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INVESTIGATION OF IN-VIVO PENETRATION AND DISTRIBUTION OF NANOMETRIC TiO_2 IN TROPICAL ALBINISTIC SKIN BY SEQUENTIAL ADHESIVE TAPE STRIPPING

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ABSTRACT: The non-invasive adhesive tape stripping technique was used to evaluate dermato-pharmacokinetics of nanometric titanium dioxide in tropical albinistic skin. Ten sequential strippings were conducted on exposure sites on the forehead, inner and upper forearms of three oculocutaneous albinism individuals 26+/- 4 years old, 15 minutes post dosing of 6.75mg/cm^2 of a 5% titanium dioxide cream specifically designed to retard actinic damage in albinistic persons. The strips were subsequently acid treated and analyzed for titanium content by ICP-AES. All the applied titanium was recovered from the surface and upper layers of the stratum corneum of all participants from all body sites. The average recovery of titanium was 98.50± 0.66%.No titanium was detected in strips 9 and 10 from all sites. On the inner forearm, on average 67.92± 0.95% titanium was localized on the surface (strip1and the cotton swab), 29.41± 0.60%was recovered in the upper stratum corneum strips 2-5. The small remainder was recovered from the lower strippings. On the upper forearms the average recoveries were 61.86± 0.72% Ti (surface), 34.29± 0.61% (upper stratum corneum). On the forehead the recoveries were 54.94± 0.34% (surface) and 40.55± 1.79 % (upper stratum corneum). Our results confirm that nanometric titanium ions in treatments will not pose systemic exposure risks through skin penetration when used in tropical oculocutaneous albinism treatments. The results also confirm that albinistic individuals exhibit regional differences in skin profiles due to actinic exposure that influence dermato-pharmacokinetics.

INTRODUCTION: Albinism, also called achromia is a severe form of amelanosis. It is characterized by the skin's congenital inability to synthesize the bio-polymer, melanin [1, 2].

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Melanisation (melanin production) is one of the two ways through which the human skin protects the deeper dermal structures from actinic damage [3]. Through 'ultrafast internal conversion', melanin has the capacity to absorb harmful Ultra Violet Radiation (UVR) and dissipate it as harmless energy and water thereby protecting the underlying skin structures and appendages.[4] The second mechanism of protection against actinic damage is through keratinisation, whereby the skin basal cell membrane hyper-proliferates and thickens to

protect the dermal layer and retard cell damage [5]. This epidermal thickening is typically viewed as rough skin on actinically over exposed anatomical sites. The impaired melanisation in albinistic persons makes them highly susceptible to all forms of actinic onslaughts including but not limited to sunburn, skin roughness, solar urticaria, inflammation and various other solar induced skin cancers [6]. The only natural defense against UVR onslaughts in albinistic persons (though inadequate) is keratinisation which is commonly observed as severe skin roughness especially on the outer forearms, on the face, around the neck area and on all other solar exposed skin sites [5].

Oculocutaneous Albinism (OCA) refers to pigmentation deficiencies manifest in the hair, skin and eyes of humans, while those deficiencies or errors localized to the eyes are described as Ocular Albinism (OA) [2, 6]. The condition has a much higher prevalence in Sub Saharan Africa, affecting 1 in every 1000 persons, which indicates a twenty fold increase compared to the rest of the world average prevalence which is 1 in every 17 000 persons[7]. The degree of melanisation in albinistic persons ranges from partial to complete absence and consequently the general phenotype of amelanistic individuals has a wide range of characteristics that depend on the remaining non-melanin pigmentation available [8]. Observations from this research show that hyper keratinisation is a function of actinic exposure, therefore, due to variations in UVR exposure extent on regional anatomical skin sites, the skin profiles of individual albinistic persons found in the tropics varies greatly over an individual's body depending on extend of exposure to UVR.

Through adhesive tape stripping Tokumura *et al* (2006) demonstrated regional differences in skin profilometry, hydration and corneocytes biochemistry in normal skin types [9]. The authors also demonstrated in a separate study the relationship between corneocytes stripping, dermal irritations and seasonal factors [10] which are of dermato-pharmacokinetic concern. Loffler *et al* (2004) also demonstrated differences in spontaneous desquamation which are depended on anatomical site due to differences in composition and structure of the inter-corneocytes lipids [11]. Studies by Hostynek *et a*l (2001) illustrated the penetration depths differences of nickel salts based on anatomical site skin physiology [12]. These demonstrations call for greater attention to technical detail when considering designing of treatments for persons with compromised skins that also vary a lot over the entire body like albinistic persons. The inverse relationship between decreasing pigmentation levels and increasing rate of skin permeation has also been demonstrated through various other published studies [12]. However all these and other studies were conducted on normal healthy skin [13, 14] and no systematic evaluation on dermato-pharmacokinetics has been carried out on tropical albinistic skin.

In the present study, we report the results of a clinical study assessing the distribution and penetration depth of nanometric titanium dioxide in albinistic skin on three different regional skin sites, i.e. the forehead, outer forearm and the inner forearm. The objective of the study was to determine the extent of penetration and skin reservoir distribution of nanometric TiO_2 (CAS number 13463-67-7) in oculocutaneous albinistic skin typically found in the tropics when formulated in actinic damage retarding treatments. The study also investigated the influence of regional anatomical differences in skin exposure sites on dermato-pharmacokinetics and potential for systemic exposure across genetically compromised albinistic skin.

An actinic damage retarding cream incorporating 5% nanometric titanium dioxide for its proven sun blocking effects was specially designed for albinistic persons within the tropics. The formulation also incorporated *Trichilia emetica* fixed oil for its wound healing and moisturizing effects as well as *Aloe excelsa* extract for its soothing and anti-inflammation effects. Volatile essential oils were excluded from the formulation due to their potential to influence skin diffusion parameters [15].

MATERIALS AND METHODS:

Human subjects:

Three OCA volunteers participated in the study (2 female, 1 male: aged 23-30 years, mean 26 ± 4).

Ethical approval was obtained from the University of Zimbabwe, Joint Research and Ethics Committee under Parirenyatwa group of hospitals. Informed consent was obtained from all subjects prior to the study. A specialist dermatologist certified that volunteers exhibited no other significant skin disease except for characteristics of actinic exposure prevalent in tropical albinistic persons including freckles, patches, macules, wrinkles, accentuated expression lines (premature aging) and hyper-keratinization on the facial and neck area. The outer arms were heavily keratinized but free from any primary or secondary skin lesions in all participants, the inner forearms were not hyper-keratinized and were also free from both primary and secondary skin lesions. The general phenotype of all three participants was confirmed to be OCA2 albinism by a certified dermatologist. For each anatomical site investigated, experiments were conducted on the same subject, and all subjects had all three anatomical sites investigated. Subjects were instructed not to use any other cosmetic cream or treatment for 3 days prior to the experiments except for a specially designed base cream. The studies were carried out in Harare , Zimbabwe (altitude 1200m) in November 2013, (mean temperatures 29.5^{o}C, mean relative humidity 41%)

Materials:

The nanosized titanium dioxide dispersion (lot number MKBN8669V) was obtained from Sigma Aldrich, Germany, and the specifications were, 43-47% w/w in xylene, (<100nm DLS particle size). Transpore® polypropylene adhesive tape, 50mm width, with acrylate adhesive obtained from 3M, South Africa was used for stripping. The rest of the starting materials were Cosmetic Ingredient Review (CIR) approved ingredients obtained from suppliers and sources indicated in **Table 1**.

TABLE 1: STARTING MATERIALS USED IN THE STUDY

Starting material	Suppliers and sources
Stearic acid	Savanna fine Chemicals South Africa
Glycerol Monostearate (GMS)	
Cetyl alcohol	
Liquid Paraffin	Engen, South Africa
Petrolatum	
Triethanolamine	Merck Chemicals South Africa
Petroleum ether	Astra Chemicals Zimbabwe
EDTA	University of Zimbabwe, School of Pharmacy
Carbopol 940®	
Glycerin	
Mono Propylene Glycol (MPG)	
Methyl paraben	
Propyl paraben	
Trichilia emetica	
Aloe excelsa	
Castor oil	
Cocoa butter	
Lanolin	
De ionized water	
Adhesive Tape	3M South Africa
Titanium IV oxide nano dispersion	Sigma Aldrich , Germany

Methods:

Formulation of base cream O/W emulsion dosage form:

The actinic damage retarding cream was formulated as follows: a water phase containing deionized water, glycerin, MPG, colorant, caustic potash, methyl paraben, Carbopol ® and EDTA was heated to 90^{o}C in a thermal jacketed heating vessel. In a separate vessel, the oil phase was prepared by adding all the oil miscible ingredients and heating them to 90^{o}C. These included lanolin, *Trichilia emetica*, cocoa butter, glycerol mono stearate, liquid paraffin, castor oil, stearic acid, cetyl alcohol and propyl paraben. After maintaining the stated temperatures for 5 minutes, the oil phase was slowly added to the water phase while vigorously agitating with an emulsifying mixer at 2200rpm. Triethanolamine was then added to buffer the emulsion pH and facilitate viscosity adjustment by Carbopol®. The O/W emulsion cream was then cooled down naturally to 50^{o}C. The *Aloe excelsa* and fragrance were incorporated into this cooled state.

The required TiO_2 was inputted into the base cream at the expense of an equivalent amount of water to create the treatment cream.

Two different cream formulations were therefore prepared, a standard base cream with all materials except for the titanium IV oxide and the treatment cream containing 5% w/w titanium IV oxide (3.08% Ti). The Ti concentration in the treatment cream was determined by ICP-AES analysis before the albinistic skin absorption investigations.

TABLE 2: BASE CREAM FORMULATION

Material	Usage %
Stearic acid	4
Cetyl alcohol	3
Glycerol monostearate	2
Cocoa butter	1
Trichilia emetica	2
Liquid paraffin (heavy)	1
Petrolatum	1
Glycerin	3
Monopropylene glycol	2
Carbopol 940®	0.07
Methyl hydroxybenzoate	0.2
Propyl hydroxybenzoate	0.2
Caustic Potash	0.4
Triethanolamine	0.4
Nanometric TiO_2	5
Watermelon fragrance	0.03
Approved FDC Colorant	0.0055
Trace *Trichilia emetica*	0.5
Aloe Excelsa extract	2
EDTA	0.4
Distilled Water	qs

Determination of cream pH:

The pH was determined by dissolving 5 g of the cream in 50 ml deionized water in a 100 ml beaker. A Jenway 3510 pH meter was used to analyze for the pH. The equipment was pre-calibrated using buffer pH 7 and buffer pH 4. Determinations were performed at room temperature in triplicate.

Tape stripping:

Skin application of formulations and sample collection: With the aid of the specialist dermatologist, three application sites were selected on each volunteer (**Fig. 1**). The areas were naturally free from terminal hair; vellus hairs present on sites were removed by special clippers 1 hour before the application of the test material. The selected sites were cleaned by wiping with de-ionized water moistened cotton swabs and dried with a heat blower air stream for 30 seconds.

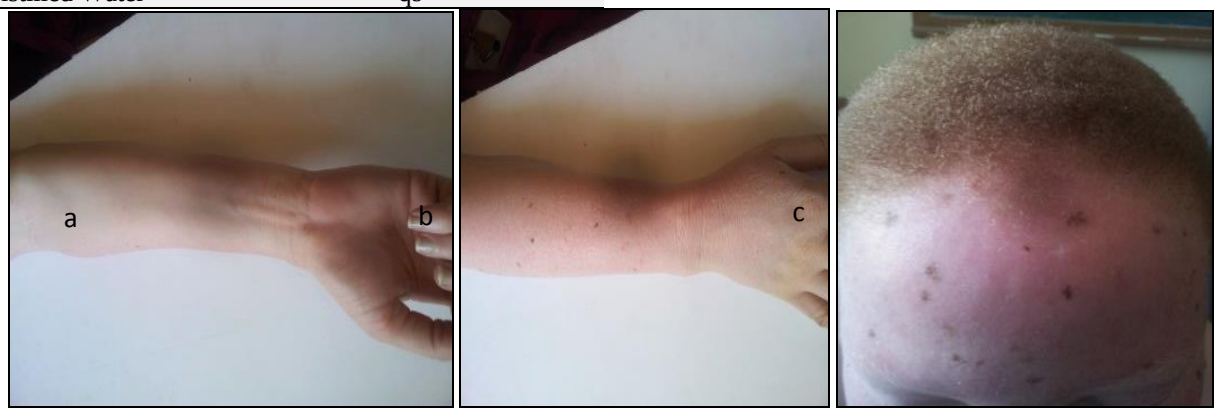

FIG. 1: SELECTED ANATOMICAL SITES (a) THE INNER FOREARM, (b) OUTER FOREARM OF THE SAME ARM AND (c) THE FOREHEAD OF AN ALBINISTIC VOLUNTEER SHOWING THE ANATOMICAL SITE BASED VARIATIONS IN ACTINIC DAMAGE ON THE SAME INDIVIDUAL

On each of the three test sites, a 50mm width Transpore® adhesive tape was used to demarcate a template study area measuring 40mm x 100mm before stripping. The test area was therefore the stenciled area left by the gaping hole within the adhesive tape perimeter (**Fig.2a**) below. The template was fastened to guarantee reproducibility of sequential stripping from the site. A 0.30ml (0.27g) aliquot of the treatment cream was applied onto the selected area using a syringe. The treatment was homogeneously distributed over the selected area and left for 15 minutes. Throughout the study, due care was taken not to touch or disturb the test site. After 15 minutes the test sites still with the template stencil was repeatedly wiped clean using a dry cotton swab to remove unabsorbed material. The cotton swabs were placed in a glass test tube for extraction and analysis of recovered Ti. The demarcated area was marked with a felt-tip marker and the template adhesive tape was removed from the site.

The 50mm width stripping adhesive tape was cut into 15cm strips and the strips were subsequently applied over the demarcated area. The area extracted from was therefore 75cm^2 and abundantly exceeded the 40cm^2 test area. The stripping adhesive tape was applied successively from tape 1 up to tape 10 on the site and pressed over using a glass rod roller to smooth out all creases and remove all air pockets. An empty sheet of paper was placed between the tape and the roller so as to

avoid any transfer of material to the back of the tape. The roller was rolled over back and forth ten times so as to maintain reproducible uniform pressure and achieve optimal bonding between the adhesive tape and the stratum corneum. Using tongs the adhesive strips were gradually removed from the skin in one draw lasting at most 5 seconds. The first strip was placed in the glass test tube containing the cotton swab used to remove excess material. Strips 2-5, 6-8 and 9-10 were put in 3 separate glass test tubes respectively.

To all the test tubes containing tape strips including the first one combined with the cotton swab, 5ml of nitric acid was added and shaken by a rotary shaker for 15 minutes. The resultant acid extract was diluted to 10ml with deionized water and subsequently analyzed by Inductively Coupled Plasma - Atomic Emission Spectrum (ICP-AES Varian; Wavelength 336nm, external calibration, linear range 0.05-10 mg/l).

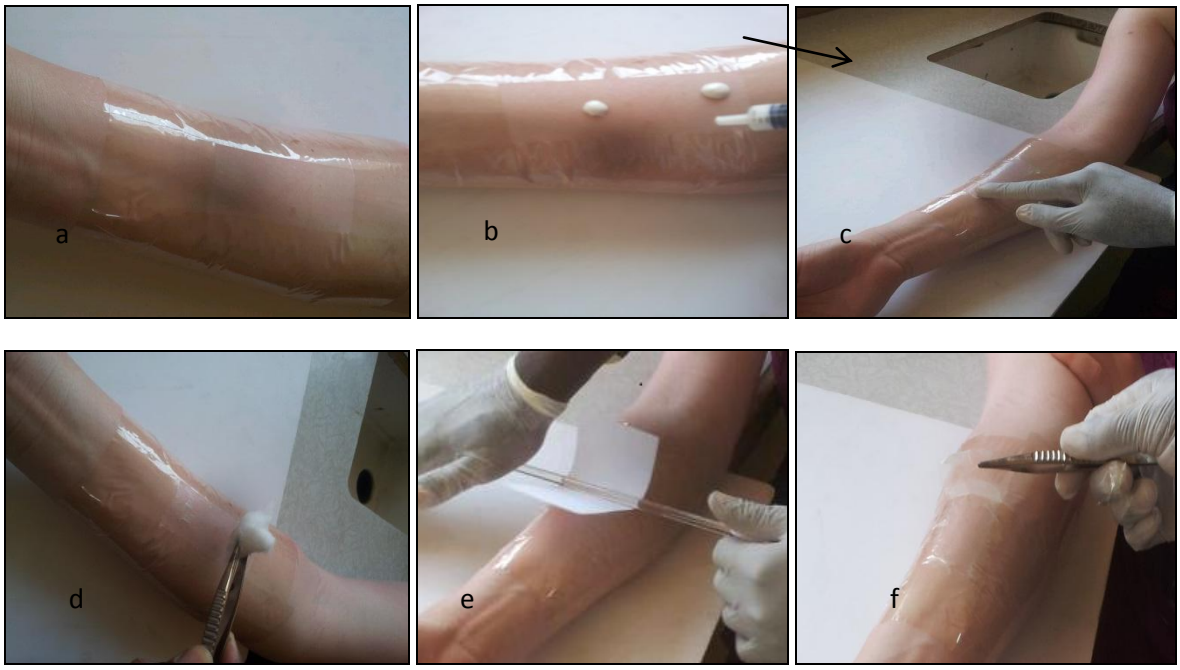

FIG. 2: ADHESIVE TAPE STRIPPING METHODOLOGY ON AN ALBINISTIC FOREARM (a) DEMARCATION OF THE SELECTED SITE WITH AN ADHESIVE TAPE TEMPLATE (b) APPLICATION OF TEST MATERIAL ON SITE (c) SPREADING THE CREAM (d) REMOVAL OF SURFACE FORMULATION AFTER 15 MINUTES WITH COTTON SWAB (e) PRESSING OF ADHESIVE TAPE OVER SELECTED SITE WITH GLASS ROD AND A PAPER SHIELD (f) REMOVAL OF THE ADHESIVE TAPE USING TONGS

Negative controls for Ti content were carried out on the standard base cream without Ti, and on all reagents including deionized water and the acid, on control skin strips taken from non-exposed sites and the tape before any stripping using ICP-AES at a detection level of 50ppb.

Statistical Techniques:

Data were analyzed by the Students't test and ANOVA (where appropriate) using the Statistical Package for Social Science v 21 (IBM, SPSS, Chicago). Statistical differences were considered at $p < 0.05$. All data are presented as mean ± S.D. unless otherwise noted.

RESULTS:

Cream formulation:

The base cream showed good consistency and aesthetics. **Table 3** shows the treatment cream analytical report.

TABLE 3: CHARACTERISTICS OF THE ACTINIC DAMAGE RETARDING CREAM

Parameter	Result
Description	Off white smooth viscous cream, esthetically pleasing slippery feel when rubbed between two fingers.
pH	5.9
Ti	3.08 ± 0.3%

Skin stripping tests:

The total Ti recovered from all volunteers and all sites was in the range 97.07 to 99.76%, the mean

was 98.50±0.83% (**Fig.3**). There was no significant difference in recoveries between the male and the female volunteers. However, distribution of Ti in the skin profile was site depended (**Fig.3-4**). From the surface 67.52±0.95% was recovered from the inner forearm compared to 61.86±0.76% and 54.94±0.34% from outer forearm and forehead respectively. The mean recoveries for upper stratum corneum strippings (strips 2-5) were 29.41±0.60%,34.29±0.61 and 40.55±1.79% for inner forearm, outer forearm and the forehead respectively. No Ti was recovered from strippings 9 and 10 for all sites(**Table 4-6**). Results from forehead strips showed the widest standard deviations compared to other sites (**Table 6**).

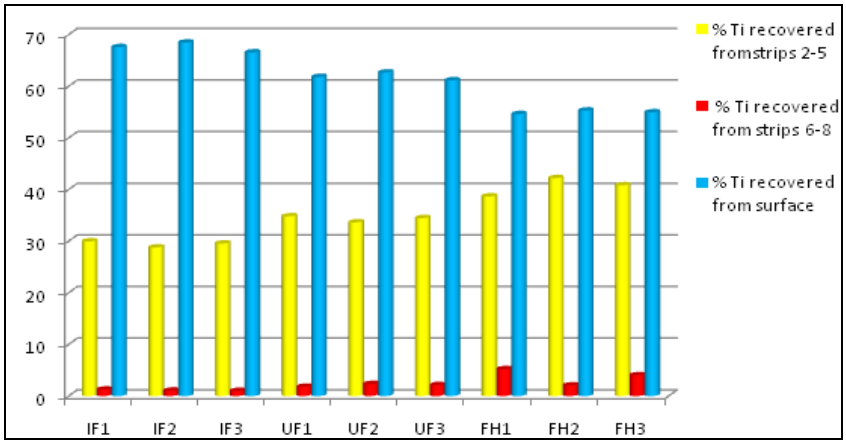

FIG.3: PERCENTAGE Ti RECOVERIES FROM ALL SITES AND SKIN PROFILES FOLLOWING APPLICATION OF 3.08% Ti CREAM

Key IF-Inner forearm, UF-Outer forearm, FH- Forehead

TABLE 4: Ti RECOVERIES FROM INNER FOREARM ADHESIVE STRIPPINGS IN THE THREE OCA HUMAN VOLUNTEERS

Formulation	**3.08% w/wTiO_2 cream (Nano)**				
Anatomical Region	**Innerforearm**				
Volunteer	1	2	3	**Average**	**StDev.S**
Total recovery %	98.76	98.23	97.07	98.02	0.86
Cotton Swab and strip 1	67.58	68.44	66.55	67.52	0.95
strips 2-5	29.94	28.76	29.54	29.41	0.60
strips 6-8	1.24	1.03	0.98	1.08	0.14
Strips 9-10	0.00	0.00	0.00	0.00	0.00

TABLE 5: RECOVERIES FROM UPPER FOREARM ADHESIVE STRIPPINGS IN THE THREE OCA HUMAN VOLUNTEERS

Formulation	**3.08% w/w TiO_2 cream (Nano)**				
Anatomical Region	**Upper forearm**				
Volunteer	**1**	**2**	**3**	**Average**	**StDev.S**
Total recovery %	98.38	98.59	97.71	98.23	0.46
Cotton Swab and strip 1	61.8	62.65	61.14	61.86	0.76
strips 2-5	34.8	33.62	34.45	34.29	0.61
strips 6-8	1.78	2.32	2.12	2.07	0.27
Strips 9-10	0.00	0.00	0.00	0.00	0.00

TABLE 6: RECOVERIES FROM VOLAR FOREHEAD ADHESIVE STRIPPINGS IN THE THREE OCA HUMAN VOLUNTEERS

Formulation	**3.08% w/w TiO_2 cream (Nano)**				
Anatomical region	**Forehead**				
Volunteer	**1**	**2**	**3**	**Average**	**StDev.S**
Total recovery %	98.45	99.54	99.76	99.25	0.70
Cotton Swab and strip 1	54.6	55.28	54.94	54.94	0.34
strips 2-5	38.65	42.2	40.8	40.55	1.79
strips 6-8	5.2	2.06	4.02	3.76	1.59
Strips 9-10	0.00	0.00	0.00	0.00	0.00

TABLE 7: AVERAGE Ti RECOVERIES FROM ALL THREE SITES FROM ALL PARTICIPANTS

Formulation	**3.08 % w/w TiO_2 cream (Nano)**				
Anatomical region	**Average**				
Volunteer	**innerforearm**	**upper forearm**	**forehead**	**Average**	**StDev.S**
Total recovery %	98.02	98.23	99.25	98.50	0.66
Cotton Swab and strip 1	67.52	61.86	54.94	61.44	6.30
strips 2-5	29.41	34.29	40.55	34.75	5.58
strips 6-8	1.08	2.07	3.76	2.31	1.35
Strips 9-10	0.00	0.00	0.00	0.00	0.00

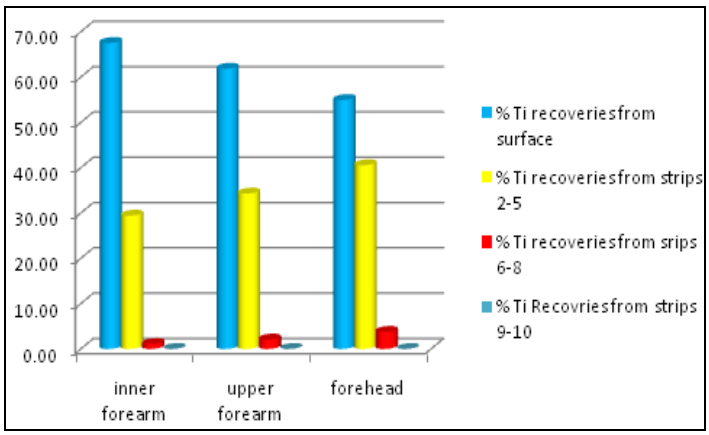

FIG.4: AVERAGE PERCENTAGE Ti RECOVERIES FROM ALL THREE SITES FROM ALL PARTICIPANTS ACCORDING TO NUMBER OF TAPE STRIPS.

DISCUSSION: It has been demonstrated that even after 50 strippings, complete removal of the stratum corneum is not possible [17], therefore tape stripping as a non- invasive technique is a very appropriate tool for this study. We studied the absorption of Ti in a commercial albinistic treatment because it is recognized that percutaneous absorption is vehicle depended [12] and analysis is best carried out with formulations as they would be used by patients. The choice of the three anatomical sites used was motivated by visual appraisal of tropical albinistic skin, the facial and neck skin is frequently the most actinically damaged. The outer (back) of the volar forearm is heavily keratinized and the inner forearm is usually the least actinically damaged of all exposed tropical albinistic skin.

The experiments were essentially carried out in summer at a location within 23.5 degrees latitude from the equator. Seasonal variations in skin Trans Epidermal Water Loss (TEWL), electrical conductance and susceptibility to dermal irritations are all higher in summer and all have effects on dermato-pharmacokinetics and skin permeability[10]. We therefore expect the results to represent a worst case scenario for dermal absorption. We also assume actinic damage in albinistic persons living within the tropics to be at its worst during this season. The application rate used in the study is also more than 3 times higher than the average expected sunscreen application recommended rate of $2mg/cm^2$ [19]. The demarcated area measuring $40cm^2$ is also within the recommended test site area of between 30 and $60cm^2$ for sunscreens.[19]

For tape stripping studies to have reproducible results, standardization of procedures and influencing conditions is paramount. The type of tape used, the application pressure and the velocity of tape removal are all investigator depended factors that can influence results [11, 17]. Seasonal conditions like temperature and humidity have well been demonstrated to influence (TEWL) and consequently dermato-pharmacokinetics [9]. Differences in spontaneous desquamation are dependent on underlying corneocytes structures which are in turn site depended. Some anatomical sites especially those adjoining joints areas are also prone to muscular movements that can affect the results. Earlier studies have confirmed that many factors mentioned above significantly affect outcomes of stripping studies[11]. In this investigation therefore, an attempt to carefully and adequately define influencing parameters and

procedures was done so as to minimize results variability.

In our studies all the Ti was recovered from the first ten strips which represent the surface and the upper layers of the stratum corneum [11, 14]. (**Fig.3**) This is in line with our previous *ex-vivo* studies on the absorption of Ti through damaged porcine skin.[20] Total Ti recovered from all sites was comparable for all sites. All Ti was confined to the surface, upper and lower stratum corneum and no Ti was detected beyond the stratum corneum. Skin permeation across the stratum corneum was not expected because for permeation to occur the active material must have a partition co-efficient between 1 and 3.9, reasonable aqueous solubility and a molecular weight below 500Da [21] which is not the case with Ti. The formulation (**Table 2**) was based on typical Cosmetic Ingredient Review (CIR) approved ingredients. The ingredients did not include any material that could facilitate transdermal mobility or promote skin absorption. The formulation as an actinic damage treatment was expected to stay on the skin periphery where Ti would refract UVR. The pH was adjusted to 5.9 (**Table 3)** by the buffering agent (Triethanolamine) to minimize potential for skin irritation due to wide discrepancies between the treatment and African albinistic skin pH which in our previous studies was found to be between 5.8 and 6. Albinistic skin maintained its skin integrity against percutaneous nanometric Ti absorption incorporated in the treatment formulation.

However the distribution of the nanomaterials in the stratum corneum was influenced greatly by anatomical site (**Table 4-6**, **Fig. 2**).The forehead area which exhibited greater actinic damage had much more material recovered by tape strippings 2-5 than any other site. The facial skin had marginally more wrinkles and keratinized skin than all the other sites, the material was therefore most likely logged in skin folds and crevices and could not be recovered by the cotton swab and the first strip. It was also noted that all heavily keratinized sites of the face and neck exhibited sparse terminal hair follicles not typically observed on non-hyper-keratinized areas and in normal female skin types. Sparse vellus hairs appear to be hyper-keratinized to terminal hair in all areas exhibiting rough skin. The differences between inner and outer forearms could be explained by the higher keratinisation and higher volumes of vellus and terminal hair follicles in the outer volar forearm. The accentuated roughened skin furrows and the hair ducts could have trapped the material and prevented it from being recovered from the surface. It is also recognized that there is a difference in the number of cell layers and thickness of the stratum corneum between the forehead and the forearm [22]. The fewer layers on the forehead could have facilitated a faster movement of Ti from the surface to lower stratum corneum levels.

The tape application pressure (which affects corneocytes removal rate) [11] could have been depended on underlying structures and biomechanical properties. The bone structure immediately found under the skin of the forehead could possibly have increased the tape pressure compared to forearm skin which is not immediately supported by underlying bone structures. Apart from the absence of internal exposure our studies also demonstrated that the results obtained from skin stripping are depended on the procedure, site and general skin condition. The differences in site distribution of Ti in the stratum corneum appear to be more related to extend of actinic damage rather than a direct implication that the skin on the inner forearm is less penetrable by Ti than the outer forearm and the facial area.

CONCLUSION: Our investigations show for the first time that nanometric Ti in treatments for actinic damage do not penetrate beyond the lower layers of the stratum corneum in OCA persons in tropical conditions even if the skin is actinically damaged. This may serve as evidence for safety for use in actinic damage retarding treatments for albinistic persons in tropical conditions. Our studies also confirm that albinistic dermato-pharmacokinetics are depended on anatomical site and extend of UVR exposure.

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