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Radio-decontamination efficacy and safety studies on optimized decontamination lotion formulation

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ABSTRACT

Objective of the present study was to optimize decontamination lotion and to evaluate its relative decontamination efficacy using three radio-isotopes (Technetium-99m, Iodine-131 and Thallium-201) as contaminants with varying length of contaminant exposure (0–1 h). Experiments were performed on Sprague Dawley rat's intact skin and human tissue equivalent models. Rat's hair was removed by using depilator after trimming with scissors. Relative decontamination efficacy of the optimized lotion was investigated and compared with water as control. Static counts were recorded before and after decontamination using single photon emission computed tomography (SPECT). Measured decontamination efficacy (DE) values were analyzed using one way ANOVA and Student's *t*-test (p value < 0.05) and were found statistically significant. Decontamination efficacy of the lotion was observed to be $90 \pm 5\%$, $80 \pm 2\%$ and $85 \pm 2\%$, for the ^{131}I, ^{201}Tl and ^{99m}Tc radio-contaminants respectively on skin. Reduced contaminant removal was recorded for the skin which was cleaned by depilator (50–60%). Skin decontamination was found more efficacious for rat skin decontamination than the human tissue equivalent model. Decontamination efficacy of the lotion against ^{99m}Tc was recorded $70 \pm 15\%$ at 0–1 h on the tissue equivalent model. In vitro chelation efficacy of the lotion was also established by using the instant thin layer chromatography-slica gel (ITLC-SG) and >95% of ^{99m}Tc was recorded. Neither erythema nor edema was scored in the primary skin irritancy test visually observed for two weeks.

1. Introduction

Exposure and contamination of the human skin by radioactive materials is an occupational risk. During radiation exposure, the skin being the most superficial organ of the body, receives highest radiation dose (Meineke et al., 2003; Rojavin et al., 2011). A consequence of the external contamination with radioactive materials is the possible entry into systemic circulation followed by internal uptake of the material by specific organs (Yehezkelli et al., 2002; William et al., 1991). The most frequently contaminated areas are the faces, hands, hair and outer clothing of the personnel handling radio-activity (Nishiyama et al., 1980; Cox, 1994; Schofield, 1971 and Yeung et al., 2002). The critical site of radiation resulting from the contamination is the stratum germinativum, where proliferative cells are located. The radiation dose reaching the basal cell layer of the epidermis is predominantly due to beta and gamma radiation (Bauerova et al., 2001; Koprda et al., 2000). Skin decontamination studies using radio-nuclides with shorter half-lives provide an opportunity to evaluate the efficacy of the commercially/optimized decontamination agents and their formulations (Moore and Mettler, 1980). An in vitro technique for the decontamination of the pluton and uranium were developed and studied using two decontamination agents e.g. (Na_3Ca)DTPA and EHBP (Tymen et al., 2000). Radionuclides contribution to the penetration across the skin using intact and stripped skin models has also been evaluated and analyzed for different layers of the skin (Bauerova et al., 2001).

The radio-nuclides decontamination/removal from the skin is an important task because longer time of deposition facilitates their internalization. Extent of hazard also depends on physical and chemical properties of the radio-nuclide (Bolzinger et al., 2010; Hamano et al., 1993; Inaba and Suzuki-Yashumoto, 1979; Kirk et al., 1994; Koenig et al., 2005). ^{131}I is major uranium, plutonium fission product; comprising nearly 3% of the total products of fission (by weight). It could severely damage body due to release of 10% gamma and 90% of beta radiation (Wagner et al., 1994; Harrison, 1963). An important step in medical management of contaminated victims involves skin decontamination by rinsing with tepid water and liquid soap. Application of decontamination agents could remove more than 90% of the skin contaminants if applied within

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few minutes of the contamination (Felton and Rozas, 1960; Henson, 1972; Moore and Mettler, 1980; Nishiyama et al., 1980; Schulte, 1966). A number of topical preparations/formulations are commercially available and have been evaluated for their relative efficiency (Gregory, 1953; Kamboj et al., 2012; Levitin et al., 2003; Petitot et al., 2007; Merrick et al., 1982; Kumar et al., 2010).

Present study was undertaken using ^{99m}Tc, ^{131}I and ^{201}Tl radio-isotopes. ^{99m}Tc is the most commonly used radio-nuclide with low gamma energy emission and short half life (6.020 h). ^{131}I and ^{201}Tl produce 606 keV and 135–167 keV of gamma energy and used as skin contaminants. Ethylene diamine tetraacetic acid (EDTA) is a powerful chelating agent (Sillanpaa and Sihvonen, 1997), forming stable complexes with most metal ions. Due to its ability to sequester metal ions, it is widely used for chelating a number of heavy metals and radio-isotopes (Narola et al., 2011; Katata et al., 2006). Formulations containing EDTA offers high compatibility and lower toxicity. Therefore, EDTA was selected as a chelating agent. It was aimed to develop a self-usable skin decontamination formulation to manage the accidental release of radio-contaminants. Objective of the present study was to optimize pharmaceutical parameters of decontamination lotion formulation and evaluate its DE and skin safety. Decontamination was performed with cotton swabs soaked in optimized lotion with five times consecutively. Decontamination was performed with different length of exposures to conclude the effect of time on efficacy of the decontamination lotion. Results of the lotion were analyzed and compared with water and placebo. Advanced quantitative medicine technique was used to record the residual contaminants.

2. Materials and methods

2.1. Materials

^{99m}Tc sodium pertechnetate and ^{131}I were obtained from Regional Centre for Radiopharmaceuticals, Board of Radiation and Isotope Technology (BRIT), Delhi, India. ^{201}Tl was obtained as a gift from the Nuclear Medicine Department of the All India Institute of the Medical Sciences (AIIMS), Delhi, India. Symbia True point SPECT-CT gamma camera, USA, was used for static counts and whole body imaging of the contaminated body surfaces.

Di-sodium edetate (Merck Ltd, Mumbai, India), sodium carboxymethyl cellulose (CDH Ltd., Mumbai, India), methyl paraben, propyl paraben (Titan Biotech Ltd., Rajasthan, India), triethalonamine (Fisher Scientific, Mumbai, India) and propylene glycol (CDH Ltd., Mumbai, India) were used other chemicals/reagents used were of analytical grade.

2.2. Methods

2.2.1. Experimental models

Decontamination efficacy studies of the lotion were performed on 2–3 months old healthy male Sprague Dawley rats (weighing 300 ± 20 g) and on human tissue equivalent model. Animals were allowed to acclimatize for one week before to start of the experiments in controlled environment (centrally air-conditioned with 100% fresh air replacement) at ambient temperature of $22 \pm 3\,^{\circ}$C with relative humidity of $50 \pm 10\%$, and 12 h light/dark cycle. Experimental protocols were approved by Institutional Animal Ethics committees (IAEC) vide no. INM/IEAC/2010/07/007.

2.2.2. Preparation of the lotion

For the preparation of lotion disodium EDTA was dissolved in water, methyl paraben sodium and propyl paraben sodium were added to it and stirred till it becomes clear. The solution was stirred further for 15 min. Sodium carboxy methyl cellulose was added to it with continuous stirring to avoid the formation of lumps. Propylene glycol was added and the volume was made up with purified water. Prepared formulation was filled in lacquered plastic containers and stored at room temperature for further evaluation.

2.2.3. Physical evaluation of the lotion formulation

2.2.3.1. pH. To determine pH 1.0 g lotion was accurately weighed and dispersed in 100 ml purified water. The pH of the dispersion was measured using digital pH meter, which was calibrated before use with standard buffer solution at 4.0, 7.0 and 9.0. The measurements of pH were done in triplicate and average values are calculated (Bozic et al., 1997).

2.2.3.2. Spreadability. To determine the spredability of formulation, 0.5 g of lotion was placed within a circle of 1 cm diameter pre-marked on a glass plate of $20\,\text{cm} \times 20\,\text{cm}$, over which a second glass plate was placed. A weight of 500 g was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due to lotion spreading was observed (Soares et al., 2005).

2.2.3.3. Extrudability. To determine extrudability a closed collapsible tube containing formulation was pressed firmly at the crimped end. When the cap was removed, formulation extruded until the pressure dissipated. Weight in grams required to extrude a 0.5 cm ribbon of the formulation in 10 s was determined. The average extrusion pressure in grams was reported.

2.2.3.4. Viscosity. The viscosity of the formulations was determined as such without dilution by R/S CPS Plus Rheometer (Brookfield Engineerring Laboratorie, Inc., Middleboro, MA, USA) using spindle #C 50-1 having diameter of 50 mm and RHEO3000 software.

2.2.4. Contamination of the experimental model

One day before commencement of the experiment hairs of the rats were clipped-off/depilated. Freshly prepared ^{99m}Tc (11.1 ± 0.185 MBq) was used for skin contamination. Since emitting energy of the ^{131}I and ^{201}Tl is higher these were selected at lower doses at 3.7 ± 0185 MBq only for all study. Radio-isotopes were mixed in appropriately 0.1 ml of saline and applied over thoraco-abdominal area and/or tissue equivalent model ($5\,\text{cm} \times 5\,\text{cm}$) patch using a syringe plunger. Contaminated surface was allowed to air dry. Lengths of exposure of the contaminants over the applied area were 0–1 h.

As per experimental protocol, animals were divided into 4 groups with 6 animals in each group.

Group I – Decontaminated with water.
Group II – Decontaminated with placebo.
Group III – Decontaminated with optimized formulation (0.5% of API).
Group IV – Decontaminated with optimized formulation (1.0% of API).

2.2.5. Decontamination protocol

Decontamination was performed by using cotton swabs (3 cm radius) soaked in 5 ml of the optimized lotion. Procedure was performed in encircle movement from the periphery of the contaminated area toward the center. Five consecutive decontamination attempts were performed. Each attempt was completed within 1 min. Before and after each decontamination attempt, static counts (kilo counts per seconds) and images were taken from gamma camera. Acquisition time for recording static counts and images were selected as 3 min. Camera parameters selected for the whole body imaging and static counts was at zoom level 2 with both detectors and 256×256 matrix sizes. Region-of-interest (ROI) software was used for count statistics.

Table 1
Common characteristics of the radio-contaminants used in the study.

S. no.	Isotopes	Mass	Energy	Half-life	Mode of decay
1	^{99m}Tc	98.91	140 keV	6.020 h	– to ^{99}Ru
2	^{131}I	131	606 keV	8 days	– to ^{131}Xe
3	^{201}Tl	201	135–167 keV	3 days	– to ^{201}Pb

2.2.6. In vitro chelation efficacy

In vitro chelation efficiency (quantitative chelation) of the disodium edetate in the lotion was evaluated by using instant thin layer chromatography-silica gel (Bonacucina et al., 2004). 100 mg of disodium edetate was labeled with dry 37 MBq of ^{99m}Tc (IAEA Report) and allowed to mix in the 10 ml of freshly prepared lotion. Another 10 ml of the freshly prepared lotion containing 100 mg of EDTA was allowed to mix with the 37 MBq of liquid ^{99m}Tc and incubated for 0.5 h. 20 μl of each sample was applied on the ITLC strip and placed into beakers containing 100% acetone as mobile phase. After 15 min strips were removed from the beaker and cut into two parts (40:60 ratios). Static counts were measured using gamma well-type counter (Capintec, USA). Labeling efficiency of the EDTA was calculated by using the formula given below:

In vitro chelation efficiency was calculated by using the formula.

$$\text{Efficacy} = \frac{B}{B+T} \times 100$$

where B is the bottom of the ITLC strip and T is the top of the ITLC strip.

2.2.7. Skin irritation/safety studies

Primary skin irritation test was conducted on Sprague Dawley rats in two groups ($n = 6$) to determine the potential of lotion to produce irritation after a single topical application. Hairs were removed 1 day before applying the test lotion. 5 ml of the lotion (with/without API) soaked in cotton were applied and covered with 5 cm × 5 cm 4-ply gauz pad. The pad and entire trunk of each animal were then wrapped with semi adhesive plaster tape to avoid dislocation of the pad. Animals after dosing were caged individually. After 24 h cotton with gauz pads were removed. Following exposure, dermal irritation e.g., erythema and edema were evaluated for 2 weeks using method of Draize et al. (1994). Temperature at the site of the application of the lotion was also measured with the infra red camera and was found with normal range.

2.2.8. Data analysis

2.2.8.1. Decontamination efficacy. The effectiveness of the decontamination was expressed as decontamination factor (DF). It is the ratio of contamination level of applied activity before decontamination to the contamination level after decontamination. Results analyzed by the counts remaining after each attempt of the decontamination.

$$\text{DF} = \frac{\text{contamination level of materials or component before decontamination}}{\text{contamination level measured immediately after decontamination}}$$

The percentage of contamination removed from the applied surface area was calculated by

$$\text{Percent contamination removed} = \left(1 - \frac{1}{\text{DF}}\right) \times 100.$$

DF for the ^{99m}Tc, ^{131}I and ^{201}Tl radio-isotopes was calculated 9–10 respectively at the fifth consecutive decontamination attempt.

2.2.9. Statistical analysis of the decontamination efficacy

Decontamination studies were performed in triplicates for each group. The mean for each data point was calculated from the three replicates and the error bars calculated from the standard deviations of the distributions. In each case, data are presented as mean ± standard deviation. Data were analyzed by one-way analysis of variance (ANOVA) with PASW statistics 18 software (USA). Results were found statistically significant and concluded at $p < 0.05$.

3. Results and discussion

3.1. Characterization of lotion

Pharmaceutical properties such as pH, spreadability, viscosity, extrudability of the formulations are very much critical to the successful development of the formulation. Optimized lotion was found to be clear liquid, transparent and uniform in consistency. pH value of the optimized lotion formulation ranged from 7.2 to 7.3 which are very close to skin pH. Spreadability of the formulation was 13.2–13.4 cm respectively. The extrudability of formulation was found to be 0.30 g which implies the ease of application of the lotion.

3.2. Decontamination efficacy

Efficacy of the optimized decontamination lotion was compared with water and placebo (without decontaminating agent). All the radio-nuclides studied differed in their half-life and emitting ionizing radiation energy (Table 1). They were decontaminated in order to calculate the efficacy with respect to the length of exposure. The results obtained were summated for each combination of contaminant and lotion, and the mean count remaining after each decontamination attempt was calculated. The striking result is that the first two decontamination attempts were able to decontaminate 85 ± 5% of the applied activity over 0.5 h while <5% of the applied activity was removed in the successive five attempts. Fig. 1(a–c) shows the decontamination of the ^{131}I radio-iodine, ^{201}Tl and ^{99m}Tc with lotion (0.5% EDTA) at 0.5 h length of exposure was highly effective. Chelating agents forms complexes with the radio-isotopes and facilitate to remove the contaminant. It shows that lotion could effectively chelate the radio-iodine and also could prevent entry into systemic circulation through cutaneous absorption. Decontamination delayed long after radio-nuclide exposure was potentially effective to remove the radio-iodine from skin surface. Fig. 2 shows the decontamination efficacy of lotion at 0.5 h length of exposure with ^{99m}Tc in both the studied models. Results clearly indicate that the decontamination attempt within 0.5 h of contamination could easily remove ~90% of the applied activity while over that it was reduced by 5–7% only. Decontamination lotion was found more efficacious (85–90%) for the rat skin than the human tissue equivalent model (80–82%). Radio-isotopes possess tendency to tightly bind to the skin protein or may move toward the hair follicles reduces its efficacy up to 85–88% at 1 h study. Figs. 1 and 2 demonstrates the quick reduction in percentage activity removed with the first and second decontamination attempt. This is presumably due mainly to the chelation reaction between loosely bound contaminant and the active ingredient of the lotion. These

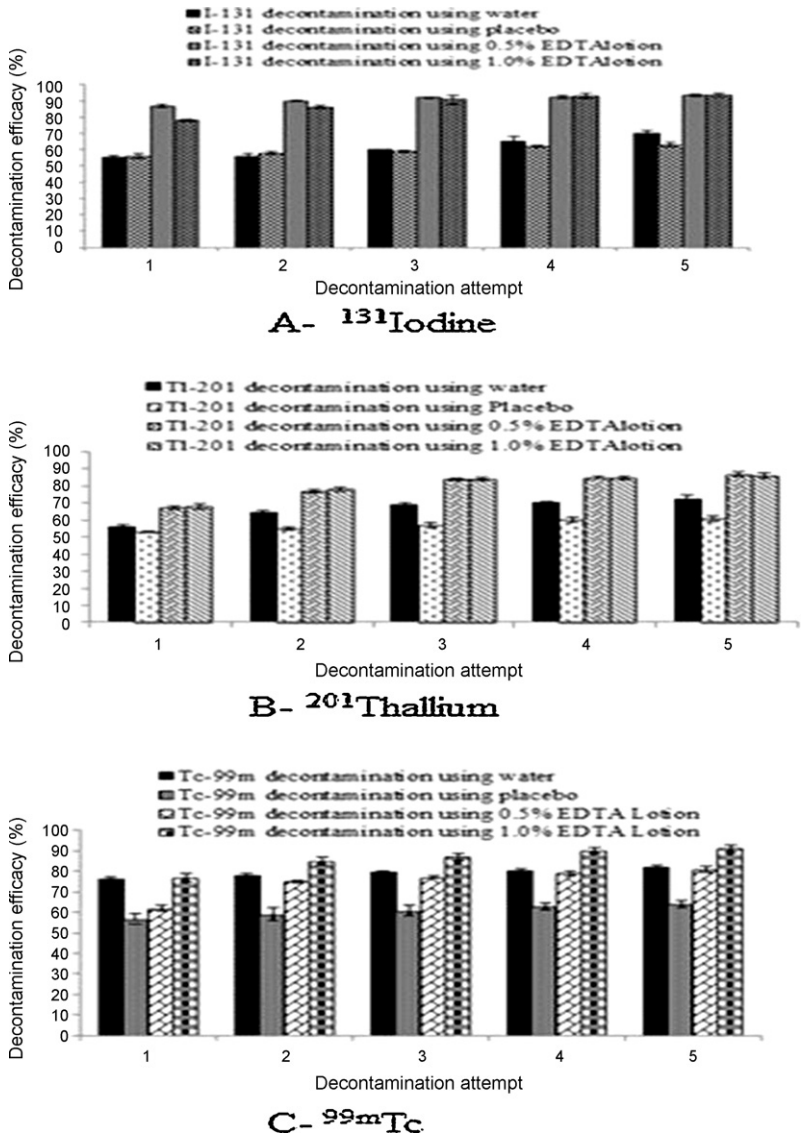

Fig. 1. Decontamination efficacy (%) of the lotion formulations containing 0, 0.5 and 1% EDTA against Iodine-131, Thallium-201 and Technetium-99m as radiological skin contaminants as compared with water.

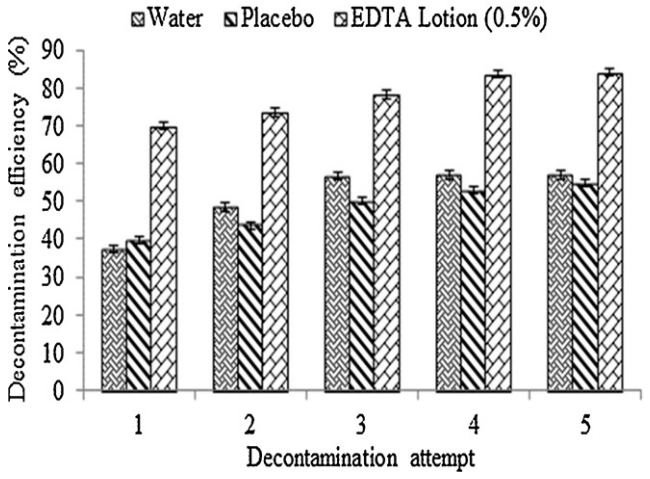

Fig. 2. Decontamination efficacy of the repeated decontamination attempts using water and lotion formulations containing 0 and 0.5% EDTA against ^{201}Tc as radiological skin contaminant.

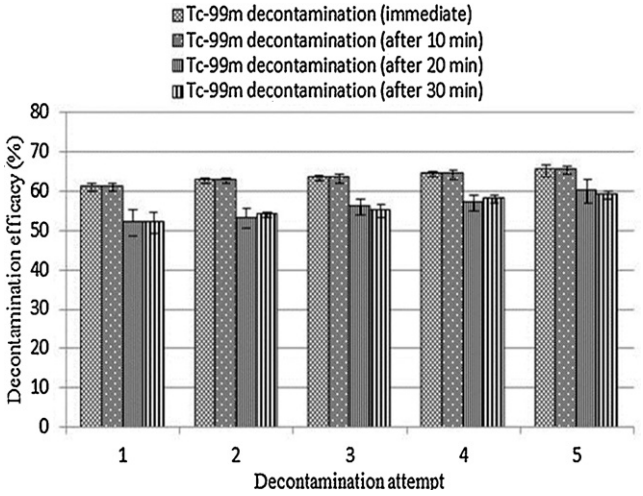

Fig. 3. Decontamination efficacy of the repeated decontamination attempts using water and lotion formulations containing 0 and 0.5% EDTA against ^{99m}Tc at different time points on rat skin (after applying depilator).

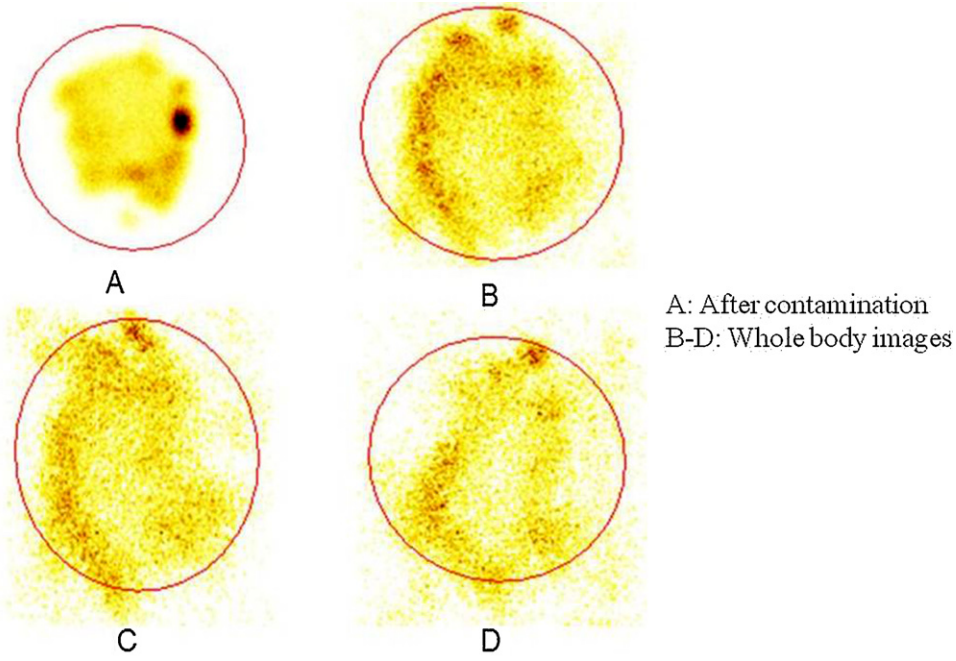

Fig. 4. Whole body images of the rat showing quick internalization of ^{99m}Tc within 0.5 h after contamination.

common factors in the entire first and second attempt were apparent to a much smaller degree in successive attempts. Thus it is in the third, fourth and fifth attempts that the truly comparative values of the decontamination attempts were assessed (Figs. 1 and 2).

Further analysis by calculation of the standard deviations of the means, and using these figures to compare the significance of the results shown in Figs. 1 and 2 is significantly better than 1 h length of the contaminant exposure. It could also be noticed that the contaminant residual values of the ^{131}I and ^{201}Tl have very little difference. Decontamination lotion with the 0.5% of the API was found most effective and there was a very little difference when compared to 1.0% of lotion. Fig. 3 shows the decontamination of the tissue equivalent which summarizes results of DE after applying depilating formulation at 0–0.5 h of contaminant exposure, was dramatically reduced to 50–60% only for ^{99m}Tc contaminant. After application of the depilator the outer dead skin cells (stratum corneum) and hair follicles root may also be exposed to facilitate the incorporation of the activity toward inner cell layers. Whole body images of the rat show quick internalization of the applied activity into the systemic circulation (Figs. 3 and 4).

In vitro chelation efficiency of the EDTA with ^{99m}Tc was found >95%. It indicates that disodium edetate could effectively chelate the dry radio-isotopes (>95%) while liquid activity was bounds to the EDTA was 40% only. It is also noticed that the potential physical and chemical interactions between active ingredient and excipients could affect the stability and efficacy of the formulation. Efficacy depends on active drug/excipient interactions, such as incompatibility, acid base reaction, and physical changes (Bharate et al., 2010). Skin decontamination studies using EDTA solution at 10% was performed and evaluated for ^{99m}Tc as skin contaminant. Ex vivo skin permeation study was performed using Franz cell chamber on rat skin and it was found <2% of the EDTA permeated over 24 h (ex vivo and in vivo).

3.3. Skin toxicity

Neither erythema nor edema was observed at any treated site during study. All animals survived, gained weight and appear active and healthy. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behavior. Skin patch where formulation was applied found to normal e.g., no erythema and edema.

4. Conclusion

The decontamination procedure with the use of soap and water removes most of the external contaminants. But the accidental release of a number of radio-isotopes in the environment could contaminate water also thereby limit its availability or sometimes it may be scarce. In view of this the self usable skin decontamination lotion formulation has been developed for immediate application after the release of the contaminant. Within 0.5 h of the contamination, application of the optimized lotion formulation could effectively remove >90% of the activity. No significant difference in the efficacy was found at 0–1 h. The optimized lotion was more efficacious for body surface than the surface decontamination of the human tissue equivalent. This work is a paradigm for the selection of the decontamination formulation based on chelation/complexion. This lotion formulation was found to be safe, effective and non-irritant.

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