1 (100 mg drug)	1.75 ± 0.08
T2 (200 mg drug)	0.43 ± 0.07*

Table 4: Observation of ulcer index in cold restraint stress-induced ulcers

Treatment group	*Ulcer index*
Control 5 mL/kg normal saline)	1.43 ± 0.05
Ranitidine 50 mg/kg)	0.28 ± 0.03*
T1 (100 mg drug)	1.10 ± 0.06
T2 (200 mg drug)	0.33 ± 0.05*

Nonetheless, this work seems to offer the first experimental proof that the ranitidine and ibuprofen microsponge formulation has a potentially advantageous effect at therapeutic levels, outperforming traditional tablets in terms of their acid-inhibitory capacity.[19]

Effect of Test Drug in Stress induced Cold Restraint Ulcers

Following administration of the experimental medications, the ulcer index in the cold restraint stress-induced ulcer model was shown to be considerably lower than prior therapy. This reduction was statistically significant ($p < 0.05$). Test drug T2 showed 0.33 ± 0.05 ulcer index at 200 mg/kg dose (Table 4).

CONCLUSION

Finally, the effects of the tri-layer tablets comprising ranitidine and ibuprofen as analgesics and antiulcer in animal studies were encouraging. Results show that compared to controls, groups treated with tablets had a considerable decrease in pain, as shown by an increase in latency and a decrease in the frequency of writhing movements during the hot plate test. Even more impressively, the tri-layer tablets significantly reduced ulcer indices after acetic acid and cold stress-induced ulcer development. These findings highlight the efficacy of multilayered tablet formulations in treating pain and ulcerative disorders. Still, we need more studies to figure out how these effects work and how to make the formulation better for clinical trials. This research sets the stage for future studies to examine the effectiveness of multilayered medication delivery systems in treating gastrointestinal and pain-related complicated diseases.

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