Original Research Article

Skin decontamination cream for radiological contaminants: Formulation development and evaluation

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Abstract

Background: Increased use of the radioactive materials in the field of research, medical, nuclear power plant, and industry has increased the risk of accidental exposure. Intentional use of the radioisotopes by terrorist organizations could cause exposure/contamination of a number of the population. In view of the accidental contamination, there is a need to develop self-usable decontamination formulations that could be used immediately after contamination is suspected. **Materials and Methods:** Present work was planned to optimize and develop self-usable radiation decontamination cream formulation. Various pharmaceutical parameters were characterized. ^{99m}Tc- sodium pertechnetate was used as radiocontaminant. Static counts were recorded before and after decontamination using single photon emission computed tomography. **Results:** Decontamination efficacy of the cream was found to be 42% ± 3% at 0-0.5 h after the exposure. Primary skin irritancy test was satisfactory as no erythema or edema was observed visually after 2 weeks of the formulation application. **Conclusion:** The decontamination studies proved the potential of EDTA to remove the radiological contaminants effectively.

Key words: Cream, decontamination, decontamination factor, efficiency, radio-isotope

INTRODUCTION

Unintentional exposure to whole body radiation has become a serious threat in recent years owing to exposure of workers in atomic reactors, following a mishap or spillage from radiation facilities.[1-4] Exposure to radionuclide scattered by a radiological dispersion device or deposited as fallout after a nuclear power plant accident or detonation of an improvised nuclear device could result in contamination of a significant number of individuals.[5] External contamination occurs as a consequence of exposure to radioactive dust or other radioactive materials. Internal contamination is uptake of radioactive material in the body through intact/broken skin, inhalation (deposition of contaminant in respiratory tract and lungs by inhalation of resuspended material), or ingestion of radioactive materials transferred from contaminated hands. Internalized radionuclides may cause both acute and chronic radiation injury and increase an individual's risk of developing cancer.[6-8] This damage and risk can be mitigated by the use of decorporation agents that reduce internal contamination.

Decontamination is the safe removal of hazardous substances from areas, where it is not wanted.[9] The basic principles of decontamination include removal, elimination of spread, decay (if applicable), and effecting necessary process of decontamination in case where time and necessity dictates that there is no alternative.

Decontamination must be done quickly as the contaminant may be absorbed through the skin, where it can cause internal damage. Decontamination methods for radiological incidents primarily include washing with water, concentrated surfactants or acids, applying abrasives or duct tape, and steam cleaning. Personnel decontamination methods differ from those used for materials primarily because of the possibilities of injury to the subject. Washing with water can remove a significant percentage of contaminant, if it is done within first few minutes of detection. The remaining contaminant requires specific decontamination strategies. However, it requires a lot of water, and the treatment and safe disposal of contaminated water is another issue.[10-13]

Different methods have been used for skin decontamination and number of topical preparations/formulations have been

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developed and evaluated for their relative efficiency for removing radioactive contamination.[14,15]

Merrick *et al.*,[16] compared four different methods for the removal of radioactive contaminants ($^{99m}Tc^{m}$ pertechnetate, ^{23}I, and ^{51}Cr) from skin. They used soap and water, liquid detergent, detergent foam, and dermabrasive: a mildly abrasive skin cleanser. The findings suggested that dermabrasive is the preferred agent for the removal of contamination from skin, as it was equally effective at removing both fixed and unfixed contaminants. Similarly, Gregory[17] compared 10 cleansing agents for removing radioactive contamination from workers' hands and found that Windsor soap and a mixture of equal parts of soap powder and wood flour to be the two most effective agents for cleansing the hands of contamination with substances containing uranium and radium. The aim of present study is to develop self-usable decontamination formulations for topical radiological contaminants. The formulations should be such that they minimize formulation runoff and maintain required wet contact time between the detected agent and the formulation. The formulation should have low or no toxicity, nonirritant to the skin, high effectiveness, with lowest possible cost.

MATERIALS AND METHODS

Materials

^{99m}Tc-sodium pertechnetate was obtained from Regional Centre for Radiopharmaceuticals, Board of Radiation and Isotope Technology, New Delhi, India. Disodium ethylenediaminetetraacetate (EDTA) was purchased from Merck (Merck Specialties Pvt. Ltd., Mumbai, Maharashtra, India), Stearic acid and Paraffin liquid from Qualikems (Qualikems Fine Chem Pvt Ltd, Vadodra, India), Triethanolamine from Thomas Baker (Thomas Baker (Chemicals) Pvt. Ltd., Mumbai, Maharashtra, India), methyl paraben sodium and propyl paraben sodium were purchased from Titan Biotech Ltd. (Rajasthan, India). Other chemicals/reagents used were of analytical grade.

Preparation of cream

For the preparation of cream, disodium EDTA was dissolved in water, methyl paraben sodium and propyl paraben sodium were added to it and stirred till it became clear. Triethanolamine was added to it and the solution was stirred for 15 min. This constitutes the aqueous phase. Hard paraffin, soft paraffin, cetosteryl alcohol, and stearic acid were melted in a china dish on a water bath at a temperature of not more than 60°C and liquid paraffin added when the temperature was around 60°C. Both the aqueous and oily phases were heated to a temperature of around 60°C and oily phase was added to aqueous phase with continuous stirring. Gentle stirring was continued till a smooth cream was obtained. Table 1 gives the composition of different formulations with formulation codes.

Evaluation of cream

The formulations were evaluated for the following parameters.

Drug content

The drug content in the formulations was determined as reported by Kamboj *et al.*,[18] 5 g of topical cream was dissolved in distilled water using mechanical stirrer (Remi, Mumbai, India). The sample was sonicated (US – 250 W, Altrasonics, Mumbai, India) for 3 min and filtered through Whatman filter (Whatman International Ltd, Maidstone, England). Aliquot (1 mL) of the prepared solution equivalent to 1.25 mg of disodium edetate was taken and mixed with 1 mL of ferric chloride solution (500 μg/mL) and suitably diluted with 0.1 N HCL media to get a concentration of about 25 μg/mL and the samples were analyzed spectrophotmetrically at 270 nm.[18]

pH

1.0 g cream 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 were calculated.[19]

Spreadability

One of the criteria for a topical formulation to meet the ideal qualities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which formulation readily spreads on application to the skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability was determined by placing 0.5 g of cream within a circle of 1 cm diameter pre-marked on a glass plate of 20 × 20 cm, over which a second glass plate was placed. A weight of 500 g was allowed to rest on the upper glass plate for

Table 1: Composition of formulation

Ingredients	Composition (w/w)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Disodium EDTA	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Soft paraffin	10	10	10	12	12	12	12	12	12
Hard paraffin	-	-	15	15	25	25	25	25	25
Liquid paraffin	5	5	5	4	3.5	3.5	3.5	3.5	3.5
Cetosteryl alcohol	5	5	5	5	5	5	5	5	5
Stearic acid	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Triethanolamine (mL)	-	-	-	-	-	1	2	3	3.5
Methyl paraben sodium	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Propyl paraben sodium	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Purified water	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100

EDTA: Ethylenediaminetetraacetate

5 min. The increase in the diameter due to cream spreading was noted, which gives the spreadability of formulation.[20,21]

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 gram was reported.[22]

Viscosity

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

Homogeneity

The developed formulations were tested for any sign of phase separation and for homogeneity by visual inspection after the cream had been filled in the container. They were tested for their appearance and presence of any aggregates.

Stability testing

The selected formulations were subjected to a stability testing for 3 months as per ICH norms at a temperature of 40°C ± 2 °C. The formulations were analyzed for the change in appearance, pH, or drug content by procedure stated earlier.

Decontamination efficacy studies of the skin decontamination formulations

The prepared formulations were tested for their skin decontamination efficacy. Experimental protocols were approved by Institutional Ethics Animal Committee, Institute of Nuclear Medicine and Allied Sciences, New Delhi. Three groups of Sprague-Dawley rats were used for the studies. Thracoabdominal areas (5×5 cm^2) of the rats were shaved before 24 h using scissor. On the day of experiment, animals were externally contaminated with ^{99m}Tc-sodium pertechnetate (200 μCi/0.2 mL saline) with equal dose. The contaminated skin surface was allowed to air dry after that scintigraphic image and counts (static, 180 s) were taken by placing rats under the gamma camera [Figure 1]. Respective formulations were applied at four different time points after application of contaminant viz., 0, 10, 20, and 30 min and static counts and images [Figure 2] were taken before (prewash counts) and after wiping (postwash counts). For decontamination, standard size cotton swabs (3×2 cm^2) soaked with the formulation was used. The procedure used for applying the formulation was from periphery toward the center in a circular motion. The formulation was applied 180 s so that maximum contaminant could be removed.

The decontamination factor (DF) was calculated as given by the formula:

$$DF = \frac{\text{Contamination level of material before decontamination application}}{\text{Contamination level measured immediately after decontamination application}}$$

Efficacy is the percentage of contaminant removed by the formulation and is given by the formula:

Efficacy (%) =1-1/Decontamination factor × 100

Skin irritation

The studies were conducted on Sprague-Dawley rats. All animals were caged individually. Formulation with or without decontamination agent soaked in cotton was applied on animals and secured firmly in place with adhesive plaster. After 24 h, cotton was removed and animals were observed 7 days for body weight, any sign of erythema and edema.[23,24]

RESULTS AND DISCUSSION

The pH of the formulation was determined in triplicate and average values were calculated. The pH was found to be 6.8 ± 0.53 for EDTA cream, which was very near to the neutral pH, thus the formulation can be used without the risk of irritancy to the skin. This also indicated that the selected ingredients of the formulation did not alter the pH of the formulation [Table 2].

The spreadability of formulations was found to decrease by increasing the concentration of hard paraffin and reducing the concentration of liquid paraffin. The spreadability of the different formulation was found to vary from 9.0 ± 0.4 to 6.5 ± 0.3 cm as the concentration of hard paraffin was increased from 15% to 25%. Although the increase in concentration of hard paraffin decrease the spreadability of the cream, incorporation of hard paraffin is necessary as it imparts proper consistency to the cream. Formulation F2 that is devoid of hard paraffin had a consistency that is more inclined toward the lotion rather than the cream. The values of spreadability indicate that the cream was easily spreadable by small amount of shear. Extrudability is an important parameter for evaluating cream formulation. The extrudability of formulations corresponds to the force

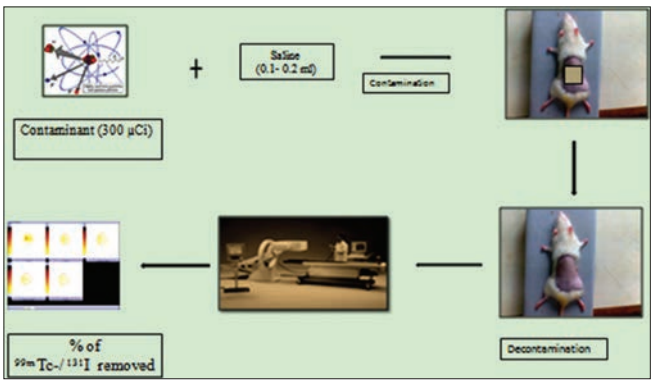

Figure 1: Procedure for efficacy evaluation of formulations

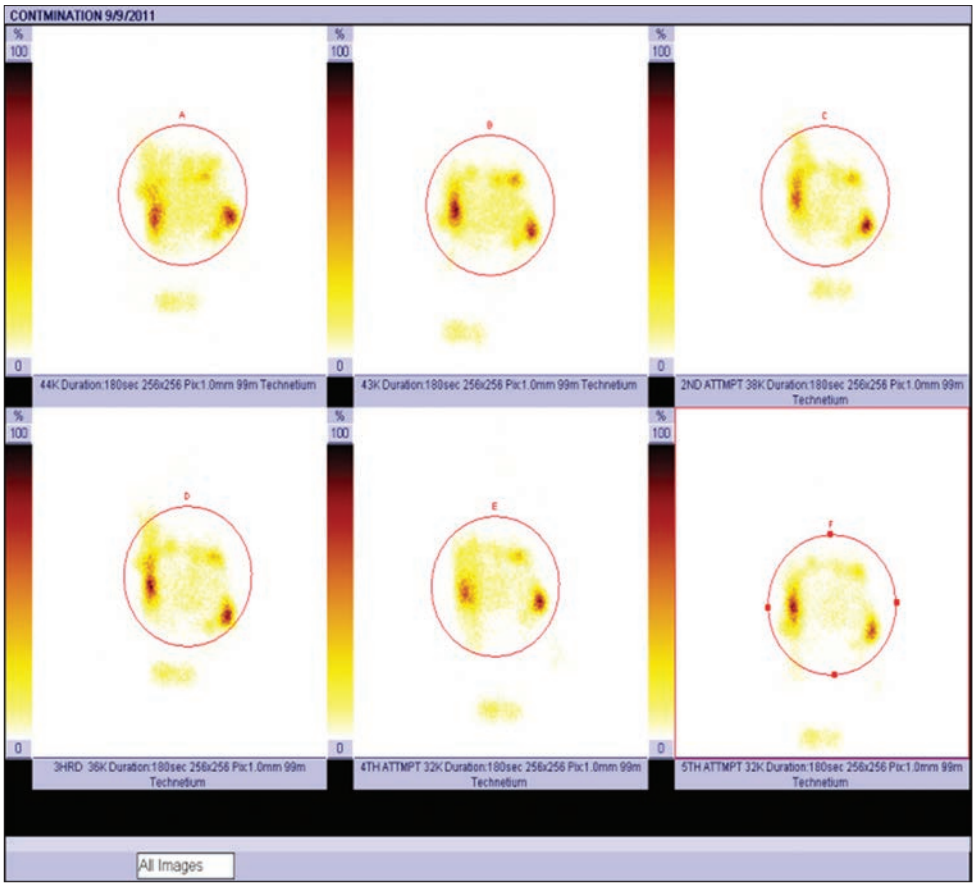

Figure 2: Scintigraphic images of decontamination attempts

Table 2: Evaluation of formulation

Formulation	Drug content (%)	pH	Spreadability (cm)	Extrudability (gram)	Appearance	Viscosity (*P*)
F1	**Cream cracked due to improper stirring, could not be evaluated**					
F2	93.5±2.3	6.9±0.67	11.3±0.19	63±5	Good	165±4
F3	96.0±1.9	6.8±0.48	9.3±0.2	69±3	Average	185±3
F4	97.5±1.3	6.9±0.43	8.9±0.2	73±3	Good	190±4
F5	98.0±1.8	6.8±0.68	6.5±0.5	107±5	Average	220±5
F6	98.5±1.4	7.1±0.39	6.7±0.2	110±3	Good	228±6
F7	98.3±1.6	6.9±0.35	6.8±0.2	120±3	Good	220±4
F8	96.5±0.7	6.8±0.53	6.5±0.2	115±5	Good	235±3
F9	97.7±1.3	7.1±0.79	6.6±0.15	118±3	Average	230±3

that is required to remove the formulation from the tube. In case of emergency, the victim is not in a position to press the container/tube due to pain. If the extrudability is more, it requires application of high force to remove the formulation for application. The extrudability was found to be 115 g for formulation F8. The results of spreadability and extrudability indicated that the formulation could be applied easily without being runoff. This assures that the formulation maintains a good contact time with the detected agent, which is necessary for the decontamination as EDTA forms chelates and decontaminates the agent. The viscosity of formulation increases as the amount of soft paraffin was reduced and hard paraffin increased. The viscosity of formulations was found to be 235 *P* and 230 *P* for formulations F8 and F9, respectively.

During the stability studies, the homogeneity was uniform and no significant variation in pH was observed [Table 3]. Considering the accelerated stability studies and physiochemical parameters, batch F8 was selected for skin decontamination studies.

Decontamination efficiency

The study was aimed to evaluate the decontamination efficiency of the formulated cream. ^{99m}Tc with a short half-life (6.020 h) and low gamma energy emission is the most commonly used radionuclide. From the decontamination studies, it was found that the cream could remove about 42% ±3% of the contaminant, if applied immediately [Figure 3]. Delayed application of cream by 10, 20, and 30 min was also evaluated considering the fact that a lag time period is there before the emergency response team

Table 3: Accelerated stability of optimized formulation

Formulation code	Months	pH (±SD)	Drug content %
F7	0	6.9 (±0.35)	98.3±1.6
	1	6.9 (±0.88)	98.0±1.8
	2	6.7 (±0.75)	98.2±2.6
	3	6.8 (±0.36)	97.4±2.2
F8	0	6.8 (±0.53)	96.5±0.7
	1	6.8 (±1.20)	96.1±1.1
	2	6.7 (±0.98)	96.3±1.0
	3	6.8 (±0.96)	95.9±0.9
F9	0	7.1 (±0.79)	97.7±1.3
	1	6.9 (±0.84)	96.9±1.6
	2	6.9 (±0.36)	96.5±1.4
	3	6.8 (±0.88)	96.7±0.9

SD: Standard deviation

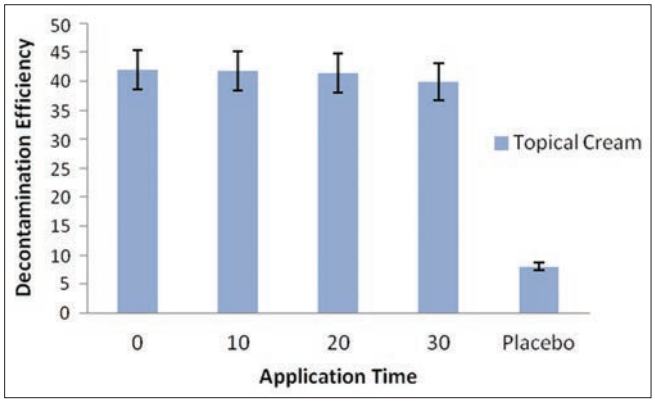

Figure 3: Decontamination efficiency of the optimized cream

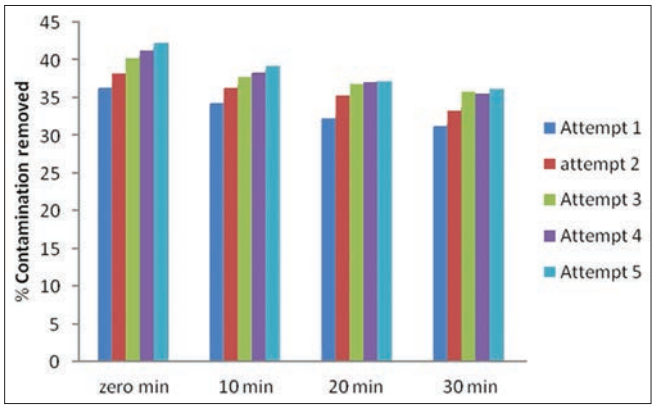

Figure 4: Percentage (%) of contamination removed at different decontamination attempt

to reach and provide first aid. The delay in application by 0.5 h reduces the efficiency of formulation to 36% ± 3%. Applying the formulation after 10 and 20 min could remove about 39% ± 3% and 37% ±3% of the contaminant, while the placebo could remove only 09% ±3% of applied contaminant. The decrease in efficacy of the cream with time may be due to internalization of the contaminant and possible covalent bonding with skin tissues proteins. Since single application was not enough to remove the contaminant, different decontamination attempts were performed. It was observed that the first two attempts were able to remove most of the contaminant [Figure 4]. In subsequent attempts, the amount of contamination removed was reduced significantly. In the 4th and 5th attempts, there was not much difference in the efficiency of cream.

The skin irritancy studies indicated that the cream is safe to apply. There were no signs of gross toxicity, adverse pharmacologic effects, or abdominal behavior. No sign of erythema and edema was observed on the skin patch, where formulation was applied and the patches were found to be normal.

CONCLUSION

It has been observed that optimized batch produces the cream with good consistency, homogeneity, spreadabiltity, and stability. Since, the cream is water washable it has wider prospects to be used as a topical drug delivery system for decontamination of skin. The decontamination studies prove the potential of EDTA to remove the radiological contaminants, effectively. The low efficiency of cream could be increased by incorporating a higher concentration of active agent and requires further studies. The work is an initiative in the direction to explore the potential of EDTA-based formulation for radiological decontamination.

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