PREPARE AND EVALUATE A FORMULA TO OVERCOME LIMITATION OF BETAMETHOSNE TO PENETRATE THROUGH TOPICAL ADMINISTRATION: EMULGEL

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Abstract

The aim of the present study was to formulate a formula of Betamethosne as emulgel. The model drug Betamethosne is a pharmacologically anti-fungal activity. Betamethosne has tendency to bind intracellular glucocorticoid receptor which then bind to DNA of infecting micro and ultimately effect gene expression. The selected hydrophobic drug were difficult to administer through trans-dermal route but through this modified emulgel approach provide a double layered control on drug release.

For gel preparation Carbapol 934 and Hydroxypropyl methylcellulose K15M were used. Working medium temperature, mixing speed, mixing time and pH were studied as formulation working variables. Formulation code E6ABc3 was found best formulation on the basis of drug release pattern, stability and Ostwald ripening. Possible way of drug molecule transportation was studied with the help of SEM study and found that there was no sign of keratolysis.

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INTRODUCTION

Topical drug administration is a localized drug delivery system. Topical Drug delivery Topical drug delivery systems skin serves as one of the most easily accessible routes for drug administration. Stratum corneum has been regarded as the major barrier to penetration of substances in to and through the skin (Sharma S.,2019). However, the presence of stratum corneum on the surface makes it selective towards applied drugs or delivery systems. Pharmaceutical gels are having many advantages in respective to application, stability as well as in view of patient compliance with one major disadvantage that is hydrophobicity. This major limitation can be perfectly overcome by incorporating one point called emulsion. Emulgel formulation is a combination of two formulations ie gel and emulsion. Both the formulations have their own advantages and disadvantages (Baibhav joshi, et.al, 2011).

Topical preparations has many advantages including that, these formulations are very easy to administer and easy to withdraw as well. This type of formulations has been known to release their drug in faster release and complete release. (Dhobale Shankar, et.al,2018) These category of formulation has super most advantage that they could ease penetration of both categories of drug molecules; hydrophobic as well hydrophilic molecules. The only point has to be consider will a proper selection of vehicle to disburse the drug molecule to effectively at the site of administration.(Shahin M, et.al., 2011)

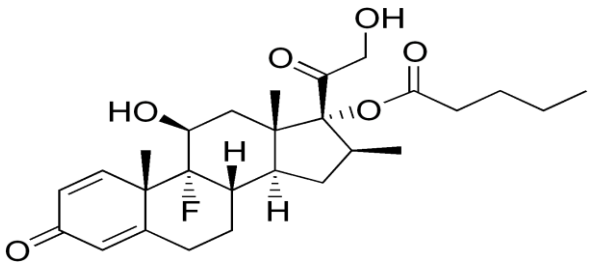


Figure No.1: Chemical Structure of Betamethasone Valerate

Betamethasone Valerate is used to treat a variety of skin conditions (e.g., eczema, dermatitis, aller gies, rash).

Betamethasone Valerate reduces the swelling, itching, and redness that can occur in these types of conditions. Chemically called as [(8S,9R,10S, 11S,13S,14S,16S,17R)-9-fluoro-11-hydroxy-17-(2-hydroxyacetyl) 10,13,16-trimethyl-3-oxo-6,7,8, 11,12,14,15,16 octahydro cyclopenta [a] phenanth ren-17-yl] pentanoate. It comes under Anti-inflammatory agent. Solubility profile if drug is like: Soluble in water (<1 mg/ml at 25° C), methanol, DMSO (95 mg/ml at 25° C), ethanol (58 mg/ml at 25° C), and chloroform (Monograph USP-NF 2009).

METHODOLOGY

Betamethasone Valerate was obtained as a gift sample from HFA Formulation, Selaqui, dehradun. Carbopol 941 P, Carbopol 934, Hydroxy propylemethyl Cellulose K15M were of analytical grade and of Central Drug House (P) Ltd., methyl paraben, propylene glycol, triethanolamne and all other chemicals used were of analytical grade and were used without any type of further chemical up gradations.

Method:

Gel preparation method:

- The calculated quantity of carbopol 940 / carbopol 941, propylene glycol, and methyl paraben was detached in distilled water. The carbopol dispersion was set aside at rest for 24 hours to allow for the complete engorgement. Then the blend carbopol was homogeneously mixed with non-stop stimulating, ultrasound, and hot plate to outline gel characteristic. Dispersal obtain was neutralized with mandatory quantity of triethanolamine to achieve pH around 5.0. The carbopol remain in a beaker for a week at RT. Then, a concentration analogous to 5% of model drug was diluted by means of propylene glycol and more to the carbopol. (Martin A.,et.al.,2006).

Table No.1: Formula design of gels

Sr. No.	Formulation code	Polymer name	Ratio	Soaking time (Hr)
1.	G_A	Carbopol 941 P: HPMC K15M	1:0.5	24
2	G_B	Carbopol 941 P: HPMC K15M	1:1	24
3.	G_C	Carbopol 941 P: HPMC K15M	1:1.5	24
4.	G_D	Carbopol 941 P: HPMC K15M	1:3	24
5	G_E	Carbopol 941 P: HPMC K15M	2:0.5	24

Table No.2: Finalized gel formula for study:

Sr. No.	INGREDIENTS	Gc
1.	Carbopol 941 P(gm)	0.5
2.	HPMC K15(gm)	1.5
3.	Methyl paraben (gm)	qs
4.	Propylene glycol(ml)	9.5
5	Triethanolamine(ml)	1

Emulsion preparation method :

Wet gum method was used to prepare proposed emulsion and optimized the same method for a stable and better emulsion.

Wet gum method: In this method, the magnitude of oil, water, and emulsifier are the equivalent (4:2:1), but the type and technique of integration are different. The 1 part of gum is mixed with 2 part distilled water till paste of mucilage appearance formed with clicking sound; followed by the 4 division oil is further gradually, in portion, while triturating in same direction of rotation. After all the oil is added, the mixture is triturated with a good enough speed for minimum 10-15 minutes as for a fine emulsion. Then additional ingredient may be added as in the continental method. The triturating speed and direction must be same throughout the process as it may result in a more stable emulsion.

Emulsions were prepared with distilled water and castor oil and different mixture of emulsifiers in order to stabilize the system for a longer period of time.

Table No. 3: Formulation design of emulsion

Formulation Code	Working tempt. (^{0}C)	pH	PEG-6000 (%w/w)	Glycerine (%w/w)	Olic acid (%w/w)	Emulsifiers (15% w/v))			
						Span60 (%w/v)	Tween60 (% w/v)	Lecithin (% w/v)	NaCl (%w/v)
E-1A	35	6.0	5.24	-	2.35	2	12	-	1
E-1B	40	6.8	-	5.24	-	2	12	-	1
E-2A	35	6.0	5.24	-	2.35	-	12	2	1
E-2B	40	6.8	-	-	2.35	-	12	2	1
E-3A	35	6.0	-	-	2.35	3	12	-	-
E-3B	40	6.8	5.24	5.24	-	3	12	-	-
E-4A	35	6.0	-	-	2.35	-	14	-	1
E4B	40	6.8	2.64	-	2.35	-	14	-	1
E-5A	35	6.0	-	2.64	2.35	1.5	12	-	1.5
E-5B	40	6.8	-	-	1.78	-	12	1.5	1.5
E-6A	35	6.0	2.64	2.64	2.35	2.5	10	-	2.5
E-6B	40	6.8	2.64	2.64	1.78	-	10	2.5	2.5

* Distilled water and castor oil used in all codes for o/w.
* Stirring speed 5,000rpm
* Stirring time 25-30 min

Table no. 4: Selected formulas of Betamethasone Valerate (with ethanol) for further study

Formulation Code	Working tempt.* (^{0}C)	Rotation speed (rpm)	pH	Mixing Time (Min)	Eth. (V/V%)	Emulsifiers (14% w/v)			Aid
						Span80 (%w/v)	Span20 (%w/v)	Tween60 (% w/v)	NaCl (%w/v)
E-6ABc1	10	5000	6	25-30	2	11	2	1	2
E-6ABc2	10	5,000	6	25-30	4	11	2	1	2
E-6ABc3	**10**	**5,000**	**6**	**25-30**	**8**	**11**	**2**	**1**	**2**
E-6ABc4	10	5,000	6	25-30	16	11	2	1	2
E-6ABc5	10	5,000	6	25-30	32	11	2	1	2

* 10^{0}C temperature was maintained with the help of continuous ice bath of mixture.
Eth : Ethanol (96%).

Evaluation methodology:

Viscosity

Brookfield viscometer assembled with type "D Spindle" was used for viscosity determination. Calculated amount of prepared formula of gel was filled in a beaker and D-spindle dipped perpendicularly into the gel. One precaution must while placing of spindle was none other than gel imparts any resistance in movement of spindle. The placed spindle was move (rotated) in gel at

gradually increasing shear rate 0.5 rpm to 5 rpm. At each successive increase of speed reading on the dial were noted. The viscosity of prepared formula was finalized by several time repeating the same procedure and multiplied by the correction factor given with catalog of using viscometer.(Debnath S.,et.al., 2014)

Spreadability (Kumar L, *et al.,* 2010**)**
Spreading efficiency of prepared gel and emulgel was determined by the apparatus consisting two plane glass slides and a arrangement of applying pressure on slide for the purpose of spreading of applying gel. In order to determining spreading, we tried to resemble that process of "slip" and "drag" process. In which one plane glass slide is fixed on wooden box; sample of prepared semisolid formula placed over it, and put one more plane glass slide over it. A sandwich appearance of assembly gel/emulgel in-between two glass slides was assembling. A weight of 100gm was placed over upper slide and left for 1 min. to 2 min. to expel the air entrapped in-between the slide and; after expelled air now the layer of emulgel was uniform and get maximum contact required to give a complete adherence to slide. Upper slide was hooked with wire hanged by weighed (gradually increasing) applied a shear force in tangential direction. Whole assembly was kept till upper slide travel over second slide till 7.5 cm movement.

A short covered path length indicates good spreadability index and lower covered path length or higher time taken to cover similar path length indicates poor spreadability index. Spreadability can be calculated by using the following formula:

S= M.L/T
Where, S= spreadability,
M = Weight tied to upper slide
L = Length of glass slides
T = Time taken to separate the slides completely from each other.

Extrudabilitya**(**Mohammad MI, 2004**)**
This is the force essential to extrude the crammed from the container. The procedure adapted for determination of the required force in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibit subsequent plug flow. In presenting study, the method adopted for evaluating emulgel and emulgel extruded from collapsible tube on which weight was positioned in order to extrude the packed emulgel from the container in specified period of time. In the case of lesser applied weight in order to extrude the filled more is extrudability more the weight required more will be the value. Finalize the extrudability value after took minimum three individual value then calculate average value. Value of extrudability was calculated with the help of following formula.
Extrudability = Applied weight to extrude emulgel from tube(gm) / Area(cm^2)

Swelling Index:a**(**Sanjay Jain, 2007**)**
In present study, swelling index of emulgel formula was determined by; one gram of the prepared emulgel was taken on aluminum foil paper. Placed that aluminum foil paper in a beaker filled with phosphate buffer pH 6.8. Kept the beaker undisturbed at constant temperature. After different time intervals withdraw the sample from medium and placed them in order to drying those samples. Reweighed those samples after complete drying of the samples.

Swelling of the samples was calculated with the help of following formula:
Swelling Index (SW) % = [(Wt – Wo) / Wo] × 100.
Where, (SW) % = Equilibrium percent swelling,
Wo = Original weight of emulgel at zero time
After time t, Wt = Weight of swollen emulgel

Ostwald ripening (Monica Rao,, et.al,2013):
Ostwald ripening is an investigational phenomenon in solid (or liquid) solutions which describe the evolution of an in homogenous grounding over a long storage time.

Ostwald ripening happening on the actuality that molecules nearby on the surface of a globules are thermodynamically less stable than that of those until that time well arranged and crowded in the bulk area. Larger the size of particles, which are in their lower surface to volume ratio, consequences in a lesser amount of energy.

Determination of pH and Physical appearance: (Shalaby S, et.al., 2001)
The value of pH of 1% aqueous solution of the emulgel were measured by pH meter. Prepared emulgel were inspected visually for their physical appearance like dispersion quality, homogeneity, sediment regimen of globules present in emulsion and overall consistency.

Drug content: (Monica Rao, et.al., 2013)
The drug content of the formulation was confirmed by kept one gram of formula in the medium in 100ml of DM water : methanol (7:3) (drug completely dissolve in medium). After 24 hours filter the medium and prepared different dilution of

the concentrate. After getting absorbance of prepared dilution with the help of UV-Vis spectrophotometer using wavelength (260nm) . Drug content was calculated by using regression equation of prepared under bear's range.

In-vitro study:
In-vitro diffusion study was carried by using rat skin. Franz diffusion cell was used study drug transfer rate. Formula (1 gm) was placed in donor compartment on semi-permeable membrane. That semi-permeable membrane was the separating line in-between donor and receiver compartment. Diffusion medium phosphate buffer pH 6.8 was filled in receiver compartment and continuously stirred by Teflon bead at 50rpm temperature of the medium was maintained at 37 ± 2^0C. Samples were collected with-in one hour regular time interval till seven hours.

Mechanism of drug penetration:
Skin of sacrificed albino mice was saved and used for penetration studies. After applying, the formulation onto the upper dorsal layer of the skin left that skin for next 24 hours. Model drug was penetrated across the skin by making his path. We can study that possible path of penetration with the help of SEM study.

Stability studies:
The stability profile of prepared formula of emulgel were carried out as per ICH guidelines. Emulgel were stored in capped glass vials at 40^0C and 4^0C for three months. After storage the samples were evaluated for their appearance, pH, spreadability, drug content etc.

RESULTS:
Model drug characterization:
Model drug Betamethasone Valerate was characterized by FTIR (KBr plate method) and determination of value of absorbance maximum (UV-Vis spectroscopic method).

Gel characterization:
Polymer swelling behavior:
Swelling behavior was observed manually by visual inspection; weather there is any non-dispersed part noted as knot or any area of more dense part then other.

Table No. 5: Polymer swelling behavior

Formulation code	G_A	G_B	G_C	G_D	G_E
Polymer Swelling	Good	Good	Good	Good	Good

Viscosity appearance:

Table No. 6: Viscosity appearance

Formulation code	G_A	G_B	G_C	G_D	G_E
Viscosity appearance	Less viscous (21023cps)	Good (21786cps)	Very good (21621cps)	High viscous (22004cps)	Less viscous (22101cps)

pH value:

Table No. 7: pH value

Formulation code	G_A	G_B	G_C	G_D	G_E
pH	7.1	7.2	6.7	7.0	6.7

Spreadability:

Table No. 8: Spreadability

Formulation code	G_A	G_B	G_C	G_D	G_E
Spreadability (gm.cm/sec)	13.33	11.66	11.33	8.33	13.66

Extrudability

Table No. 9: Extrudability

Formulation code	G_A	G_B	G_C	G_D	G_E
Extrudability ($gm.cm^2$)	285.71	500.00	444.41	666.06	307.69

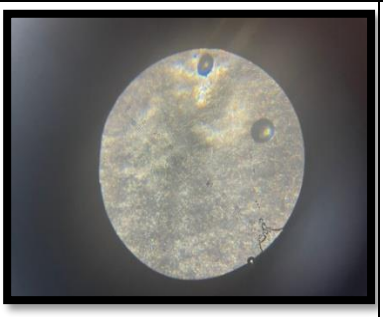
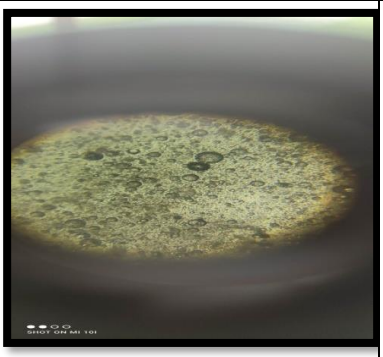
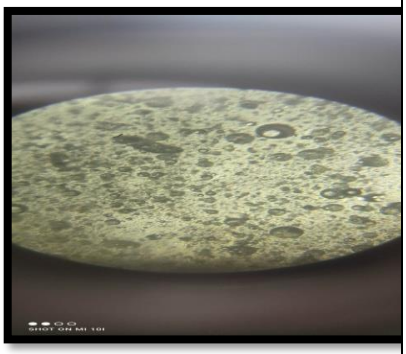
Confirmation of emulsion type:
All prepared were of oil in water categories.

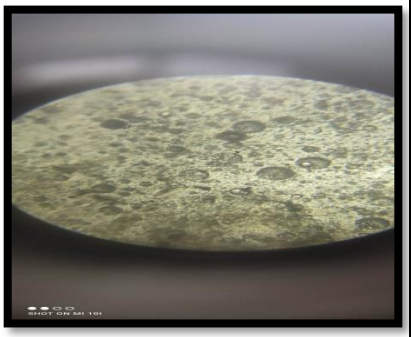
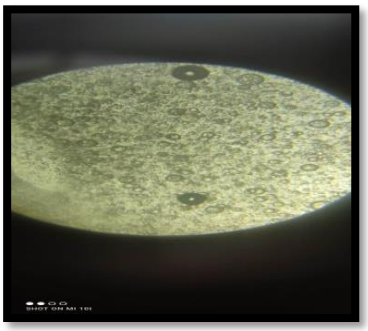
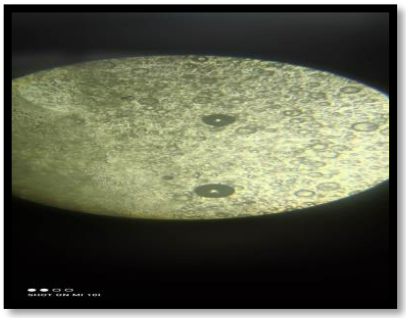
Table No. 10: Evaluation of blank emulsions

Formulation code	Dye test	Dilution test	Creaming	Globule size range (µm)	Ostwald ripening**
E-1A	o/w	Diluted with water	15	6-11	9
E-1B	o/w	Diluted with water	20	5-9	12
E-2A	o/w	Diluted with water	22	7-12	11
E-2B	o/w	Diluted with water	22	6-10	12
E-3A	o/w	Diluted with water	16	7-11	9
E-3B	o/w	Diluted with water	18	6-9	11
E-4A	o/w	Diluted with water	14	8-12	9
E4B	o/w	Diluted with water	15	7-10	10
E-5A	o/w	Diluted with water	17	6-11	12
E-5B	o/w	Diluted with water	19	5-10	13
E-6A	o/w	Diluted with water	18	6-11	11
E-6B	o/w	Diluted with water	20	6-13	12

*Creaming / Sedimentation exceeds 20% after how much time (days).
**flocculation increase size range of globules twice then that of their starting size after how much period of time (days).

Physical stability studies and inferences:
Physical stability studies were conducted by studying by preparing a slide of thin layer of emulgel and observed under binocular microscope under magnification value of 1000.

Formu. Code	Photograph of formulation ##All photographs are from BINOCULAR MICROSCOPE under "1000X" Magnification.		Remark
	Just after prepared	After 24 hour	
E-6ABc1	 Figure No. 2	 Figure No. 3	Higher pH value of formulation may cause faster rate of globule's wall dissolution, a prominent sign of instability of formula.
E-6ABc2	 Figure No. `4	 Figure No. 5	Higher value of stirring speed of agitating baffles causes very fine globular size. That fine globule may be to higher stored free energy results higher rate of rearrangements of globules (Ostwald ripening).

E-6ABc3	 Figure No. 6	 Figure No. 7	Decreasing aid concentration is good. Lower aid concentration gives more spherical and a better emulsion form. Here size and number of globules were changed in lower end and coded emulsion was present a better physical stability profile .
E-6ABc4	 Figure No.: 8	 Figure No.: 9	When we increased agitation time for emulsion preparation resulted emulsion had very fine and very instable emulsion. Globules were formed in the form of foam which fused with each other very fast ie. Ostwald ripening was very high.

***In-vitro* drug release study:**

In-vitro drug release study present that overall half of the drug released within 7 hour after application. Model drug was released in a very much-controlled manner throughout the study time. There were nothing like busting effect or not even the sign of saturation of binding sites; which indicates the transportation was not of carrier mediated.

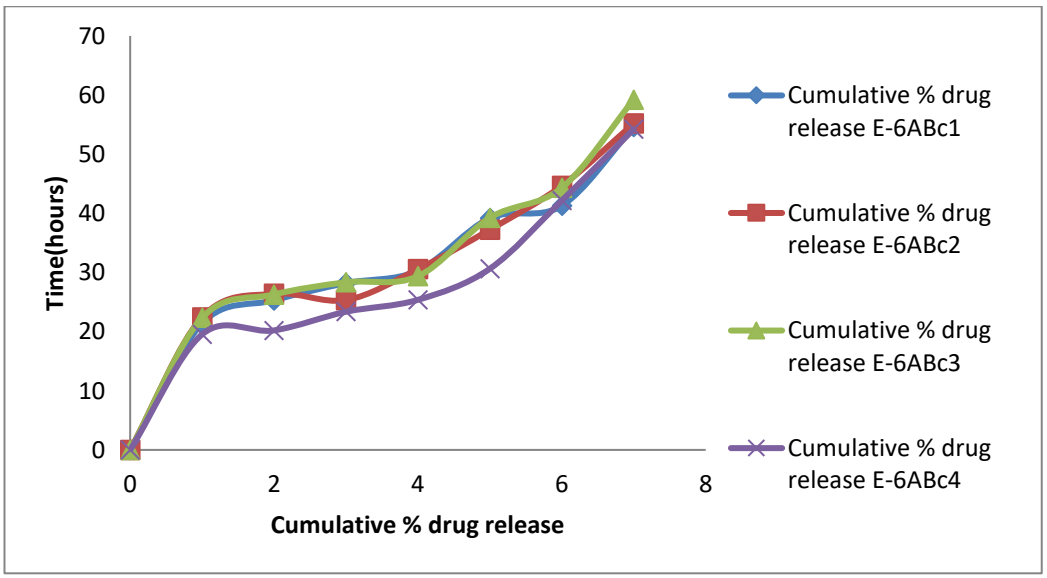


Figure No. 10: Graphical presentation of Cumulative % drug release.

SEM Analysis:

The possible penetration pathway was studied by SEM analysis. In given picture we can conclude that the penetration was through increasing the level of hydration of skin cell. That increased hydration capacity might open more channels of the barrier ie skin and provide a wider channel to enter the drug through it.

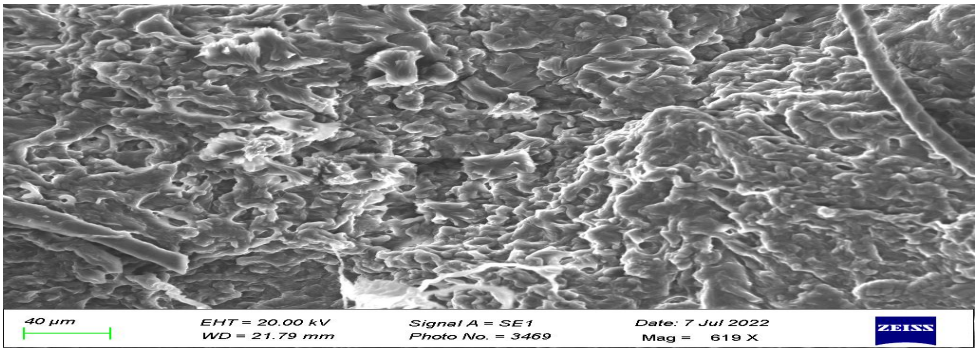


Figure No. 11: SEM of plain rat skin (before application of formulation)

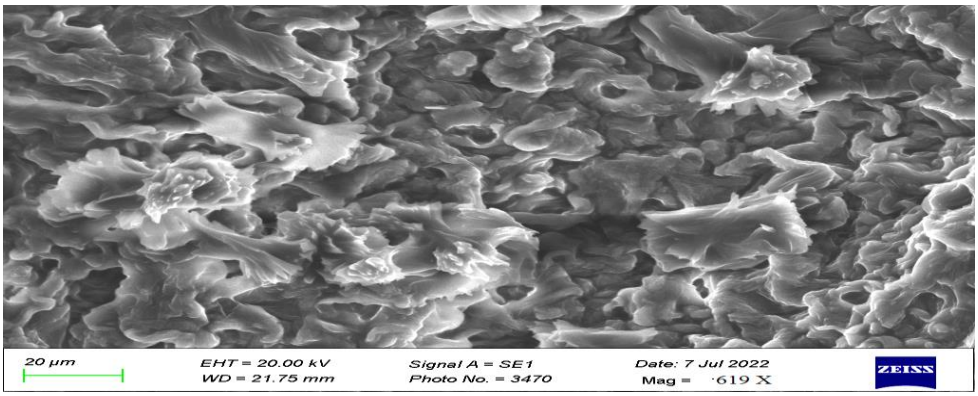


Figure No. 12: SEM of plain rat skin (after application of formulation E-6ABc3)

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