How to Cite:
Thakur, N., Kaur, B., Sharma, C., & Goswami, M. (2022). Evaluation of the dermal irritation and skin sensitization due to thiocolchicoside transdermal drug delivery system. *International Journal of Health Sciences*, *6*(S3), 3057–3066.
https://doi.org/10.53730/ijhs.v6nS3.6274

Evaluation of the dermal irritation and skin sensitization due to thiocolchicoside transdermal drug delivery system

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***Abstract*---**The skin irritation and sensitization potential of the new transdermal patch of the Thiocolchicoside formulated with Dura 87-6908 was evaluated on the rabbits and guinea pig as per the standard guidelines of OECD. Skin irritation test was performed on the rabbits by applying the placebo patch for 72 hours and dermal reactions like edema, erythema were noted. No clinical signs or dermal reactions were observed in the rabbits. Sensitization potential was measure on the guinea pig and animal was challenged to transdermal therapeutic system of the Thiocolchicoside, negative control group while group exposed to CDNB produced the sensitization reactions. These findings proved that Thiocolchicoside does not produce any dermal toxicity, irritation and sensitization and hence it is safe for dermal use.

***Keywords*---**thiocolchicoside, skin irritation, sensitization, dermal.

Introduction

Thiocolchicoside is sulfur derivative of the colchicine having IUPAC formula. It is widely used as skeletal muscle relaxant and in recent studies it has been found to be efficacious in the cancer. A mild depression on the CNS was also observed which was mainly due to the local inhibition of the GABA receptors.[1] [2]Transdermal formulations can deliver the drug locally and hence increase the

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
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Manuscript submitted: 18 Dec 2021, Manuscript revised: 27 March 2022, Accepted for publication: 09 April 2022

patient compliance. The medication can be delivered at a predetermined controlled rate.[3][4]. Newer dosage forms need to be evaluated for the toxicity evaluation before they are consumed or used by the animals.[5] Determination of the possible side effects is the key feature in the Registration, Evaluation, Authorization, and Restriction of the chemicals in the preclinical testing.[6][7]. Skin is the external barrier for the entry of pathogens more sensitive to chemical and external attack. [8]Draize in the 1940 developed a test on the Rabbits for the prediction of the hazardous effects of the chemicals on the skin. Dermal irritation and Sensitization studies are the essential components for the evaluation and characterization the events of the irritation and erythema.[9][10].

Materials and Methods

Material

Thiocolchicoside Purity 99.7% was procured from the Yarrow Chem India Ltd. Eudragit L100 was also purchased from the yarrow Chem Ltd. Dura TAK-87-6908 was graciously provided as gift sample by the Henkel Corporation USA. Chloroform and dichloromethane were supplied by the Loba Chemie India Pvt. Ltd. Release liner and Backing membrane were provide as gift samples by the 3M India.

Methods

16.36 mg of the pure drug was mixed in the 1:1 mixture of the chloroform and dichloromethane. Duratek -87-6908 was dissolved in the mixture of the Dichloromethane and chloroform and placed in the cool conditions until the use. Eudragit L100 was dissolved in the mixture of the drug and solvent mixture. Dibutyl phthalate and PEG 400 were added in the formulation. Adhesive mixture was added at end n to the formulation. It was stirred for 15minutes. This mixture was casted on the backing membrane and covered with the release liner. [11][12]
Healthy Adult New Zealand rabbits weighing (2.3-3.5 Kg, age 18 weeks) and healthy adult guinea pigs (weighing 260-320gms, age 5-8 weeks either sex were used in the study. They were placed in the stainless-steel cages, maintained on the standard laboratory diet. The animal facility was maintained at the temperature of 22℃ - 24℃ and RH of 55%±10%.[13]. Animals were given eight Days to acclimatize to the condition and then treatment was given to the animals. [14][13][12]This study was approved by the Animal Ethics committee of the Institute under the application number CU/2019/IAEC/02

Acute Dermal Irritation [15] [16]

Acute dermal irritation was performed on the healthy rabbits. The positive control group received the treatment of the Formaldehyde in the concentration of 0.8%. Placebo patch was applied to the control group while positive control group received the Thiocolchicoside patch. Hairs were shaved off before the application of the patch. The patch was applied for the 4 h on the area. Dermal Reactions were carefully observed on the applied area .No dermal reaction was observed at the 1 h ,3 h and 4h after the patch removal. The test was performed on additional rabbits. Three dermal application studies were performed and applications were

made for 7 consecutive days. The application sites were scored for erythema and edema post application at 1 h,24 h,48 h and 72h. Dermal responses were measured as per the OECD guidelines. Erythema and edema were scored on a scale of 0–4, with 0 showing no effect and 4 representing severe symptoms. Dermal responses for each animal were scored at 1h,24h and 72 h. after the removal of the patches and mean score was determined. The mean scores were summed and averaged to obtain the primary irritation index.[17][18][13]

Skin sensitization experiment

Skin sensitization studies were performed as per the modified Banerjee method and OECD guidelines. Healthy guinea pigs were assigned into three groups, Positive control that received 0.1% w/v 1- chloro-2,4-dinitrobenzene (CDNB) in 10% propylene glycol as a standard skin sensitizing agent, Negative control received the Thiocolchicoside patch and placebo group received no patch. Transdermal patch was applied to the shaved area of each animal during the induction phase After cleaning the area patch was then applied to the shaved area which was covered with an impermeable, adhesive plaster and tied to the place for a 6-h closed application. Hairs were periodically removed from the skin. At 14 days after the third induction (day 28), the test was conducted. Treated sites in both induction and challenge phases were observed and scored 24, 48 and 72 h after patch removal. All reactions were evaluated using stand scoring code. Body weights of all animals were measured before the study initiation; the animals were also observed for signs of toxicity, systemic effects and misbehaviors.[6][19][13]

Results

The results for the acute dermal reactions are summarized in the Table no 1 and Figure 1-6 given below. The change in body weight and clinical changes were noted down. no change in the body weight or clinical implications were observed in the group treated with the Thiocolchicoside transdermal patch. No dermal response like erythema scar formation or edema was observed in the rabbits. Skin sensitization results are presented in the Table no 3 and Figure 7-14 given below and three was no change in the body weight or clinical signs was observed. The skin sensitization reactions were validated by the application of the CDNB. No signs of the skin sensitization were observed in the guinea pig who received the transdermal patch treatment or the placebo patch treatment.

Discussion

Risk assessment for hazard and exposure data is necessary for formulating new substances for topical use and introducing the into the marketplace. Before establishing a substance int o the market a sound data for irritation of substance is required and hence a scientific approach should be incorporated. The purpose of the given study was to evaluate the dermal irritation and skin sensitization by the Thiocolchicoside. The dermal study showed no swelling or edema of the skin in the rabbits including the erythema.

Conclusion

Skin sensitization is produced by the T cell mediated hypersensitivity and and it induces the activation and proliferation and expansion of the T cells. The skin sensitization studies showed that there were no signs of the skin sensitization in the guinea pigs except the group treated with the CDNB. The guinea pigs were observed for additional 14 days after the patch removal for any signs of weight loss or skin reaction. These results confirmed that there are no acute or drastic skin toxicity reactions are there if the transdermal patch of the Thiocolchicoside is applied topically.

Acknowledgements

Authors are highly thankful to department of Science and Technology, Ministry of Science and technology, Govt of India for providing the financial assistance for the research work. File No SP/YO/063. Authors are also thankful to Henkel Corporation India for providing gift samples of adhesives and 3M for providing the gift samples of the release liner and backing membrane.

Conflict of interest statement

“The authors declared no conflict of interest” in the manuscript.

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Tables and Figures

Table 1
Dermal irritation Scores for Thiocolchicoside Patches

Material	Erythema	Edema
Single Dermal Study		
1 hr after the patch removal	0	0
24 hr after the patch removal	0	0
48 hrs after the patch removal	0	0
72 hrs after patch removal	0	0
Repeated Exposure		
1 hr after the patch removal	0	0
24 hr after the patch removal	0	0

48 hrs after the patch removal	0	0
72 hrs after patch remaoval	0	0

Table 2
Weight Monitoring of the Animal

Days	THC Treated(n=3)	Positive controls(n=3)	Negative Controls(n=3)
0-7	3.63±0.79	3.26±0.56	3.93±0.79
8-14	3.72±0.54	3.30±0.49	3.86±0.86
15-30	3.86±0.63	3.31±0.76	3.89±0.85
Mean wt of the (guinea pig)	3.73±0.65	3.29±0.60	3.89±0.83

Table 3
Skin Sensitization scores for Thiocolchicoside

Time	Group	Erythema					Edema					
	Score	0	1	2	3	4	0	1	2	3	4	Remarks
24 Hrs	Positive Group	-	-	2	-	-	-	-	-	-	-	-
	Patch treated Group	0	-	-	-	-	-	-	-	-	-	-
	Placebo group	0	-	-	-	-	-	-	-	-	-	-
48 Hrs	Positive Group	--	-	-	--	4		-	-	-	-	-
	Patch treated Group	0	-	-	-	-	-	-	-	-	-	-
	Placebo group	0		-	-	-	-	-	-	-	-	-
72 hrs	Positive Group	-	-	-	3	-						
	Patch treated Group	0	-	-	-	-	0	0	-	-	-	-
	Placebo group	0	-	-	-	-	-	-	-	-	-	-

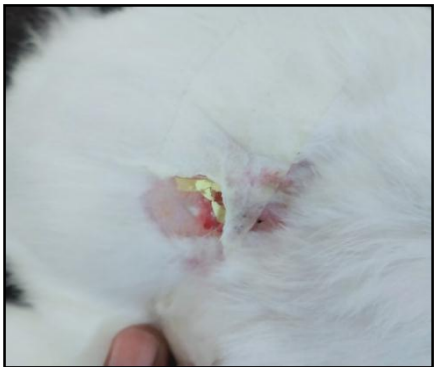

Figure 1. Skin irritation testing (Positive controls showing Dermal Reaction)

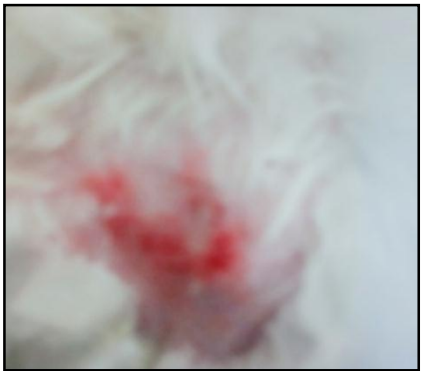

Figure 2. Skin irritation testing Positive controls erythema and edema formation

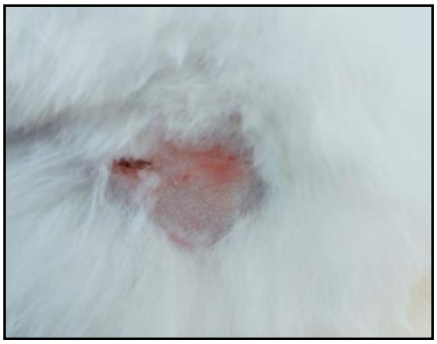

Figure 3. Skin irritation testing Positive controls showing advanced stage of dermal reaction

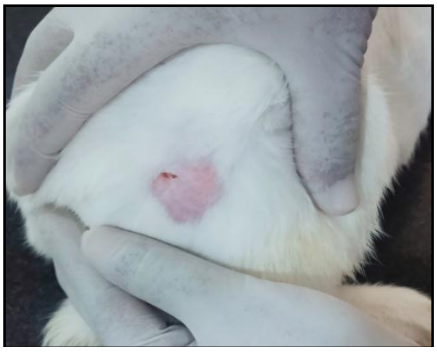

Figure 4. Depict the later recovery after the treatment withdrawal.

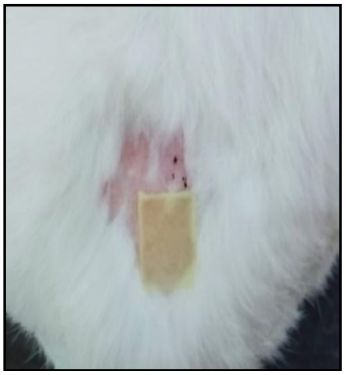

Figure 5. Showing the images of the animal treated with Thiocolchicoside patch showing no dermal reaction

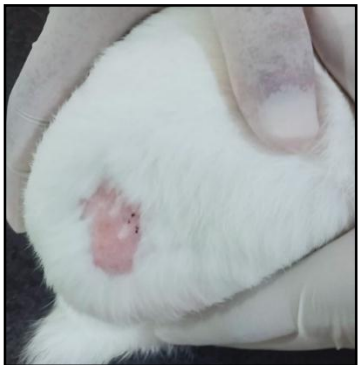

Figure 6. Skin surface after the treatment removal

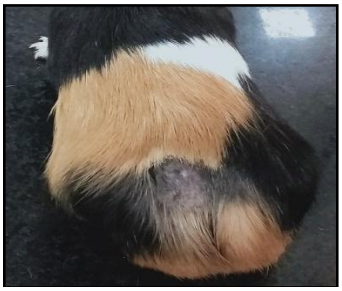

Figure 7. Skin Sensitization reactions in the positive control group; application, and observation

Figure 8. Skin Sensitization reactions in the positive control group; application, and observation

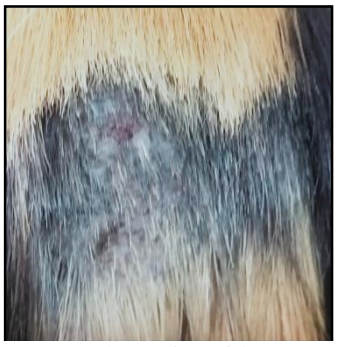

Figure 9. Depicts the skin responses

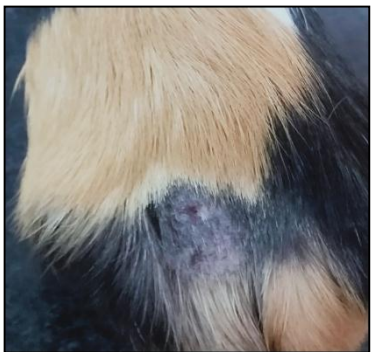

Figure 10. Depicts the skin responses

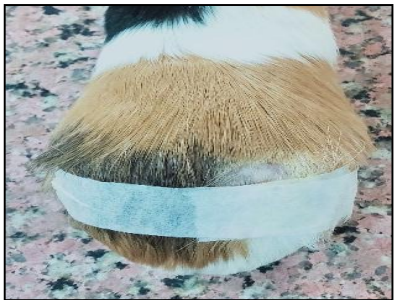

Figure 11. The animal group treated with Thiocolchicoside patch. No reaction observed

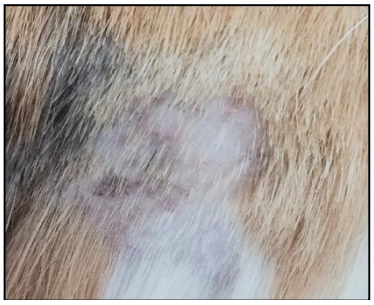

Figure 12. The animal group treated with Thiocolchicoside patch. No reaction observed

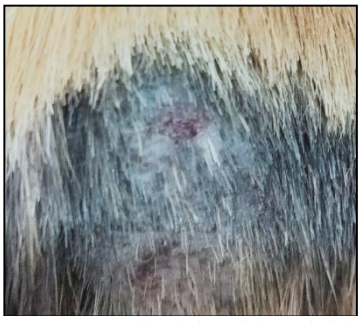

Figure 13. The animal group treated with Thiocolchicoside patch. No reaction observed

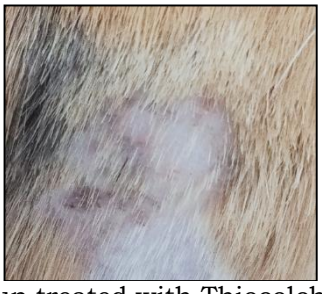

Figure 14. The animal group treated with Thiocolchicoside patch. No reaction observed