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IN-VIVO STUDIES OF OPTIMIZED L-GLUTAMINE HYDROGEL FOR ORAL MUCOSITIS

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ABSTRACT: Mucositis is a foremost acute complication in the clinical setting, occurring in a large percentage of patients undergoing cytotoxic therapy. One of the major problems with mucositis is that the underlying mechanisms behind its development are not wholly understood, which makes it extremely difficult to develop effective interventions. Animal models provide a critical source of knowledge when sampling from patients is unavailable, or interventions are yet to be fully tested. The object of the study is to evaluate the potential effectiveness of optimized L-glutamine hydrogel formulation used in the buccal cavity; we used a rat model for oral mucositis induced by 5-fluorouracil. Studies have shown that the blend of mild abrasion of the cheek pouch and two doses of 5-fluorouracil (60- 40 mg/kg) induced oral mucositis and the reduction of body weight. Optimized hydrogel formulations CP4 and GSH14 shown significant weight gain as compared to the control group. This study shows that the prepared hydrogel is effective in oral mucositis and effective to control oral mucositis. The rationale selection and combination of the materials allow the design of suitable formulation for different purposes with simplified changes in compositions.

INTRODUCTION: Mucositis is a major clinical problem in oncology, caused by the cytotoxic effects of cancer chemotherapy and radiotherapy. Mucositis is a major clinical problem in oncology, caused by the cytotoxic effects of cancer chemotherapy and radiotherapy. Oral mucositis, which is characterized by painful erythematous, erosive and ulcerative lesions of the oral mucosa, is a common complication of many cancer treatments, including myeloablative forms of bone marrow transplant therapy.

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Between 30% and 69% of patients undergoing bone marrow transplantation experience oral mucositis, and nearly all such patients experience some form of oral complications, including oral mucositis, dysfunction of the salivary glands, infection, dysgeusia, dentinal hypersensitivity, and soft-tissue pain. Mucositis may affect the mucosa of the oral cavity and gastrointestinal tract (GIT), causing mouth and throat pain, ulceration, abdominal pain, bloating, vomiting and diarrhea depending on the target tissue [1, 2, 3, 4].

While the frequency and severity of mucositis varies depending on the type of cancer or treatment, the clinical observation of variable mucositis rates among patients with similar malignancies and treatment regimens has resulted in several attempts to identify specific risk factors [5, 6].

Current toxicity risks for mucositis may be placed into two treatment categories: treatment-related and patient-related. The morbidity of all mucositis can be profound. It is estimated that approximately 15% of patients treated with radical radiotherapy to the oral cavity and oral pharynx will require hospitalization in addition, severe oral mucositis may interfere with the ability to deliver the intended course of therapy, leading to significant interruptions in treatment and possibly impacting on can also have a significant economic cost [7]. The major current treatments for oral mucositis in clinical settings are local anesthetics agents [8, 9] that coats the oral mucosa with sodium alginate [10], anti-ulcer agents, such as polaprezinc [11, 12] or rebamipide [13], and anti-inflammatory agents, such as azulene or steroids [14].

However, the precise efficacy of these drugs remains unclear. Radiation is known to generate reactive oxygen species such as superoxide radicals, hydrogen peroxides and hydroxyl radicals, and they cause injury in cells, leading to mucositis occurrence [15]. Etio-pathologically oral mucositis has five principal phases, *e.g*. initiation, up-regulation and message generation, amplification and signaling, ulceration, and healing [16]. Hydrogels are appropriate materials for the buccal drug delivery due to mucoadhesiveness, sustained-release property, good feel in the mouth, and safety [17, 18]. Hydrogels are three-dimensional polymeric networks which swell quickly by imbibing a large amount of water. Several polymeric hydrogel systems have been prepared from natural and synthetic polymers [19].

The combination of natural and synthetic polymers may provide mechanical stability and biological acceptability, acquiring from synergistic properties of both materials. The hydrogels were found stable and resilient [20]. The swelling ability and high water content of hydrogels resemble natural living tissue more than any type of synthetic material and their use in immobilization of proteins, peptides, and other biological compounds. Several studies have evaluated the benefit of oral or parenteral glutamine supplementation in cancer patients receiving chemotherapy and radiotherapy or after bone marrow transplant. L-glutamine considerably reduces the duration and severity or oral mucosa during radiotherapy. Many traditional treatments are ineffective. The basic principles of it are to relieve pain, prevent dehydration provide adequate nutrition and deal with any focus of infection such as stand the test of time approaches to the prevention of mucositis.

In present work, an attempt was made to evaluate the optimized hydrogel drug delivery systems. Attempts were made to enhance the absorption of drug and contact time to improve therapy by controlling the rate of drug release from dosage forms. Various agents like thickening or gelling agents were used to modify the rate of drug release. The ultimate aim was to evaluate the effect of optimized hydrogel formulations only to improve the bioavailability of the drug by the use of a combination of natural and synthetic polymers.

MATERIALS AND METHODS:

Materials: Carbopol 934 NF, Methylparaben, sodium glycocholate, glycerin and other chemicals of standard quality were taken from Loba Chem. India. L-glutamine was procured from Claris Life sciences ltd. India. 5-fluorouracil Inj. from Getwell Pharma Ltd., India.

Methods:

***In-vivo* Studies:** All procedure in the animal study were reviewed and approved by the Animal Ethics Committee 1413/PO/E/S/11(16-17) CPCSEA. An experiment was performed with 30 male Sprague-Dawley rats weighing 180-260 g in total. Rats were raised under the pathogen-free condition and fed *ad libitum*. They were housed individually and maintained according to the 12 h light 12 h dark schedule in a room at the approved animal house. The room temperature kept at normal. The one teaspoonful of the L-glutamine hydrogel was applied to the skin of the left whisker pad using a toothbrush as well as being applied to the intraoral region using a cotton swab. The quantity of the gel was enough for applying to the inflammatory lesions. The hydrogel was used at room temperature (23 ºC approximately). Application of the hydrogel to the left whisker pad and intraoral regions was performed after measurement of the mucositis [21-32].

Treatment Group: The rats were randomly divided into 6 groups (each number = 5). All rats were immobilized by anesthetization with

pentobarbital sodium (50 mg/kg intraperitoneally). Treatment of the 6 groups of rats before and after irritation were as follows: Group A served as the control group received no treatment, Group B, D and E received, application of the L-glutamine hydrogel formulation CP4, chlorhexidine gel (1% w/w) and GSH14 to the left whisker pad 2 days before 5-FU administration and continuous application of the L-glutamine hydrogel to the left whisker pad daily for 15 days after administration of 5-FU, respectively. Group C and F received continuous application of the L-glutamine hydrogel formulation CP4 and GSH14 chlorhexidine gel (1% w/w) and to the left whisker pad for 15 days after 5-FU application.

Induction of Experimental Oral Mucositis: Oral mucositis was induced by two intraperitoneal (i.p) administrations of 5-FU (5- fluorouracil) on the 0 and 2nd day of the experiment (60 and 40 mg/kg, respectively), according to an experimental oral mucositis model previously described **Table 1**.

TABLE 1: STUDY PROTOCOL OF ORAL MUCOSITIS MODEL

S. no.	Day of Trail	Day 0	Day 1	Day 2	Day 3	Day 4-15
1	5-FU injection	+	-	+	-	Only on day
2	Scratching	-	+	+	-	-
3	Application of formulation	-	-	-	-	Everyday

To mimic the friction to which the oral mucosa is normally subjected, the animal cheek pouch mucosa was irritated by superficial scratching with the tip of an 18-gauge needle on the day 1 and day 2, under anesthesia with chloral hydrate (250 mg/kg, i.p.). The needle was dragged twice in a linear fashion across the everted cheek pouch until erythematous changes were noted. Ulcers were assessed every other day immediately before the application of drugs **Table 1**.

Mucositis Score System: The mouths of the rats in all groups were observed daily to assess the sign of both mucositis. The extent of mucositis was gauged according to the mucositis score system.

Score 0 = normal. Score 0.5 = slightly pink. Score 1 = slightly red. Score 2 = severe reddening. Score 3 = focal desquamation. Score 4 = exudation or crusting is covering less than one-half of the lip. Score 5 = exudation or crusting is covering more than one-half of lip **Fig. 1**. This score was recorded daily from 2 days before irritation to 15 days after 5-FU application **Table 2**.

Body-Weight Change: The changes in the body-weight of the rats in each experimental group are recorded. During 15 days, a body-weight loss was seen in rats of the control group, as animals are given 5-FU orally at a dose of 60 mg/kg and 40 mg/kg. There were virtually changes in the weights of rats administered 5- FU with either chlorhexidine or L-glutamine formulations **Table 3**.

RESULTS AND DISCUSSION: In the study, a combination of intraperitoneal injections of 5-fluorouracil (40-80 mg/kg) produced a dose-dependent increase in the area of mucositis and a decrease in body weight. The findings of mucositis begin in 5 of 5 rats in Group A and 4 of 5 rats in Group B on day 3 after application of 5-FU and scratching, shown in **Fig. 1**. It began in 3 of 5 rats in Group C and in 3 of 5 rats in Group D on day 5, 4 respectively **Table 2**.

TABLE 2: SEVERITY OF MUCOSITIS IN DIFFERENT GROUPS

S. no.	Days	Score of Group					
		A	B	C	D	E	F
1	-2	0	0	0	0	0	0
2	-1	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	1	0	0	0	0	0	0
5	3	0.5	0.5	1	0.5	0.5	0.5
6	5	1	0.5	1	1	0.5	1
7	7	2	1	1	1	1	1
8	9	3	1	2	1	1	1
9	11	4	1	2	2	2	2
10	13	4	1	2	2	2	2
11	15	5	2	3	3	2	2

In Group A all-5 rats showed score 1.0 on day 5 and score 5.0 on day 15 of 5-FU application and scratching. In Group A the progression of mucositis score started to increase on day 5, and it progressively increases on days 7 it was 2.0 it goes up to 5.0 on day 15. Some rats in Group A have shown exudation or crusting **Table 2**. The time course of mucositis score in Group B started on day 5 of mucositis induction, and group B has shown

different mucositis progression after 5-FU application and scratching the mucositis score was 2 on day 15 but the progression was not effective as a control group.

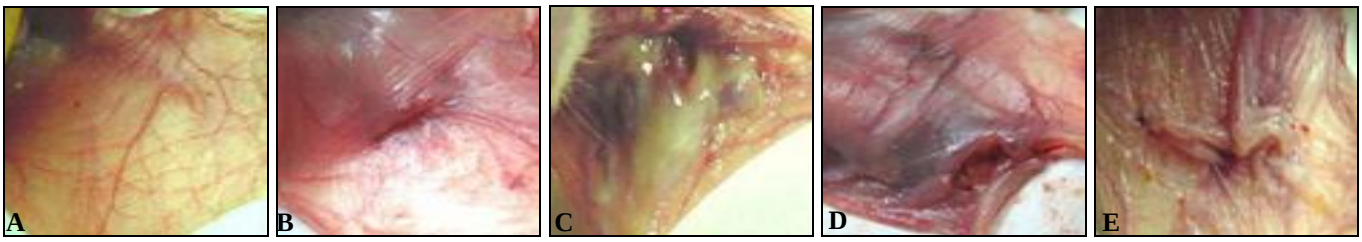

FIG. 1: MUCOSITIS SCORES (A) SCORE 0.5 (B) SCORE 1 (C) SCORE 3 (D) SCORE 4 (E) SCORE 5

The way of mucositis score in Group C and D on day 3 as 1.0 and 0.5 in almost all the animals, there is no significant difference in the mucositis score in Group C and D for 5th and 7th day. As both groups showed the same progression, but the weight change is less in Group C as compared to Group D. The increase in the rates of the mucositis score of group A and group D were significantly higher than those of Group B and C **Fig. 2**.

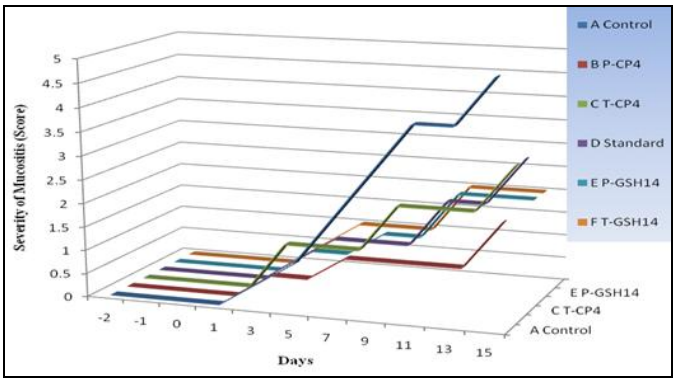

FIG. 2: THE TIME COURSE OF THE MUCOSITIS SCORE AFTER 5-FU APPLICATION AND SCRATHING

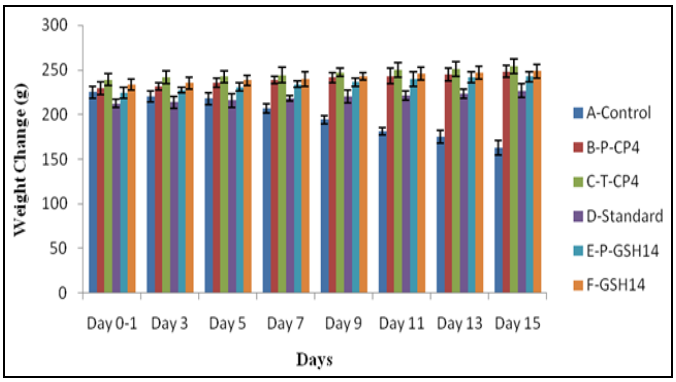

FIG. 3: WEIGHT CHANGES IN RATS BEFORE AND AFTER THE TREATMENT WITH L-GLUTAMINE HYDROGELS IN 15 DAYS

TABLE 3: WEIGHT CHANGES IN RATS BEFORE AND AFTER THE TREATMENT WITH L-GLUTAMINE HYDROGEL IN 15 DAYS

S. no.	Days	Group					
		A	B	C	D	E	F
1	Day 0-1	225.2 ± 6.7	229.3 ± 7.2	238.9 ± 6.9	212.2 ± 4.7	224.6 ± 6.3	233.6 ± 6.2
2	Day 3	220.2 ± 5.9	231.4 ± 4.3	241.6 ± 7.5	213.8 ± 6.8	227.3 ± 3.4	235.2 ± 6.8
3	Day 5	217.8 ± 6.8	235.3 ± 5.3	242.3 ± 6.3	215.7 ± 7.6	230.7 ± 4.4	238.1 ± 5.6
4	Day 7	206.6 ± 5.2	238.7 ± 4.3	243.9 ± 8.7	218.2 ± 2.9	233.9 ± 3.4	239.9 ± 8.0
5	Day 9	194.2 ± 4.8	241.3 ± 5.4	247.2 ± 4.9	220.1 ± 6.8	236.2 ± 4.5	242.4 ± 4.2
6	Day 11	181.2 ± 3.8	242.8 ± 8.7	249.8 ± 7.9	221.4 ± 4.8	239.6 ± 7.8	245.8 ± 7.2
7	Day 13	174.7 ± 7.1	245.2 ± 7.2	251.3 ± 8.1	223.1 ± 4.9	241.5 ± 6.3	246.7 ± 7.4
8	Day 15	162.7 ± 8.2	248.2 ± 6.7	254.3 ± 8.2	226.5 ± 7.8	242.4 ± 5.8	248.5 ± 7.5

During 15 days, a body-weight loss with 5-FU was found in-group A **Table 3**; the weight loss was significant in the control group. The weight gain was significant in case of group B, C, D, E and F which was treated with L-glutamine hydrogel formulations (Group B, C, E, F) and chlorhexidine gel (D) respectively **Fig. 3**. There were more tendencies towards an increase in weight gain in Group C as compared to Group B **Table 3**. The time course of mucositis score in Group E started on day 5 of mucositis induction, and group E has shown mucositis progression like Group B till 9th day. The mucositis score was increased on 11th to 13th day as 2. The mucositis score was 2 on day 15, but the progression was not effective as the control group. The mucositis progression in Group F was almost the same as the Group E. The Formulation GSH14 has shown similar results in both Groups E and F for prophylactic and therapeutic effect. The probable mechanisms of oral mucositis induced by

chemotherapy involve complex biological events mediated by several inflammatory cytokines, the direct effect of chemotherapeutic drugs or irradiation on the basal epithelium and connective tissue, and the oral microbial environment. Ulcerative mucositis results in the destruction of the oral mucosa as an anatomic barrier. The mouth thus becomes a portal of entry for enteric bacterial, viral and fungal organisms. Thus, ulceration of the oral mucosa results in an increased risk of infection, particularly when there is immunosuppression.

Mucositis viewed solely as an epithelium mediated event, which was the result of the nonspecific toxic effects of radiation or chemotherapy on dividing stem cells. It was believed that direct damage by chemotherapy or radiation therapy to the basal epithelial cell layer led to the loss of the renewal capacity of the epithelium, resulting in clonogenic cell death, atrophy, and consequent ulceration.

New research has suggested that mucositis is not just an epithelial process but involves all the tissues of the mucosa, as evidenced by recent data involving morphologic findings, proinflammatory cytokines, platelet aggregation, endothelial and connective tissue injury, and tissue apoptosis. This finding could be related to the mechanism of cytotoxicity of the chemotherapy agent used in this study. 5-FU is a competitive inhibitor of thymidylate synthetase with consequent thymidine deficiency resulting in inhibition of deoxyribonucleic acid (DNA) synthesis.

Also, incorporation into ribonucleic acid (RNA) interferes with processing and function of RNA and has been associated with toxicity. Given this, even though glutamine is essential for cell proliferation, being an important metabolic substrate for rapidly replicating cells. Different factors may be taken into account to explain the benefits of exogenous glutamine in hastening oral mucosa healing.

First, it has been demonstrated that glutamine can activate ornithine decarboxylase, a first and rate-limiting enzyme in polyamine synthesis in a dose- and time-dependent manner, thereby enhancing DNA synthesis. Also, glutamine can activate mitotic signaling pathways, including mitogen-activated protein kinases and transcription factors, leading to proliferative responses. 30 sec, previous studies have suggested that glutamine augments host defenses and may be important in glutathione synthesis thus decreasing the oxidative stress. Accordingly, our data demonstrated that the administration of glutamine increased the mucosal tissue glutathione stores in the 5-FU treated rat. It has been demonstrated that glutamine becomes essential during metabolic stress to restore tissue glutathione levels, which have become depleted [31].

Glutathione, the major intracellular antioxidant, is involved in several fundamental biological functions, including free radical scavenging, detoxification of xenobiotics and carcinogens, redox reactions, and biosynthesis of DNA and proteins, being essential to normal cell function and replication. Also, glutathione has an inhibitory effect on several cytokines. Thus, our result suggests that glutamine bioavailability by exogenous administration, restored glutathione level thereby enhancing cell protection, as well as regulating cell proliferation after exposure to 5- FU that generates toxic quantities of free radicals.

This *in-vivo* study shows that there were more weight gain recorded in-group receiving L-glutamine as compare to control and chlorhexidine treated group. Mucositis was less severe in the L-glutamine treated group as compared to control and chlorhexidine receiving group. This result indicated that the formulation could be used to treat or prevent chemotherapy-induced oral mucositis.

CONCLUSION: This *in-vivo* study shows that there was more weight gain recorded in-group receiving L-glutamine as compared to control and chlorhexidine treated group. Mucositis was less severe in the L-glutamine treated group as compared to control and chlorhexidine receiving group. The formulation GSH14 is containing natural and synthetic polymers in the defined proposition. This result indicated that the formulation could be used to treat or prevent chemotherapy-induced oral mucositis.

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