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Skin irritation study due to Electron beam cured Polyurethane based Pressure sensitive Adhesive tape in *Oryctolagus cuniculus*

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Abstract

Pressure sensitive adhesives (PSAs) have an important role in health care industry and are used in a range of medical applications from low tack PSA tapes to high tack implant adhesives. Biocompatibility of such medical devices is an urgent requirement of many agencies since, used on human body. Therefore, the materials that come in contact must be evaluated and determined to be safe for use, which may leach off of a device into adjacent tissue. Some leachables are not biologically safe and can harm the body after or during application. The study helps to determine whether materials that causes adverse effects, has immense importance before commercialization of product. In the present study an attempt has been made to assess skin irritation of a microporous PSA tape made of polyurethane (PU) acrylate by electron beam (e-beam) irradiation process. The results of the study may help in predicting the irritation potential of the test item in humans or higher mammals.

Keywords: Polyurethane, pressure sensitive adhesive tape, electron beam, biocompatibility and skin irritation.

Introduction

PSA tapes and drapes have been used for more than half a century for different of bio-medical applications such as marking, holding, protecting, sealing and masking purposes[1]. The PSA tapes to be used in medical applications should have the characteristics e.g. high level of water absorption and permeation capacities (moisture vapor transmission rate, MVTR); good peel and adhesive strength; quick initial tack; high wet strength; oil/chemical resistance; conformability to body shape and biocompatible to skin.

The early PSAs were based on natural or synthetic rubber compositions compounded with low molecular weight ingredients such as wood rosin derivatives, turpentine and heavily pigmented with zinc oxide. These adhesives serve the desired purpose but they suffer from several drawbacks i.e. hydrophobic and unable to absorb water resulting in the entrapment of water under the covered area causing skin maceration or other skin damage. Low molecular weight ingredients such as plasticizers, stabilizers, etc. present in these adhesives often penetrate into the skin causing irritation or sensitization[2,3].

Later, polyacrylate PSAs replaced rubber based adhesives, as they exhibited better self-adhesive property and did not contain the potentially allergenic modifying agents. However polyacrylate based PSAs also suffer from certain demerits i.e. often contain unreacted residual acrylic monomer as an impurity, which would irritate or sensitize skin. Although they are better in permeability towards moisture or water vapor (MVTR) than rubber-based adhesives, but are not able to absorb significant amount of moisture or water. Therefore, when used for long duration on skin or for wound care applications, they loose their adhesive property besides causing damage to the skin[3].

Hydrocolloid adhesives are more recent and found acceptable for different biomedical applications. This new class of adhesives consists of the blends of two basic components with different but complimentary characteristics; one, water soluble or swellable and the other, of tacky nature. The water swellable component is the hydrocolloid gum while the tacky viscous polymeric materials are polyisobutylene or blends of polyisobutylenes and butyl rubber. The water absorbent gum helps in absorbing transepidermal water loss or other body fluids, including wound exudates. The tacky polymeric material is used to hold devices and wound dressings; maintaining the devices on skin for several days without skin damage. However, these PSAs also suffer from the following limitations i.e. lacking quick initial tack; tend to disintegrate upon excessive water absorption and presence of residual monomer of tacky component may lead to skin sensitization[3].

Keeping above drawbacks from different systems, the latest trend in PSAs for bio-medical applications suggests that PU based PSAs would be the preferred material in future offering unique properties, not found in other adhesives i.e. good absorption capacity of water or other biological fluids; very high bond durability; adherence to a different variety of substrates; nature to perform in a large temperature range; chemical and solvent resistance and variety of options as per usage.

It has been reported that PU-based adhesives gain strength only when cured at elevated temperature by conventional thermal methods in the presence of an initiator or additives. However, such processing techniques have many disadvantages viz. evaporation of chemicals in working area; time consuming; lack of proper curing; high toxicity of developed products due to residual monomer etc[4].

In order to ensure that the curing and crosslinking is done without any adverse effects on the environment, instead of using thermal process, irradiation stands as the better option. Irradiation of PU systems can be carried out by one of the techniques: UV, e-beam, γ-radiation etc.

The e-beam process has many remarkable advantages over the other curing process e.g. a clean and environment friendly process; better control on curing characteristics; uniform and consistent product; cold process, does not use heat and toxic initiators for gaining strength of the adhesive bond; no or minimum possible residual monomer and high throughput. At the same time, product treated with e-beam technology has remarkable characteristics e.g. free of harmful substances (sterilization of product); color-stable; resistant to organic solvents: resistant to a wide range of chemicals[1, 5-7].

When PU-based PSAs are targeted to be used for the bio-medical applications, their development work is considered complete only when they are certified as biocompatible, thus the biocompatibility of the developed compositions is must before the product can be allowed for biomedical applications.

Biocompatibility is the ability of a material to perform with an appropriate host response which means no adverse impact on the body in a specific application. For the various biomedical applications, especially delicate parts of the human body that come in contact directly with the device used, it has become essential that such devices are insured to be biocompatible[8].

Among the biocompatibility tests, skin irritation is one of the most important study can be defined as notable changes in the living beings, generally the immunochemical system, by exposure to a substances such that further exposure leads to recognition by the living organisms, lead to a response that is marked by a reaction at lower doses than what would be observed in non-irritated organisms[9,10]. There are a variety of parameters that confirm whether a chemical can cause irritation or can be a contact irritant including the ability to penetrate into the skin, where it reacts with protein and be identified as antigenic by immune system[11].

Hence, present study was conducted to classify PU based PSA according to primary skin irritation effects on *Oryctolagus cuniculus* and also to evaluate local irritant effects so that development and research can proceed without undue hazard to personnel.

Material and Methods

Materials: Genomer 4269 an aliphatic urethane polyester acrylate in combination with 2-[{(butylamino) carbonyl} oxy]ethyl ester and 2-propenoic acid was procured from Rahn USA Corp., USA. It has a T_g of -15 ^{0}C, viscosity 21 Pa.s and density 1.1g/ml and water solubility <1g/ltr, used as base resin. Genomer 6043, an inert modified saturated polyester resin with a combination of 2-[{(butylamino) carbonyl} oxy] ethyl ester and 2-propenoic acid having T_g of -18 ^{0}C, flash point >100^{0}C, viscosity 19 Pa.s, density 1.13g/ml and water solubility <1g/ltr was procured from Rahn USA Corp., USA and used as tackifier. Isophorone di-isocynate (IPDI), molar mass 222.3 g/mol, density 1.06 g/cc, M.P -60 ^{0}C, B.P 158 ^{0}C, flash point 155 ^{0}C, was procured from Sigma-Aldrich, USA and used as crosslinker. Fumed silica (Cab-O-Sil) with particle size 5-50 nm, surface area 5-600 m^2/g was procured from Cabot, USA and used as thickener. All these materials were used as such without further purification in the adhesive formulations.

Preparation of PSA tape: PU-PSA composition was made using combination of tackifier and crosslinker with the base resin. In order to evaluate the PSA for its performance, a PSA tape was made by coating 0.2 mm thick and 30 g/m^2 adhesive layer on a release paper and left for air drying at room temperature for 30 minutes. The adhesive layer thus formed was ultimately transferred to the non-woven polypropylene fabric to make the PSA tape. The thickness of non-woven fabric was 0.32 mm while its weight was 90 g/m^2.

Curing of PSA tape: The dried tape samples were irradiated in air at Bhabha Atomic Research Centre, Mumbai, India, by an e-beam accelerator ILU-6. The accelerator has 2.0 MeV energy level with a conveyor speed of 3cm/sec for 10 kGy/pass and 6cm/sec for 5kGy/pass, with a pulse current of 300mA, average current 2mA and pulse frequency of 15Hz. The samples were irradiated at different doses starting from 5 kGy to 60 kGy and 25 kGy was optimized as optimum dose. The irradiated samples were further kept in vacuum oven at 50^{0}C for 1 h to avoid any kind of entrapment before packaging. Hence, developed e-beam cured PU-PSA tape is now ready of study, has certain characteristics listed in table-1.

Table-1
Characteristics of e-beam cured PU-PSA tape

Color	Physical appearance	pH	MVTR (g/h-m^2)	Peel Adhesion (N/m^2)	Shear Adhesion (N/m^2)	Initial Tack (N/m)	Shrinkage (%)
White	Solid (tape)	7.0	92±1.22	2440 ±31.72	13205 ±171.67	23 ±0.30	2.05±0.27

Study design for irritation test: Three males, young adult, New Zealand White, 2-3 Kg body weight Oryctolagus cuniculus randomly selected as a test system with topical route of administration due to a suitable model for assessing the skin irritation potential. Each rabbit cage was attached with a tag marked with the experimental details. All the animals were housed individually in metal cages with perforated floors. The room temperature was maintained at 20 ± 3 °C with 50-60 % relative humidity. The light conditions were controlled to give 12 h artificial light (8 a.m.-8 p.m.) each day. Animals were acclimatized for 7 days before the commencement of the study. Water and standard pelleted feed were freely available to the experimental animals. There were no known contaminants in the feed and water at the levels that would have interfered with experimental results obtained. 24 h before the test, the hair on the back and flanks of each rabbit were closely clipped. Animals without any blemishes on the skin were selected for the test.

Hence, this study is to evaluate the dermal irritation potential of e-beam curable PSA tape for different medical application in Oryctolagus cuniculus as per specification[12-15]. 2.5x2.5 cm^2 of the PSA tape was applied evenly on the clipped area of skin of all the three male albino rabbits and covered with gauze patch, which was kept in contact with skin by means of semi-occlusive dressing. At the termination of 24 h exposure period, the bandages/ gauze were removed and treatment sites were cleaned with wet cotton to remove any residual material.

Exposure of e-beam cured PU-PSA tape was also examined on the certain important organs of same animals. For this organ collection and slide preparation of transverse sections was done under the laboratory conditions. Prepared slides were observed for any change from the control system under polarizing microscope NIKON ECLIPSE E200 POL with the optical system CFI60 infinity optics, magnification 500X, 3600 rotary dial analyzer, 2µm course/fine focusing and 6V/20W halogen lamp illumination.

Results and Discussion

In the study, PSA tape was applied on the clipped area of skin of albino rabbits and was covered with gauze patch, which was held in contact with a semi-occlusive dressing for an exposure period of 24 h, the patch was removed and exposed area was cleaned with wet gauze patch. After exposure period, degree of irritation was observed and scored at 24 h, 48 h and 72 h after patch removal. Skin reaction at the site of application was subjectively assessed and scored after the patch removal at 24 h, 48 h and 72 h (post treatment) according to numerical system[16]. The irritation score was compared to the categories of irritation responses and reported accordingly. The combined score for erythema and oedema was calculated on the basis of table-2 and table-3 and the results are summarized in table-4.

In the study, only 24 h, 48 h and 72 h single exposure test observations were used for estimating the primary irritation index (PII). Observations made prior to dosing or after 72 h to monitor recovery were not used in the determination.

Table-2
Scoring system for skin reaction

Skin reaction	Score
Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	***4***
Oedema Formation	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well raised)	2
Moderate oedema (raised approx.1mm)	3
Severe oedema (raised more than 1mm and extending beyond area of exposure)	4
Maximal possible score for irritation	**8**
Other adverse changes at the skin sites shall be recorded and reported.	

Table-3
Primary or cumulative irritation index categories in a rabbit

Response category	Mean score
Negligible	0 to 0.4
Slight	0.5 to 1.9
Moderate	2 to 4.9
Severe	5 to 8

Table-4
Evaluation of reactions for PU-PSA tape

Skin responses	Time (h)	Score		
		Rabbit 1	Rabbit 2	Rabbit 3
Erythema	24	0	0	0
	48	0	1	0
	72	1	0	0
Oedema	24	0	0	0
	48	0	0	0
	72	0	0	0
PII		1/6 = 0.17	1/6 = 0.17	0/6 = 0
Average PII = 0.17 + 0.17 + 0.0 /3 = 0.11				

After 72 h grading, all erythema plus oedema grades at different time intervals (24 h, 48 h and 72 h) were totalled separately for each test sample and blank for each animal. The primary irritation score for an animal is calculated by dividing the sum of all the scores by 6 (two test/observation sites, three time points). In case of blank, calculated the primary irritation score for the controls and subtracted that score from the score using the test material to obtain the primary irritation score.

To obtain the PII for PU-PSA tape added all the primary irritation scores of the individual animals and divided by the total number of animals. This value is the cumulative irritation index. The categories of cumulative irritation index are based on the data relating the PII for chemicals in rabbits to the primary irritation response in humans for a number of chemicals that have been tested on both species. The cumulative irritation index was compared with the categories of irritation response (table-3) and the appropriate response category was recorded for the study (table-4).

From table-4, as combined skin irritation scores of erythema and oedema came out as 0.11 at 24 h, 48 h and 72 h after the patch removal. Hence, the test item was found to be negligible irritant to the skin of rabbit**.**

The observations reported from figure-1a to 1k of control system and figure-2a to 2k having exposure of e-beam cured PU-PSA tape (test system), it was found that there were no any significant pathological or clinical change when compared with control system. This supports that above PU-PSA tape has no any effect on important organs of *Oryctolagus cuniculus.*

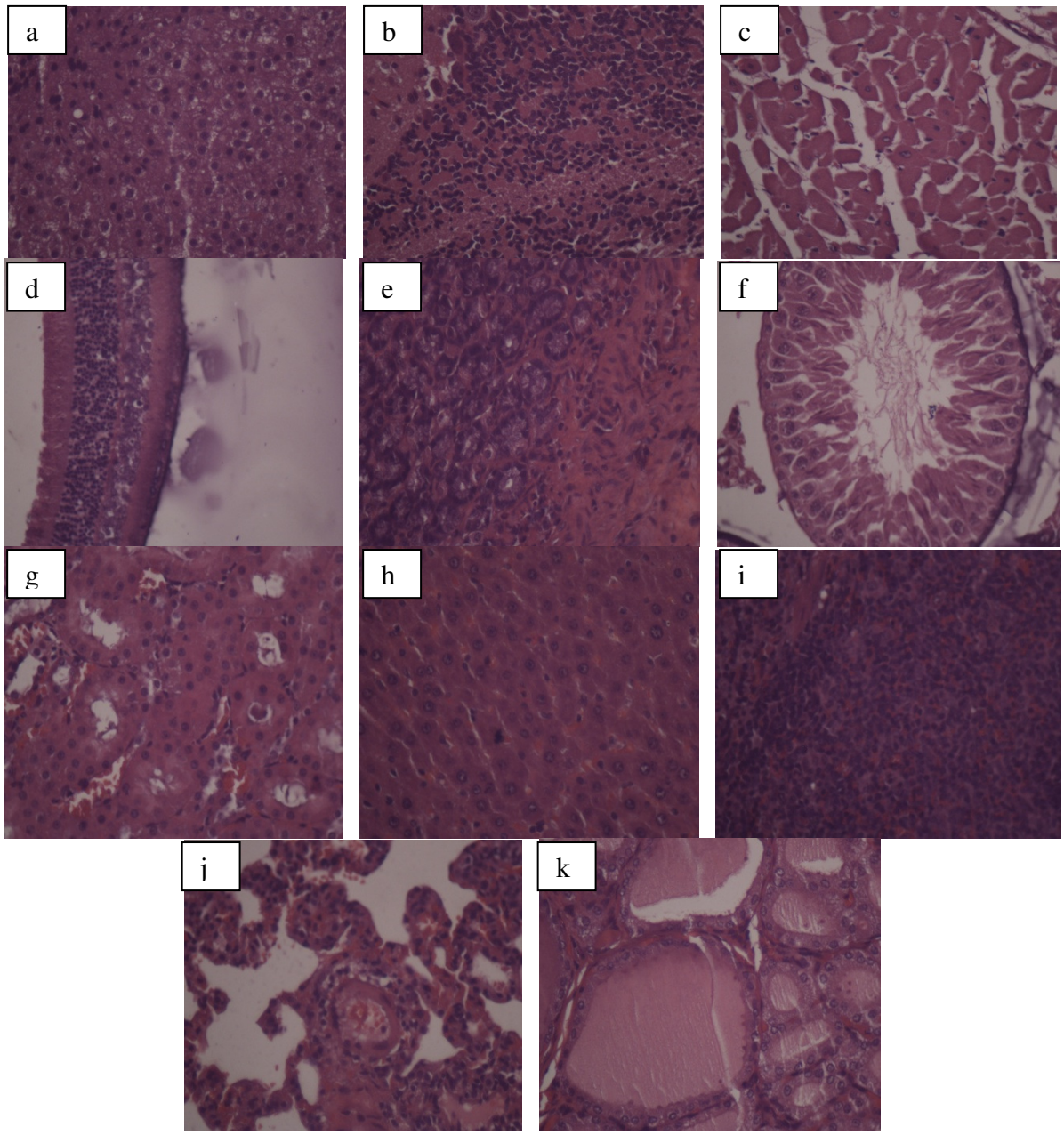

Figure-1
Transverse sections of a) adrenal gland; b) brain; c) heart; d) eye; e) gastrointestinal tract; f) testis; g) kidney; h) liver; i) spleen; j) lung; k) thyroid gland of *Oryctolagus cuniculus* without any exposure (control system)

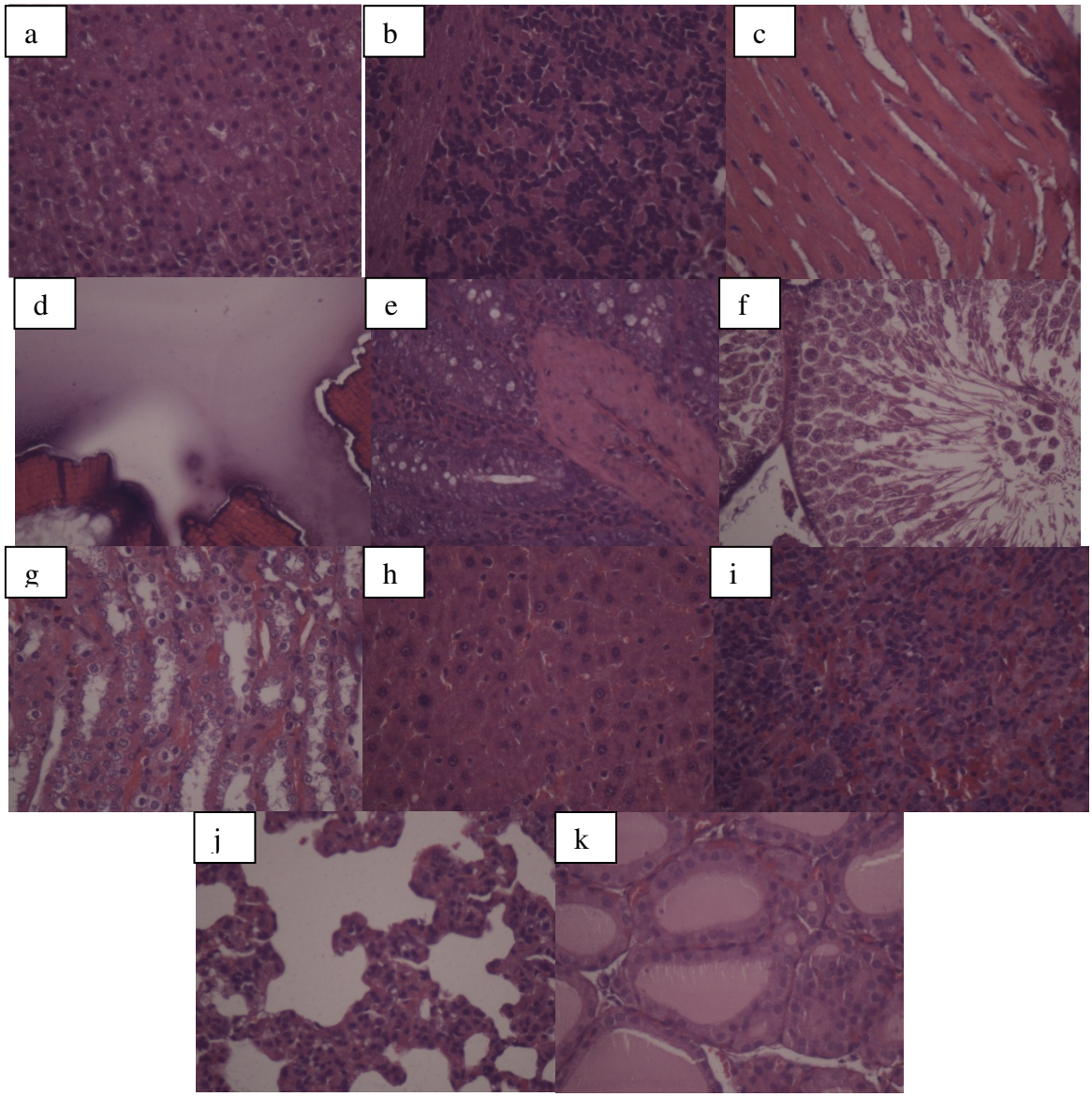

Figure-2
Transverse sections of a) adrenal gland; b) brain; c) heart; d) eye; e) gastrointestinal tract; f) testis; g) kidney; h) liver; i) spleen; j) lung; k) thyroid gland of *Oryctolagus cuniculus* having exposure of e-beam cured PU-PSA tape (test system)

Conclusion

In the present study, a work has been undertaken for development of an e-beam curable non irritant PSA tape which will retain its adhesive strength in biological environment and will be able to transfer moisture through it without accumulation in different biomedical applications. It also helps to determine whether materials that cause adverse effects after exposure for device externally applied to the body surface. Under the conditions of the study, it was found that e-beam cured PSA tape was negligible-irritant to the skin of rabbit as the combined score came out to be 0.11 at different time intervals on the basis of reactions observed after 24 h, 48 h and 72 h after patch removal. Hence, prepared PSA tapes can be used for further studies.

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