DEVELOPMENT AND OPTIMIZATION OF TERBINAFINE EMULGEL FOR ENHANCED TRANSDERMAL DELIVERY: FORMULATION, CHARACTERIZATION, IN-VITRO AND EX-VIVO ASSESSMENT.

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Abstract:
The aim of this study was to formulate and optimize a emulgel formula for the drug terbinafine. Model drug Terbinafine is a synthetic allylamine antifungal. It is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. Drug molecule terbinafine has tendency to make a depot structure at the site of administration and provide a double-layered release barrier; this nature is unwanted in case of lipophilic drug molecule.

Drug incorporated gel formula were designed with formulation additives Carbapol 934 and Hydroxypropyl methylcellulose K15M were used. Gel forming polymers were soaked for minimum 24 hour for complete expansion. Working variables for emulgel formation were 35^0C, blending speed 25000rpm and pH 5. Gel formulation code G_G was selected after examination of viscosity, pH value, extrudability, spreadability and good enough polymer swelling behaviour. Emulsion formula E-6ATc$_2$ and emulgel formula G_G E-6ATc$_2$ were the best formula, which present 0.950 and 0.991 regression coefficient of their drug release pattern. Scanning Electronic Microscopic study of freshly sacrificed and saved rat skin present no sign of keratolysis. Treated rat skin was swelled which indicted that drug molecule were penetrated only after opening of channels through swelling of keratin layer.

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Introduction:

Emulgel is a category of formulation having properties of two formulations; emulsion and gel. This formulation comes under two-phase formulation category. Here in this category a thermodynamic unstable emulsion try to getting stable for with the help of gel. Now in these days emulgel formulations are very alluring picture, as they are with many advantages like enhanced rate and flux of penetration, longer period of drug release, giving better bio-availability as well as a more stable formulation.

Emulgel formulations are a better option of topical administration of both hydrophilic and hydrophobic drug molecules and specially drugs of higher molecular size.

The use of gels and emulsions as combined dosage form results into formation of emulgel showing dual release. With this approach, the use of polymers with enhanced effect in release pattern has been emerged providing sustained and controlled release. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. These emulgels show major advantages on novel vesicular system as well as on conventional systems in various aspects. Emulgels have several favorable properties for dermatological use such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance. So emulgels can be used as better topical drug delivery systems over present systems. The use of emulgels can be expanded in analgesics, anti-inflammatory, anti-fungal, anti-acne drugs and various cosmetic formulations **(**Anu Hardenia, *et.al.,* 2014**).**

In current study, we formulate and evaluated emulgel formulation of terbinafine. Terbinafine is a widely used drug of anti-fungal category. Terbinafine has low water solubility nature, this makes model drug is a suitable candidate for emulgel formulation.

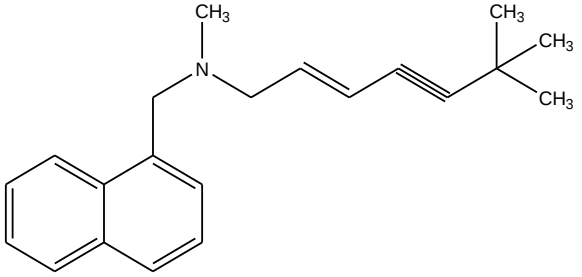


Figure No. 1: Chemical Structure of Terbinafine

Chemical name of model is [(2*E*)-6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalen-1-ylmethyl) amine. Terbinafine is a synthetic allylamine antifungal. It is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. This is a white or almost white powder. Very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone, (USP-2009).

Topical formulations are having advantages together with that, these category of formulations are very effortless to administer and effortless to remove as well. This category of formulations has been identified to release their loaded amount of drug molecules in a faster release rate and complete release amount. (Dhobale Shankar, *et.al,*2018) This category of formulation has great advantage that they could penetration of both categories of drug molecules; hydrophobic and hydrophilic drug molecules. The only point has to be consider will a appropriate assortment of medium to disburse the drug molecule to effectively at the site of administration ie skin.(Shahin M, *et.al*., 2011)

METHODOLOGY

Terbinafine 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 designed measure of carbopol 940 / carbopol 941, propylene glycol, and methyl paraben was saturated in distilled water. The polymer carbopol dispersion was set aside at rest for 24 hours to allow for the complete engorgement. Then the blend carbopol was homogeneously blended with continuous, ultrasound, waves 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. An equivalent concentration that to be 5% of study's drug was diluted with the help 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 :

Emulsion were prepared by using "wet gum method" and optimization was done the same method for a stable and better performing emulsion.

Wet gum Method: 2%v/v of de-ionized water is mixed thoroughly with 1%w/v of surface active agents until a thick creamy liquid and forming of pre-emulsion completed. That pre-emulsion was then added by 4%v/v oil and subjected to comparative higher shear forces by using hot-plate magnetic stirrer with ambient temperature condition. That higher rate of agitation break and dispersed globules homogenously which helps to achieve a stable emulsion.

Emulsion were designed and prepared with de-ionized water, castor oil and different combination of emulsifiers. Prepared emulsion were stable and homogenous in visual appearance.

Table No. 3: Formulation design of emulsion

Formulation Code	Working tempt. (^{0}C)	Rotation speed (rpm)	pH	Mixing Time (Min)	API (mg)	Emulsifiers (15% w/v))			
						Span60 (%w/v)	Span20 %w/v)	Tween60 (% w/v)	NaCl (%w/v)
E-1AT	35	25,000	6	25-30	250	11	2	2	5
E-2AT	35	25,000	6	25-30	250	11	2.5	1.5	5
E-3AT	35	25,000	6	25-30	250	11	3	1	2
E-4AT	35	25,000	6	25-30	250	11	3.5	0.5	5
E-5AT	35	25,000	6	25-30	250	11	4	-	5
E-6AT	**35**	**25,000**	**5**	**25-30**	**250**	**11**	**2**	**2**	**5**
E-7AT	35	25,000	5	25-30	250	11	2.5	1.5	5
E-8AT	35	25,000	5	25-30	250	11	3	1	2
E-9AT	35	25,000	5	25-30	250	11	3.5	0.5	5
E-10AT	35	25,000	5	25-30	250	11	4	-	5

Table no. 4: Selected formulas of Terbinafine(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-6ATc1	35	25000	5	25-30	2	11	2	2	5
E-6ATc2	35	25,000	5	25-30	4	11	2	2	5
E-6ATc3	35	**25,000**	**5**	**25-30**	**8**	**11**	**2**	**2**	**5**
E-6ATc4	35	25,000	5	25-30	16	11	2	2	5
E-6ATc5	35	25,000	5	25-30	32	11	2	2	5

* 35^{0}C temperature was maintained with the help of hot plate.

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,*aetaal*.,a2010**)**
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.

Extrudability (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: (Sanjay Jain,a2007**)**
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.

***Ex-vivo* study:**

Ex-vivo 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^{0}C. 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^{0}C and 4^{0}C for three months. After storage the samples were evaluated for their appearance, pH, spreadability, drug content etc.

RESULTS:

Model drug characterization:

Model drug Terbinafine 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.

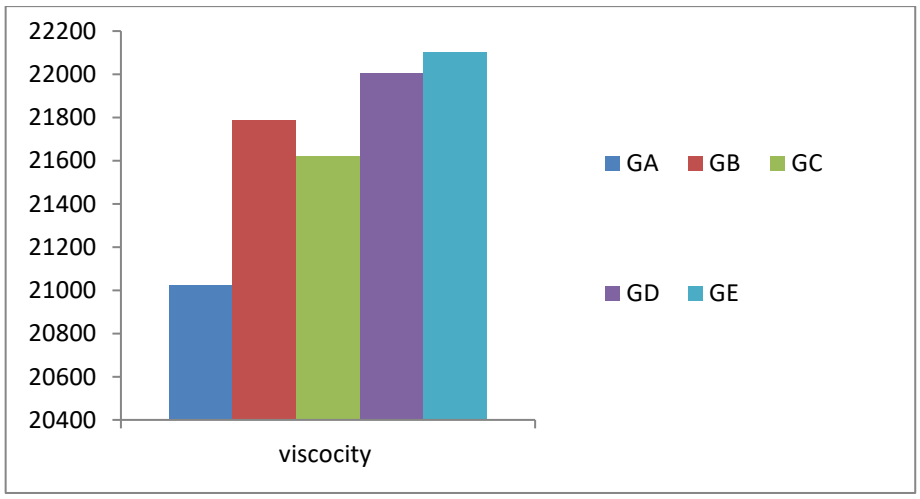
Table No. 5: Polymer swelling behavior

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

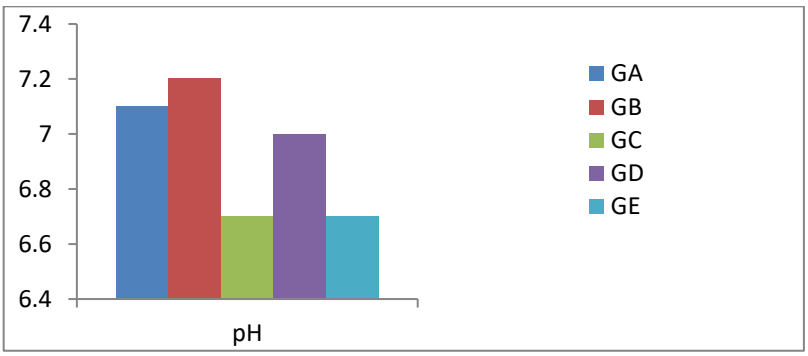
Formulation code	G_A	G_B	G_C	G_D	G_E
Viscosity appearance	Less viscous (21023cps)	Good (21786cps)	Very good (21621cps)	High viscous (22004cps)	Less viscous (22101cps)



pH value:

Table No.7: pH value

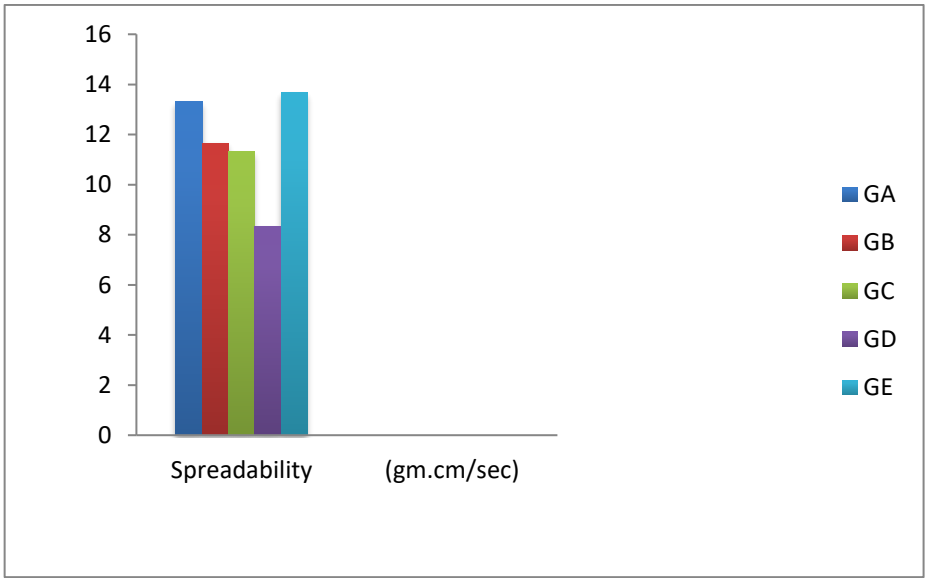
Formulation code	G_A	G_B	G_C	G_D	G_E
pH	7.1	7.2	6.7	7.0	6.7



Spreadability:

Table No. 8: Spreadability

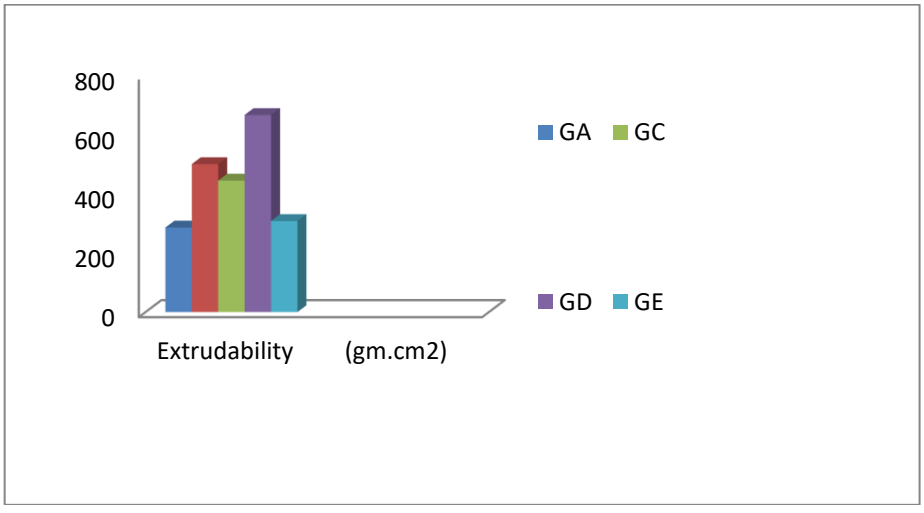
Formulation code	G_A	G_B	G_C	G_D	G_E
Spreadability (gm.cm/sec)	13.33	11.66	11.33	8.33	13.66



Extrudability

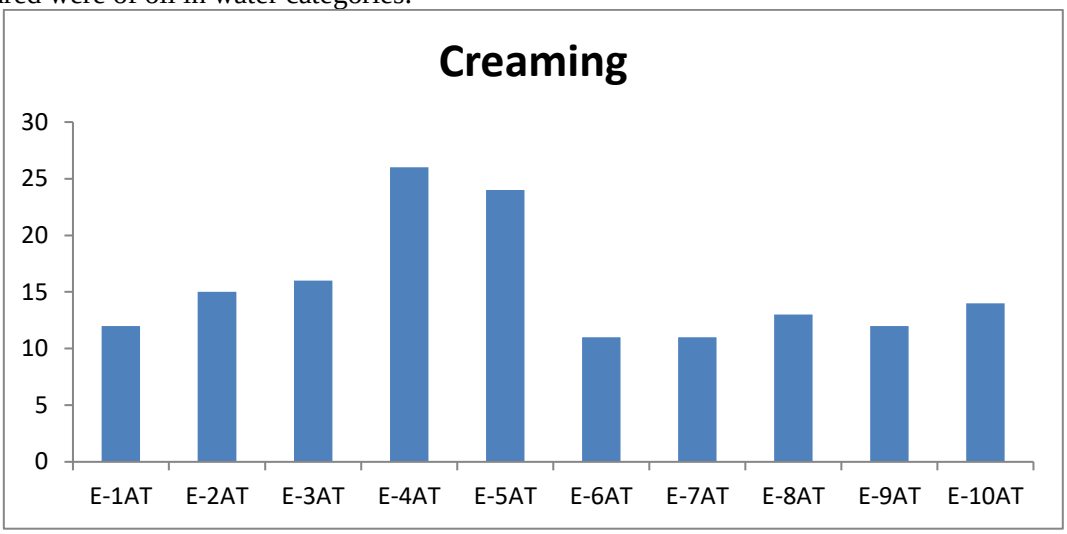
Table No. 9: Extrudability

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.



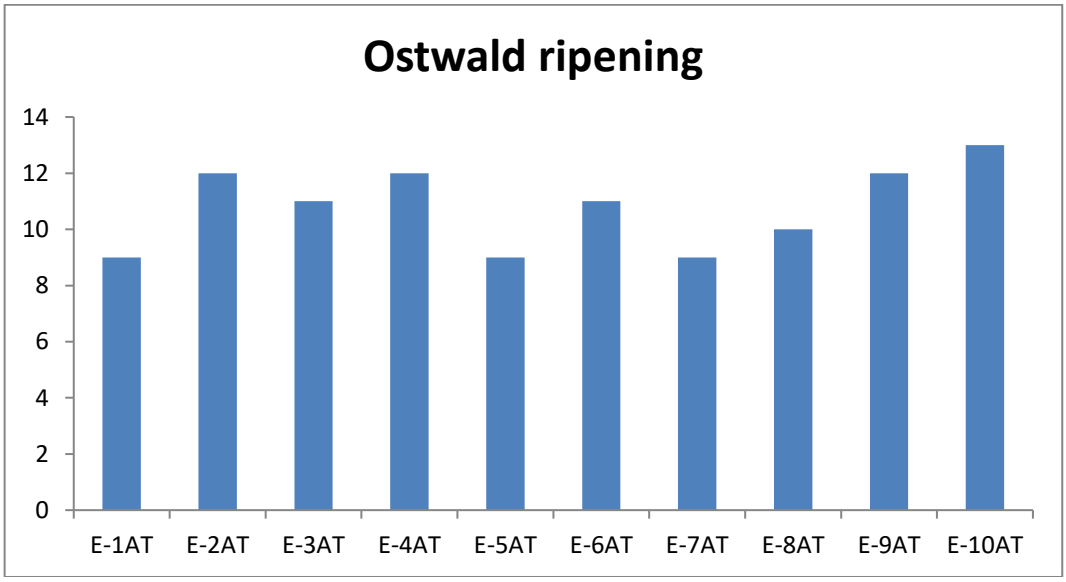


Table No. 10: Evaluation of blank emulsions

Formulation code	Dye test	Dilution test	Creaming	Globule size range (µm)	Ostwald ripening**
E-1AT	W/O	Not Diluted with water	12	5-9	9
E-1AT	W/O	Not Diluted with water	15	3-9	12
E-12AT	W/O	Not Diluted with water	16	3-10	11
E-3AT	W/O	Not Diluted with water	26	3-11	12
E-4AT	W/O	Not Diluted with water	24	2-10	9
E-5AT	W/O	Not Diluted with water	11	6-10	11
E-6AT	W/O	Not Diluted with water	11	8-11	9
E-7AT	W/O	Not Diluted with water	13	6-10	10
E-8AT	W/O	Not Diluted with water	12	4-10	12
E-9AT	W/O	Not Diluted with water	14	3-10	13
E-10AT	W/O	Not Diluted with water	11	6-10	11

*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).

***In-vitro* drug release results:**

In-vitro drug release study of present task

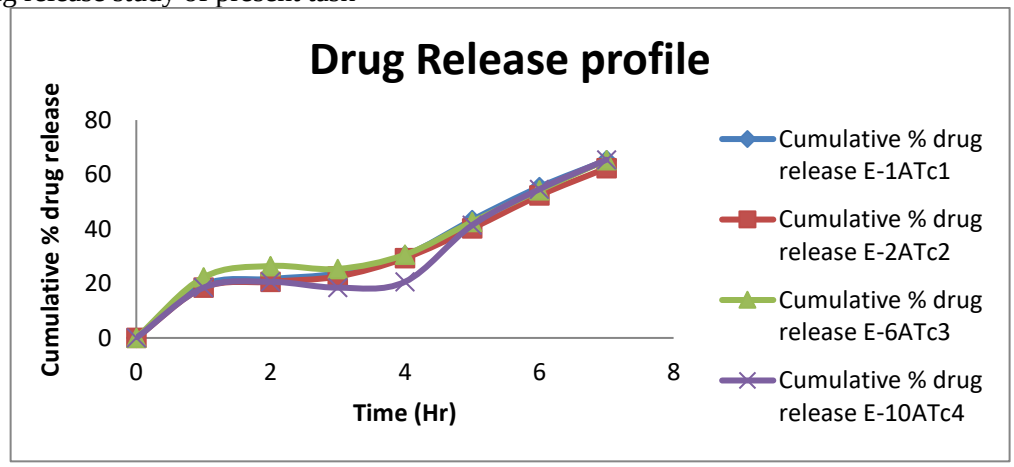


Figure: Graphical presentation of Cumulative % drug release.

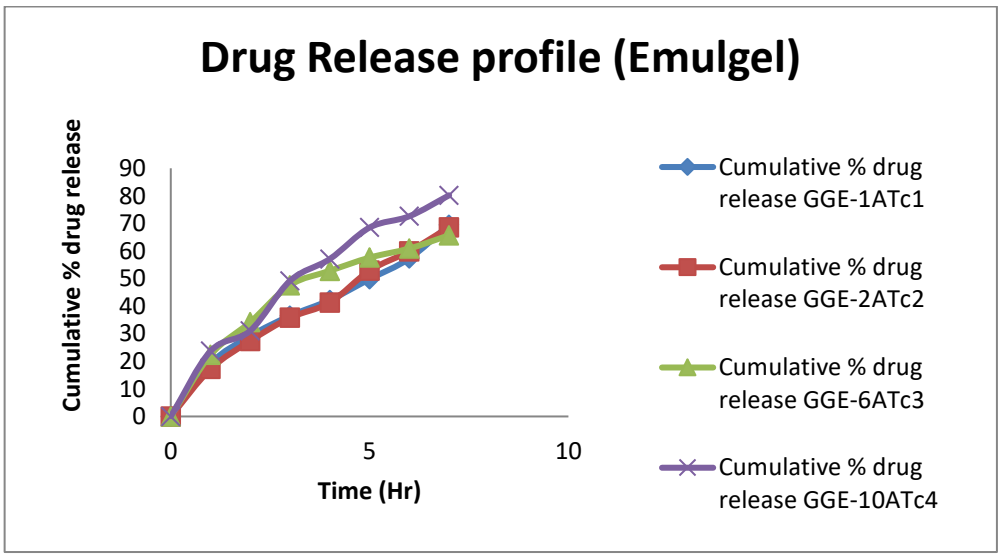


Figure: Graphical presentation of Cumulative % drug release

Table : Coefficient of regression of zero order release

	E-1ATc1	E-2ATc3	E-6ATc2	E-10ATc4
R^2	0.950	0.924	0.950	0.883
	G_GE-1ATc1	G_GE-2ATc3	G_GE-6ATc2	G_GE-10ATc4
R^2	0.955	0.974	0.991	0.990

SEM Analysis:

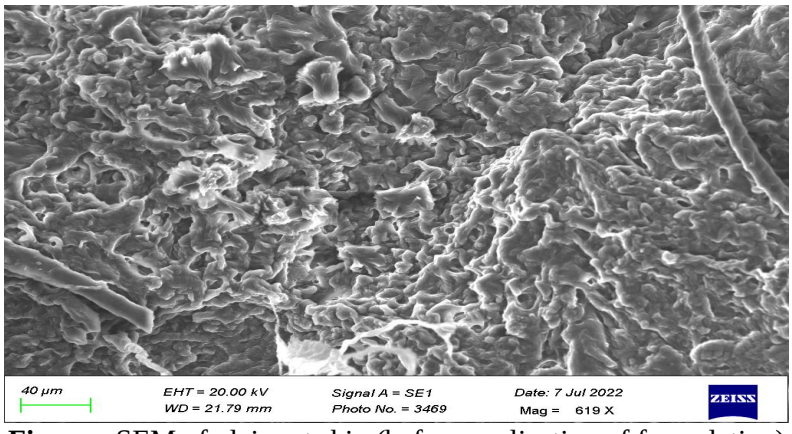


Figure : SEM of plain rat skin (before application of formulation)

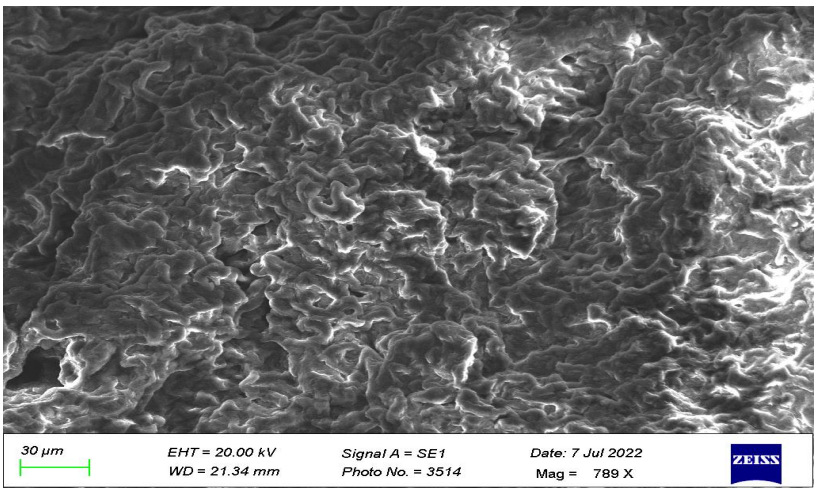


Figure : SEM of treated rat skin (after application of formulation G_GE-6ATc3)

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