Explor Anim Med Res.
Vol. 14, Issue 1, 2024
DOI: 10.52635/eamr/14.1.68-75

ISSN 2277-470X (Print), ISSN 2319-247X (Online)
Website: www.animalmedicalresearch.org

Research Article

ACUTE DERMAL IRRITATION AND SKIN SENSITIZATION STUDY OF MESOPOROUS ANTIBACTERIAL BIOACTIVE GLASS MICROSPHERE IMPREGNATED SURGICAL COTTON GAUZE DRESSING MATERIAL ON RABBITS AND GUINEA PIGS

Debolina Dattaray[1*], Payal Roy[2], Raja L[1], Jui Chakraborty[2], Tapan Kumar Mandal[1]

Received 08 January 2024, revised 19 June 2024

ABSTRACT: A study was undertaken to evaluate the skin sensitization and acute dermal irritation of Mesoporous antibacterial bioactive glass microsphere impregnated non-woven surgical cotton gauze (MABGmscg) dressings on shaved rabbits and guinea pigs. This study complied with guidelines 404 and 406 of the Organization for Economic Co-operation and Development (OECD). In the dermal irritation test, three different MABGmscg dressings were applied to the shaved skin of rabbits at three separate sites for four hours. The results demonstrated that the dressings did not cause unfavorable reactions, such as inflammation, erythema, or edema, on the unbroken skin of rabbits. As a result, MABGmscg dressing material was considered practically non-irritating based on its rating of primary irritation index. In the case of the Buehler test, three different doses of the MABG (mscg dressing) were used to initially sensitize the guinea pigs. They were later challenged at different sites with patches applied for 24 hours. The MABG dressing patches did not trigger any skin reactions when tested with various doses of the MABG (mscg dressing). These findings collectively indicate that the MABGmscg dressing did not induce any skin irritation or sensitization upon direct skin application in laboratory animals.

Keywords: Mesoporous antibacterial bioactive glass, Rabbits, Dermal irritation, Skin sensitization, Guinea pigs, Dermal application.

INTRODUCTION

Hemostasis is an indispensable measure in emergency medical trauma situations. Advancement in the field of medical biology and protective equipment has somehow still not been capable enough to combat the fatal traumatic hemorrhage challenge for both military and civilian cases [1]. Around 50% of deaths in military settings occur due to exsanguination. Reports of uncurbed bleeding caused due to traumatic road accidents involving stray animals such as cattle, dogs, cats, and goats can also be witnessed. Uncontrolled bleeding in such scenarios can cause the injured animals to die. One of the best ways to lower patient mortality is through prompt action from the injured individual or the on-scene personnel. Therefore, much attention is given to the development of an alternative method for controlling hemorrhage, especially topical hemostatic dressing material. Though bleeding from extremities can usually be controlled by applying direct pressure or by tourniquet, but in severe cases little can be done to control bleeding from complex chest, abdomen, or pelvic wounds [2].

[1]*Department of Veterinary Pharmacology and Toxicology, West Bengal University of Animal and Fishery Sciences, Belgachia, Kolkata, 700037, India.*
[2]*Bioceramics and Coating Division, CSIR-Central Glass and Ceramic Research Institute (CSIR-CGCRI), 196, Raja S. C. Mullick Road, Kolkata, 700 032, India.*
**Corresponding author. e-mail: debolinadattaray10@gmail.com*

Many studies have been conducted to develop efficient dressing materials from various sources [3]. Commercially available dressings, such as Hemcon, Celox, Trauma Dex, and QuickClot, are typically made from natural polymers, synthetic polymers, or are kaolin clay-based materials, but they often come with inherent drawbacks. The kaolin clay-based QuickClot, for example, operates through a localized exothermic reaction, potentially resulting in further tissue damage [4]. Additionally, it has poor biodegradability. These materials frequently do not offer instant hemostasis upon application to a wound, leading to increased blood loss in comparison to alternative agents [5]. Other chitosan-derived hemostats, like Hemcon and Celox, can cause allergic sensitivity reactions and have poor adhesion at the wound site. Furthermore, these preparations often lead to re-bleeding when the dressing is changed [6]. The chitosan-based indigenous preparation (Axiostat) is reported to show batch-to-batch variation in performance. Furthermore, these dressings might not be reliable for managing hemorrhage in coagulopathic patients [7]. Thus, there is a continuous quest for a hemostatic device that can overcome all of the shortcomings of the current hemostatic dressings and is also efficient, affordable, portable, and simple to use.

Bioactive glass is composed of 80% SiO_2, 15% CaO, and 5% P_2O_5, which are distinctly different from the conventional non-mesoporous counterparts. Bioactive glass was first developed by Hench and colleagues [8]. Mesoporous bioactive glass (MBG) possesses well-structured channel networks and a considerable specific surface area. These characteristics enhance hemostasis by stimulating factor XII (Hageman coagulation factor) and additional clotting proteins. Additionally, the abundant polar silanol groups and negative charges on their surfaces play a role in promoting coagulation by initiating the intrinsic pathway of the coagulation cascade [9]. The glass surfaces possess a surface energy greater than 60 dyne/cm^2, which accelerates clot formation, a phenomenon known as the 'glass effect' [10]. Furthermore, when hydrated, MBGs release Ca^{2+} ions, concentrate blood components via capillary absorption of fluid-phase media, and possess an inorganic core that is insoluble and robustly aids thrombosis [11]. The spherical morphology of MBG enhances hemostatic potential compared to irregularly shaped counterparts, due to shorter R times and a faster coagulation rate [12]. This activity is attributed to the Si/Ca ratio, high surface area, and porosity of MBGs. Recently, various trace elements such as silver (Ag^+), magnesium (Mg^{2+}), gallium (Ga^{3+}), zinc (Zn^{2+}) [4], cobalt (Co^{2+}), cerium (Ce^{3+}) [13], titanium (Ti^{++}) [14], and tantalum (Ta^{++}) [15] have been incorporated into the glass network, providing unique characteristics beneficial for biological applications in healthcare, such as hemostasis. Consequently, a hemostatic dressing composed of mesoporous antibacterial bioactive glass (MABGmscg) has been developed [16]. This dressing is designed to achieve hemostasis with antibacterial properties, suitable for use in arterial bleeding during military combat and civilian trauma situations.

Various policy-making Organizations like the Occupational Safety and Health Administration (OSHA), European Economic Community (ECC), Food and Drug Administration (FDA), The Organization for Economic Co-operation and Development (OECD), and Consumer Product Safety Commission (CPSC), have established regulatory guidelines for identifying hazardous chemicals to the skin and protecting consumers from their harmful effects. These regulatory mandates require results from particular assays aimed at assessing the impacts of chemicals on the skin before their registration, transportation, or marketing [17]. Therefore, this study was conducted to assess whether the MABGmscg dressing causes skin irritation, corrosion, immune response triggers, urticaria, or non-inflammatory pain responses when applied to the bare skin of rabbits and guinea pigs.

MATERIALS AND METHODS

Animal care and maintenance

New Zealand white rabbits (*Oryctolagus cuniculus*), with body weights ranging from 1.2 to 2.0 kg and aged 17 weeks, along with healthy guinea pigs (males and females) weighing between 300-380 g and aged 5-6 weeks, were procured from the State Centre for Laboratory Animal Breeding (SCLAB) located in Kalyani, West Bengal, India. The animals used in the experiment were housed in polypropylene cages and had unrestricted access to standard commercial pellets provided by EPIC® Feeds, Kalyani, West Bengal, along with ad libitum access to Aqua-Guard filtered water. Guinea pigs were additionally supplemented with Vitamin C and given fresh green grass and vegetables ad libitum. Upon arrival, each animal underwent a clinical examination and was marked for identification using an aqueous solution of picric acid (1:1000 w/v). The female animals were nulliparous. The experimental animals were sorted into groups and accommodated in a climate-controlled room with

maintained temperature in the range of 25±3°C, relative humidity ranging from 50% to 60%, 12-hour day-night cycle, and 15 to 21 air exchanges per hour. They underwent a 7-day acclimation period to the laboratory setup before the initiation of the experiment, enabling them to adapt to the new surroundings and alleviate any stress from transportation. Only animals in good health were utilized for the studies. The Institutional Animal Ethics Committee approved the experiments (No. 763/GO/Re-S/ReRc-L/03/CCSEA/39/2022-2023), and the experimental protocols complied with OECD guidelines 404 and 406.

Test articles and fabrication protocol

The non-woven surgical cotton gauze dressing impregnated with Mesoporous Antibacterial Bioactive glass microsphere (MABGmscg) was formulated by CSIR-CGCRI, Kolkata [14]. This experiment aimed to test the placebo patches for acute dermal irritation in rabbits and skin sensitization in guinea pigs. All reagents utilized were of analytical-grade quality.

Experimental design

Acute dermal irritation study

The acute dermal irritation test was performed following the guidelines outlined in OECD 404, Acute Dermal Irritation Test (2015) [18]. Healthy New Zealand white rabbits with intact skin were chosen for the experiment. A 6 cm² area on the back of each rabbit was shaved without abrading the skin 24 hours before the experiment. A surgical gauze dressing (2.5 cm x 2.5 cm) impregnated with 0.5 g of MABG powder was applied to the bare skin. The dressing was covered with a gauze patch and fastened using non-irritating adhesive tape (leucoplast). After 3 minutes, the initial patch was taken off. Following the absence of any notable skin reaction, a second patch was placed at another location and removed after 1 hour. Based on the results, the exposure was extended to 4 hours, and a third patch was applied for this duration. The experiment was reiterated with two extra rabbits to validate the preliminary observations, as no dermal reaction was observed in the initial rabbit. The animals underwent examination for signs of erythema and edema according to the grading guideline table (0-4 score). Responses were evaluated at 60 minutes and subsequently at 24, 48, and 72 hours following patch removal (as outlined in Table 1). The dermal response scores for each animal (the combined results for erythema/eschar formation or any kind of unfavorable reactions) at 1, 24, 48, and 72 hours post-patch removal were aggregated and then divided by three to derive the mean irritation score per time point. The average values across all observed time points were totaled and then the average was done to ascertain the primary irritation index (PII).

Skin sensitization study

The skin sensitization study adhered to OECD Guideline 406, titled "Skin Sensitization [19], and the Buehler method [20]. Healthy adult Dunkin Hartley guinea pigs (5-6 weeks old, weighing 300-380 g) were used. One day before the initiation of the experiment, the guinea pigs were allotted to four groups of 5 males and 5 females each: Group I (control group, n = 10), Group II (lowest dose group, n = 10), Group III (medium dose group, n = 10), and Group IV (highest dose group, n = 10). The three different concentrations selected for the experiment were Dose I (lowest dose) = 200 mg/kg B.W., Dose II (medium dose) = 500 mg/kg B.W., and Dose III (highest dose) = 1000 mg/kg B.W. The control group guinea pigs were treated with a 1% Tween 80 solution, which was evenly spread on surgical cotton gauze and applied to the shaved area for direct skin contact. Each guinea pig had a 5 × 6 cm² area on their left flank shaved using sterile shaving blades and antiseptic soap. On the first day of induction, three different doses of MABG-impregnated surgical gauze were applied to the shaved region. The MABG dressing was sealed with impermeable, non-irritating adhesive tape and held in contact with the skin for 6-hour closed applications. The same application procedure was repeated on the same test area (after clipping the fur) of the corresponding flank from days 6 to 8, and subsequently, from days 13 to 15. On days 27-29 of the experiment, a challenge exposure was performed. For the challenge, the untreated flank of animals in both the groups receiving treatment and the control was shaved. Two 2 × 2 cm² areas were delineated on both the right and left flanks, with the median line serving as the axis of symmetry. During challenge exposure, the guinea pigs of the control group were treated with a solution containing 1% Tween 80, while the animals of the treatment group received dressings impregnated with different concentrations of MABG. The patches were kept in contact with the skin for 6 hours. Dermal reactions were assessed at 24 and 48 hours following the removal of the patches according to the criteria of Magnusson and Kligman [21].

Statistical analysis

Data from various experiments were expressed as Mean ± SEM. All data were analyzed using one-way ANOVA with SPSS V-23.0 software, and the significance between groups was compared using the Least Significant Difference (LSD) post-hoc test.

RESULTS AND DISCUSSION

Dermal irritation study

The findings from the acute dermal irritation investigation are outlined in Table 1, and Fig. 2a, 2b, and 2c. No dermal reactions, such as erythema or edema were detected in animals treated with MABG-impregnated dressing material. The Primary Irritation Index (PII) for this group was determined to be 0.

Table 1. Grading of skin reactions (Dermal responses: mean score).

Duration	Erythema and eschar formation	Oedema formation
1 h after removal of patch	0	0
24 h after removal of patches	0	0
48 h after removal of patches	0	0
72h after removal of patches	0	0
Primary Irritation Index (PII)	0	0

[Dermal response was recorded according to OECD TG 404 (2002a). Mean value of dermal responses = (Total value of erythema and eschar formation + total value of oedema formation) / 3. Primary irritation index (PII) = (mean value at 24 h + mean value at 48 h + mean value at 72 h)/3].

Skin sensitization study

The findings from the skin sensitization experiments involving MABG-impregnated dressing material are depicted in Fig. 3a, 3b, 3c, and 3d. No clinical signs were evident in the MABG-treated groups. Following the challenge with various doses of MABG-impregnated dressing material or in the control groups, no instances of erythema or edema were observed.

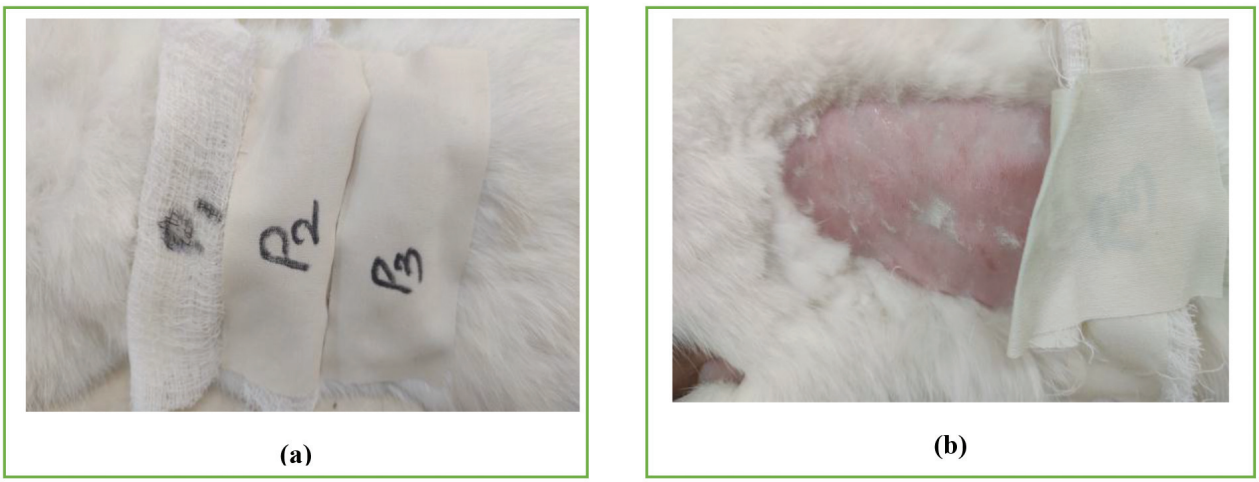
Skin irritation can be defined as localized inflammation triggered by factors other than sensitized lymphocytes or antibodies but by direct tissue damage (necrosis) resulting from the application of certain chemicals. Chemicals capable of inducing inflammation upon single exposure are classified as active irritants, while those causing necrosis and scar tissue formation are termed corrosives [22]. Given the potential for skin contact during chemical application or transport, regulatory agencies require screening of chemicals for their potential to cause skin corrosion or irritation following topical application. Additionally, the severity of skin irritation depends on factors such as dose, duration of contact, and dosing interval. The intensity of the reaction may also escalate with increasing concentration of the chemical [23]. Therefore, the analysis of dermal irritation or sensitization effect of the material was to be performed, since hypersensitivity, infection, or cellular toxicity are the other challenges, that can be faced by the application of topical hemostatic agents. Silica-based mesoporous bioactive glass (MBG) has garnered global interest recently due to its notable characteristics, including excellent biocompatibility, minimal cytotoxicity, thermal stability, well-defined channel structures, significant pore volumes, and negatively charged surfaces. The disparity in electronegativity between oxygen and metallic atoms enhances blood coagulation upon contact, demonstrating its effectiveness in promoting hemostasis [4]. Hence, the current experiment evaluated the irritation and skin sensitization effects of MABG-incorporated dressing material on the skin of rabbits and guinea pigs. Such irritation and sensitization studies are crucial steps in safety assessment. As compared to the control animals, no skin irritation was observed in rabbits in the present study after application of the MABG powder-impregnated non-woven surgical cotton gauze as evidenced by no appearance of erythema and edema on the application site. The primary irritation index (PII) is calculated as the average of intact and abraded skin scores at 24, 48, and 72 hours. Agents yielding a PII of 2 or higher are generally considered mildly irritating [24]. However, our findings indicate a PII score of 0 following the application of MABGmscg dressing, suggesting no adverse effects on the skin of rabbits. The United Nations recommends evaluating dangerous goods transportation based on exposure times of 3 minutes, 1 hour, and 4 hours. Additionally, assessments are conducted at 1,24, 48- and 72 hours post-dosing to assess the chemical's irritation potential [17].

The initial assessment of a substance's predictive potential to induce delayed hypersensitivity in humans often involves testing in guinea pigs. Various responses, including the development of visual dermatitis and the assessment of erythema and edema using descriptive scales, are typically evaluated. This test varies significantly in terms of the route of exposure, use of adjuvants, induction interval, and the number of animals involved [25]. The Buehler test in guinea pigs [26] employs the topical application of the test substance, which aligns with our intended route of application. However, in guinea pigs, no erythema or edema

Table 2. Mean body weight with SEM of guinea pigs used in skin sensitization study following application of MABGmscg dressing at different doses (n = 6).

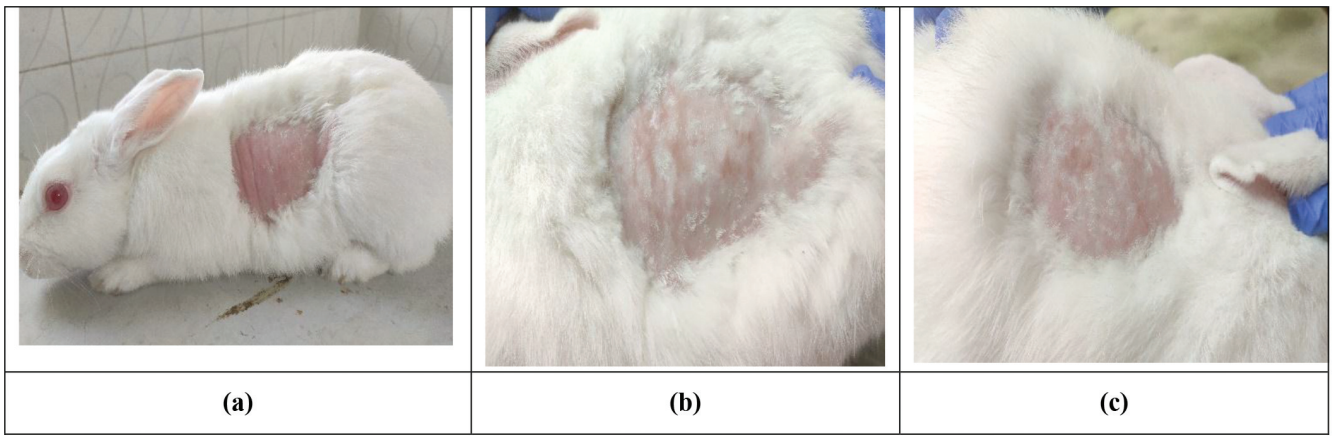
Group	Day				
	0	7	14	21	28
I	303.00 ± 2.75	306.12X± 5.50	315.62± 5.44	321.00 ± 5.46	328.58X ± 5.27
II	306.50 ± 2.64	318.22Y ± 3.72	327.18± 3.36	331.47± 2.23	343.51Y± 2.14
III	306.98 ± 3.00	314.10 ± 3.58	314.78± 5.66	324.52 ± 3.98	333.95± 4.78
IV	300.97 ± 2.72	310.37± 2.85	319.42± 4.81	333.23± 4.33	334.65± 4.00

[The superscript X and Y depict significant difference in body weight among groups on various days interval. The data is represented as Mean ± SEM. where, Group I: Control (1% Tween 80), Group II: Dose I (200mg/kg BW of MABG) impregnated dressing material, Group III: Dose II (500mg/kg BW of MABG) impregnated dressing material, Group IV: Dose III (1000mg/kg BW of MABG) impregnate dressing material].



(a) (b)

Fig. 1. Representative photographs showing the application of MABGmscg dressing on the shaved skin of rabbits. [1a-depicts application of 3 patches of MABG (0.5g) mscg dressing on shaved skin of rabbits, 1b- Patch application site after 1 h of MABGmscg dressing application on the shaved skin of rabbits].



(a) (b) (c)

Fig. 2. Photographs showing bare skin of rabbits after removal of MABG (0.5g) mscg dressing. [2a depicts the patch application site, 24 hours after dressing removal, 2b depicts the patch application site, 48 hours after dressing removal, 2c depicts the patch application site, 72 hours after dressing removal].

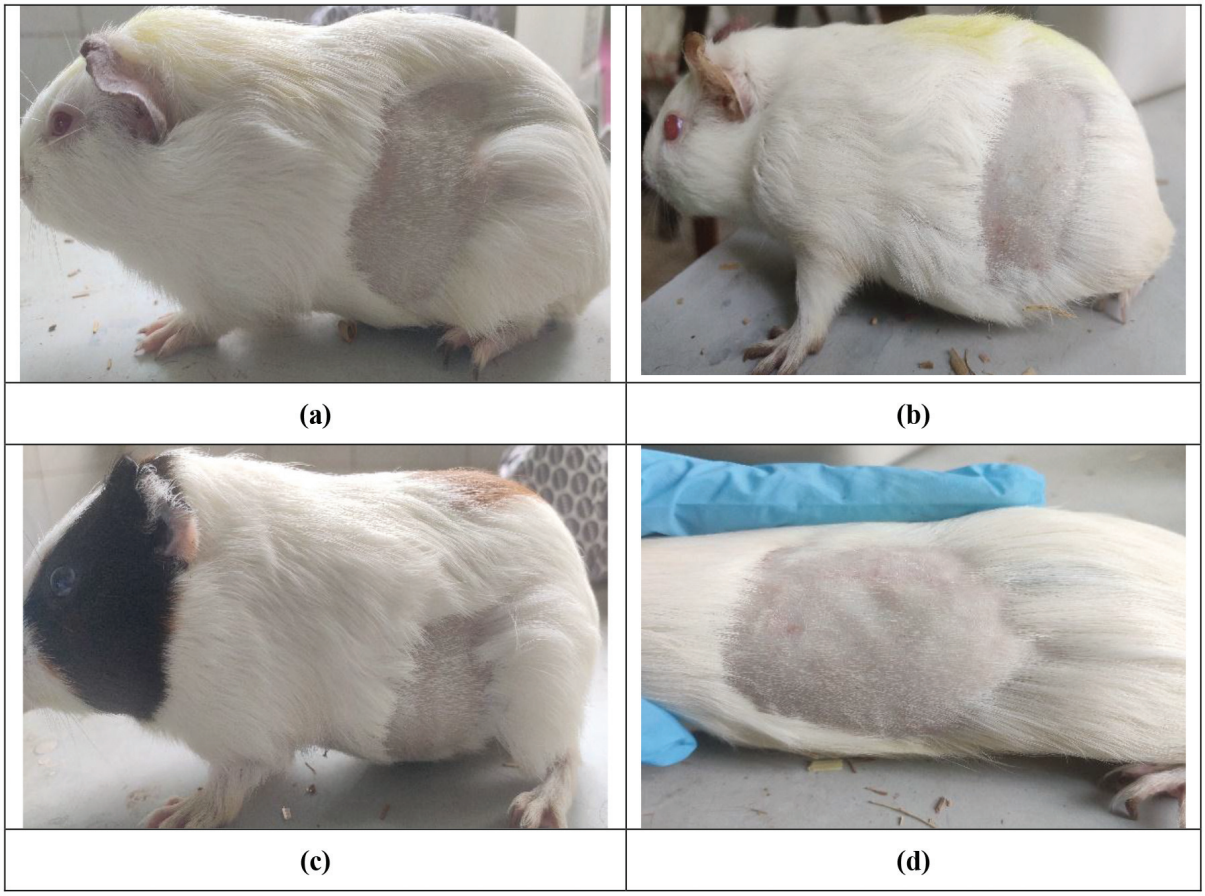


Fig. 3. Photographs showing bare skin of guinea pigs after removal of different doses of MABG impregnated dressing. [3a depicts the application site, 24 hours after the end of challenge with lowest dose in guinea pig, 3b depicts the application site, 24 hours after the end of challenge with medium dose in guinea pig, 3c depicts the application site, 24 hours after the end of challenge with highest dose in guinea pig, 3d depicts the application site, 48 hours after the end of challenge with highest dose in guinea pig].

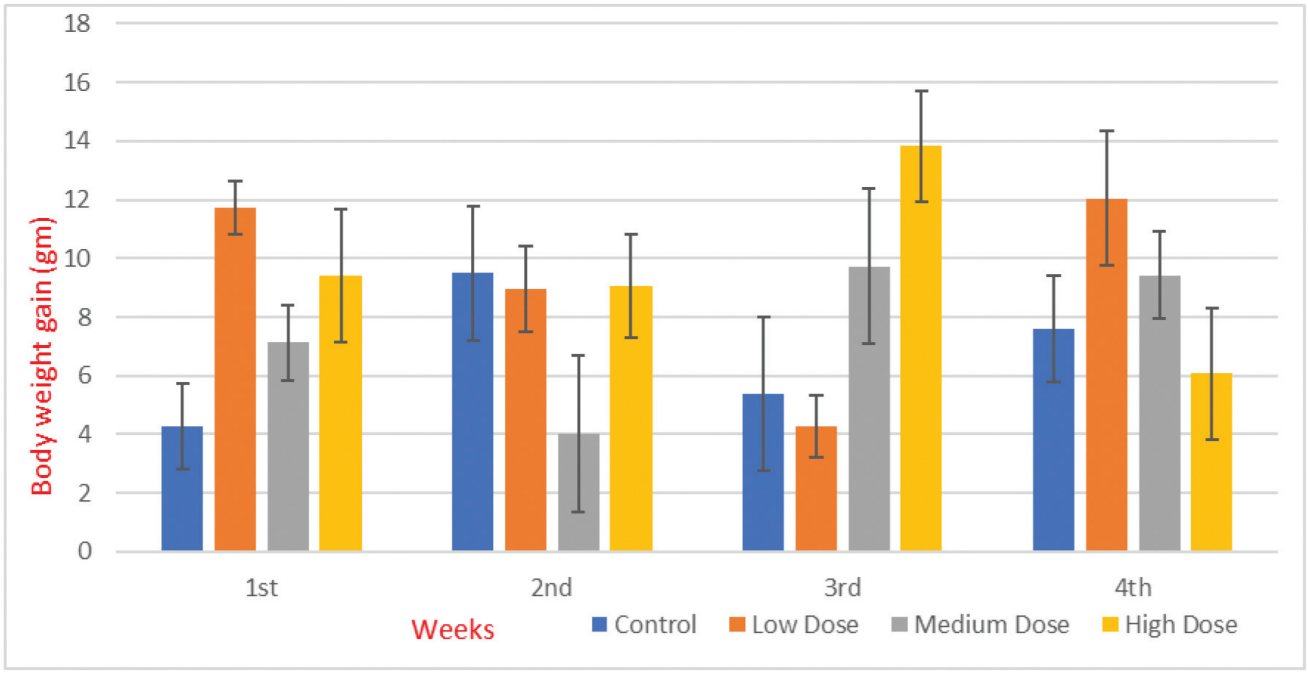


Fig. 4. Graph representing body weight gain in guinea pigs of different groups over the weeks.

formation was observed, after MABG-impregnated dressing was applied to the shaved skin of guinea pigs. Furthermore, significant toxicity or interference is frequently linked to nutrient absorption, as evidenced by reductions in body weight [27]. The animal's body weight gain did not differ significantly compared to the animals in the control group when the animals were treated with different doses of MABG-impregnated dressing (Table 2, Fig. 4). However, on day 7 and day 28, the body weight of group II (lowest dose) increased significantly compared to group I (control). Thus, it can be deduced that the MABGmscg dressing does not tend to cause significant tissue destruction nor does it impede nutrient absorption. Although no dermal toxicity study has been performed earlier on *in vivo* models, our findings were endorsed by several *in vitro* studies. Cytotoxicity studies performed on human osteoblast-like cell lines with various extracts of mesoporous bioactive glass nanoparticles (MBGNP) in Dulbecco's Modified Eagle Medium, did not exhibit any cytotoxicity towards MG-63 osteoblast-like cells [28]. In the assessment of cell viability of HDF cells in the presence of MBG and Ga-MBG extracts, it was observed that cell viability increased over time in culture, indicating that the bioactive glasses were non-toxic to HDF cells [29]. In cell viability analysis using Ta-MBGs on bovine fibroblasts using MTT assay, again no significant effect was observed on the proliferation of fibroblast due to the presence of Ta, which suggested that incorporation of up to 5 mol% Ta was allowed on MBGs composition for achieving safe and effective hemostasis [13]. A study evaluating the irritation potential of gelatine hyaluronic acid (gel-HA) and nano-bioactive glass also found that there were no systemic signs of toxicity observed when these substances were applied to intact animal skin [30].

CONCLUSION

Topical agents are utilized as a support measure during initial bleeding control, with the expectation that any absorption through the skin will be minimal and devoid of systemic side effects. As per our findings, neither skin irritation nor sensitization occurred in both rabbits or guinea pigs, therefore, it could be inferred that the use of MABGmscg dressing is safe for application as a topical hemostatic agent, however, further detailed acute and subacute dermal toxicity studies are warranted to confirm our findings.

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Cite this article as: Dattaray D, Roy P, Raja L, Chakraborty J, Mandal TK. Acute dermal irritation and skin sensitization study of mesoporous antibacterial bioactive glass microsphere impregnated surgical cotton gauze dressing material on rabbits and guinea pigs. Explor Anim Med Res. 2024; 14(1), DOI: 10.52635/eamr/14.1.68-75.