RESEARCH ARTICLE

QbD-Driven Development and Evaluation of EGCG-Loaded Transfersomal Gel for Non-Melanoma Skin Carcinoma

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ABSTRACT

The most common type of cancer is non-melanoma skin cancer (NMSC), necessitating the development of non-invasive and novel method of treatment. The current research study is focused on the design, development, and evaluation of a transfersomal gel loaded with epigallocatechin-3-gallate (EGCG), a bioactive compound with significant anti-cancer properties. After establishing anticancer properties of EGCG using cell lines and in silico studies, transfersomes were formulated using Box-Behnken Design (BBD). Optimization was done with three factors and three levels The optimized transfersomal gel exhibited significant physicochemical characteristics. Smaller V.S., improved Z.P. and high EE facilitated enhanced skin penetration as proved by *in vitro* and *ex vivo* studies using porcine skin. These findings demonstrated the potential of transfersomal formulation in enhancing the transdermal delivery of EGCG, paving the way for effective approaches for managing non-melanoma skin cancer. Further, clinical studies can enhance the potential and application of this bioactive molecule.

Keywords: Epigallocatechin-3-gallate (EGCG); skin permeation; transfersome, QbD, Non-melanoma skin cancer; Ex-vivo studies; A431 Cell lines.

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INTRODUCTION

Non-melanoma skin carcinoma poses significant health concerns due to its high occurrence and potential for local recurrence and metastasis.[1] Current treatment options for NMSC include cryotherapy, surgical excision, topical chemotherapy and photodynamic therapy.[2] However, these conventional treatments are associated with various limitations, including potential scarring, incomplete removal of tumor cells, and other adverse side effects. Hence, there is an increasing demand for innovative therapeutic strategies that can enhance treatment efficacy while minimizing invasiveness and associated complications.[3] Epigallocatechin gallate (EGCG), a key constituent has gained considerable attention because of its potential anti-cancer properties.[4] Despite these promising properties, the clinical application of EGCG is limited by its poor skin penetration, limited bioavailability, and susceptibility to degradation upon exposure to environmental conditions such as light and oxygen.[5] Advanced drug delivery options have evolved as an encouraging solution to enhance the delivery and efficacy of EGCG for topical applications.[6] One such system is the transfersome, a novel vesicular carrier characterized by unique composition of phospholipids and edge activators, which grants it exceptional deformability. This flexibility allows transfersomes to penetrate underlying layers of the skin, facilitating the effective delivery of phytoconstituents like EGCG to targeted sites.[7] Transfersomes can significantly improve the bioavailability and efficacy of lipophilic and hydrophilic drugs while providing controlled release. The incorporation of EGCG into a transfersomal gel formulation offers numerous advantages for the targeted treatment of NMSC. Transfersomal gels can not only enhance the stability and solubility of EGCG but also provide an optimal environment for sustained and localized drug release, improving patient compliance and therapeutic outcomes.[8] Moreover, the ability of transfersomes to reach deeper skin layers can potentially augment the anti-cancer effects of EGCG, thereby enhancing its efficacy against non-melanoma skin cancer.[9]

MATERIALS AND METHODS

Materials

Pure EGCG was obtained from Sigma Aldrich. Soya lecithin, phosphatidylcholine, Tween 80 (Polysorbate 80), Ethanol were sourced from CDH. Phosphate-buffered saline (PBS) was prepared from analytical-grade reagents. Statistical Software STAT-EASE was used for data analysis and optimization. Fresh porcine ear skin obtained from local slaughterhouse. All materials were handled according to standard laboratory protocols, ensuring accuracy, reproducibility, and safety throughout the experimental processes.

Methods

In-vitro anti cell proliferation activity of EGCG

Cell proliferation assay: 1.5×10^6 A431 cells/mL, Cell viability was measured spectrophotometrically absorption was recorded spectrophotometrically.[10]

Quality target product profile (QTPP) for transfersome

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Table 1: QTPP for transfersome.

QTTP	Target	Explanation
Vesicle size	< 200 nm	Better penetration
Polydispersity index (PDI)	< 0.5	To determine homogeneity
Zeta Potential	> ±30	To prevent agglomeration of particles
Entrapment efficiency	> 60 %	It has an impact on safety and efficacy
In vitro release study	Immediate and rapid	For better permeation and diffusion

Table 2: Cell Lines Studies of EGCG on A431 Cells (Non-melanoma carcinoma)

		A431				
Compound name	Conc. µm	OD at 590nm n=1	OD at 590nm n=2	Average OD	% Inhibition	IC_{50}
Control	0	0.783	0.767	0.775	0	
Doxorubicin	3.125	0.697	0.686	0.691	10.79	24.92
	6.25	0.564	0.572	0.568	26.73	µM
	12.5	0.505	0.511	0.508	34.47	
	25	0.374	0.381	0.378	51.26	
	50	0.256	0.267	0.262	66.23	
	100	0.132	0.149	0.141	81.85	
S1 (EGCG)	10	0.662	0.672	0.667	12.50	122.8
	20	0.571	0.582	0.576	24.41	µg/ml
	40	0.525	0.536	0.531	30.39	
	80	0.420	0.431	0.426	44.16	
	160	0.368	0.372	0.370	51.50	
	320	0.209	0.220	0.214	71.87	

Table 3: Optimization of Drug Loaded Transfersome using BBD.

	X1	X2	X3	Y1	Y2	Y3	Y4
Batch	A	B	C	V.S	EE	DEF	Z. P
1	85	5	10	162.4±3.24	81.75±2.56	16.4±1.39	32.7±1.02
2	75	10	10	107.8±1.86	49.05±1.23	9.8±2.36	19.6±2.25
3	85	10	15	147±2.36	85.02±3.19	17±3.12	28±1.58
4	75	10	25	70±1.98	38.15±1.28	7.6±1.24	15.3±3.22
5	95	10	25	100.1±2.65	71.94±1.96	14.4±2.66	28.8±1.51
6	75	5	15	84±1.74	64.31±1.13	12.9±2.33	25.7±2.16
7	85	15	25	107.8±2.34	50.14±.42	10±3.16	20.1±1.54
8	95	15	15	130.9±2.51	70.85±1.93	14.2±2.22	28.3±2.11
9	95	10	10	187.6±3.49	58.86±2.06	11.8±2.49	23.5±2.41
10	95	5	15	127.4±2.24	67.58±2.16	13.5±3.18	27±1.76
11	85	15	10	200.9±3.48	69.76±1.97	14±2.26	27.9±1.25
12	75	15	15	71.4±1.62	49.05±1.28	9.8±1.22	19.6±2.36
13	85	5	25	218.6±3.87	81±2.39	21±2.18	28.16±1.22

Phospholipid (mg) (X1), Tween 80 (mg) (X2), Sonication Time (Minute) (X3), Vesicle Size(nm) (Y1), Entrapment Efficiency (%) (Y2), Deformability (Y3), Zeta Potential(mV) (Y4).

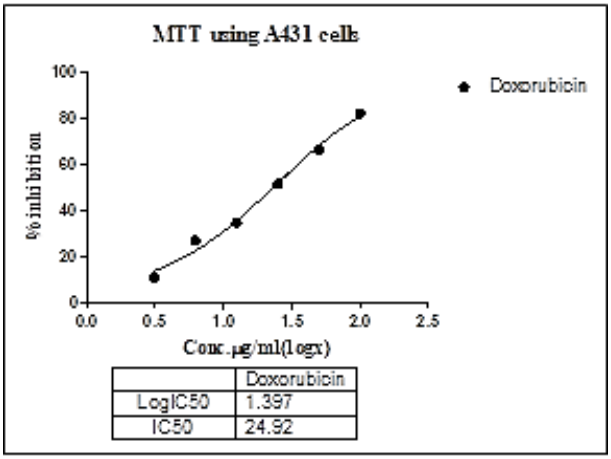
Transfersomal gel through topical route offers increased skin retention and penetration leading to improved therapeutic efficacy as described in Table. 1, and are critical.[11]

Preparation of Ultra-deformable Vesicles (Transfersomes)

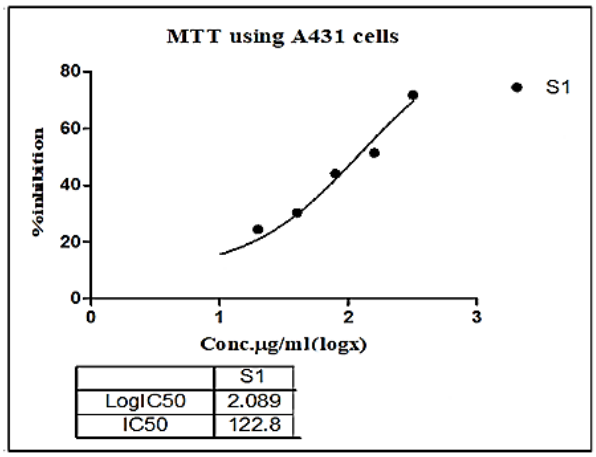
The transfersomes were prepared by the Vortex-Sonication method. Firstly, different concentrations of surfactants were added to precisely weighed phospholipid.[12] They were mixed in a buffer solution of 10% ethanol and phosphate. Phospholipid and surfactant concentrations ranged from 5-25% w/w. A test tube containing the solution was vortexed for around five minutes. The material was transferred for sonication, for approximately 15 minutes. The sonicated liquid was then put through three cycles of freeze-thaw after this operation.[13] Each of these cycles lasted for six hours. The transfersomes created by the freeze-thaw process were then extruded through a sandwich of 200 and 220 m nylon syringe filters.

Formulation of Drug Loaded Transfersomes

The topical dose of EGCG ranges from 0.05-0.1% for skin cancer. EGCG (100 mg /10 ml ethanol). The design expert software was used for optimization studies and Box-Behnken design (BBD) was employed.[14] The effects of several process parameters (Phospholipid quantity (X1), Tween 80 concentration (X2), and sonication time (X3) on Vesicle size (Y1) and Entrapment Efficiency (Y2), Deformability (Y3), Zeta potential (Y4) of transfersomes was thoroughly investigated. These independent variables



	Doxorubicin
LogIC50	1.397
IC50	24.92



	S1
LogIC50	2.089
IC50	122.8

a b

Figure 1: Cell inhibition activity of (a) standard drug (doxorubicin) and (b) EGCG on A431.

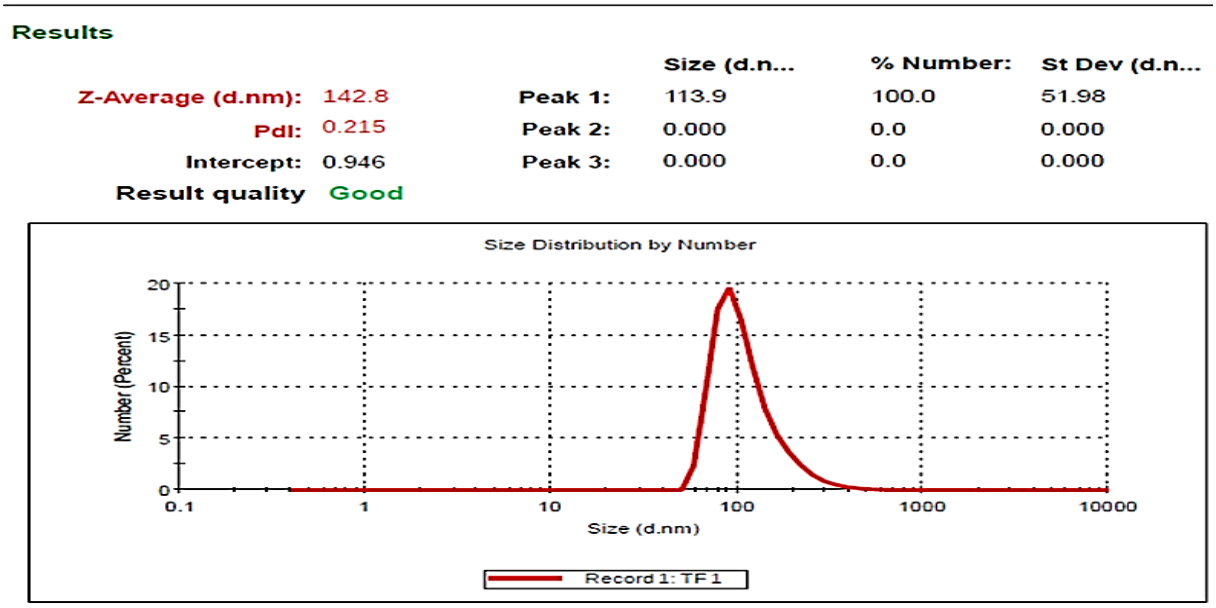


Figure 2: Particle size of optimized batch of EGCG Loaded transferosomes (TF-3).

were used in the optimum composition. A total of 13 formulation runs, including five centre points, were analyzed using Design-Expert® software to examine the impact of independent factors.[15] Polynomial equations yielded a variety of models, including the linear and quadratic. Given that the variables utilized demonstrated both individual and combined impacts on the dependent variables, the quadratic model among the available models was chosen to be the most effective one.[16]

Determination of particle size, polydispersity index, and zeta potential

The particle size, polydispersity index, and zeta potential of the prepared formulation were evaluated using diffraction light scattering (Zetasizer nano ZS, Malvern Instruments Inc, Southborough, MA) at 25 ◦C. The zeta potential measurements were done in 1ml cuvette. Water was used to match the refractive index and viscosity of the continuous phase and the experiments were performed in triplicates.[17]

Determination of drug entrapment efficiency

The prepared transfersomes was centrifuged and the supernatant (1 mL) was removed and diluted with 9 ml of phosphate buffer (pH 6.5) and the unentrapped EGCG was determined through absorbance at 210 nm using a UV spectrophotometer. After infusing the vesicle with Triton X-100, the amount of entrapped drug was determined using a UV spectrophotometer suitably diluted by phosphate buffer (pH 6.5). The vesicle was washed with phosphate buffer (pH 6.5), followed by 3 to 4 times.[18]

Table. 4 Result of all responses fitting to the model.

Response	R^2 value	P- value	Model F-value
Vesicle Size	0.9654	0.0464	9.31
Entrapment Efficiency	0.9660	0.0453	9.46
Deformability	0.9547	0.0481	7.02
Zeta Potential	0.9696	0.0385	10.64

Characterization Of Transfersome

Transmission Electron Microscopy

Transmission electron microscopy (TEM) was performed to determine the precise shape and morphology of the

Table 5: Characterization parameters of transfersome TF

Vesicle Size	Entrapment Efficiency	Deformability index	Zeta potential	Viscosity	pH	TEM
142.16 ± 5.07 nm	81.55 ± 2.56 %	19.7 ± 3.55	28.03 ± 3.98 mV	510 ± 1.5 CPS	6.4	Lamellar Vesicles

Table. 6 Permeation of EGCG loaded transfersomal gel and conventional gel on porcine skin.

Formulation Type	Flux (Jss) (μg/cm^2/h) ± SD (n=3)	Permeability coefficient (Kp) ± SD (n=3)	Skin Retention (%)
EGCG loaded transferosomal gel	94.88 ± 7.78	0.951 x $10^{-2 \pm}$ 0.08	71.03 ± 2.38
Conventional gel	38.8 ± 8.0	0.389 x $10^{-2 \pm}$ 0.72	19.22 ± 1.46

optimized transfersome suspension using Talos L120C, Thermo Fisher Scientific. The images were taken at an appropriate magnification.[19]

Preparation of transfersomal gel

The optimal transfersome TF-3 was chosen to make a gel based on permeability, drug release, deformability, entrapment efficiency, and *in vitro* characterization studies. In order to make Transfersomal gel, 1 g of Carbopol 940 was dissolved in 100 ml of phosphate buffer (pH 6.5) and pH was maintained using triethanolamine which was added dropwise. The 1% Carbopol 940 solution was allowed to stand for 24 hours for complete dispersion. The gel base was gently added to the transfersomes formulation in 1: 1 ratio with stirring.[20]

Characterization of Optimized Transfersome Gel Formulation

Spreadability

A modified apparatus consisting of two glass slides containing gel in between, with the lower side fixed to a wooden plate and upper one attached to a balance by a hook was used to determine spreadibility.[21] Spreadability was found to be 7.4.

Drug Content determination

By dissolving 1g of transfersomal gel in 100 ml of phosphate buffer (pH 6.5) for 48 h and analyzed by UV spectrophotometer at λ_{max} 210 nm and 238 nm.[22]

Viscosity & pH

The viscosity and pH of the gel and found to be 80.23 CPS and 6.4 respectively.

RESULTS

***In vitro anti* cell proliferation activity of EGCG**

It was determined prior to formulation studies to check its anticancer effect against skin cancer cell lines. The IC_{50} of EGCG against A431 was found to be 122.8 μg/ml. (Table. 2)

Quadratic model

From the results of the optimization process, it was found that all three independent variables were found to be fitting in the quadratic model as per following regression equations:

Vesicle Size =+127.40+29.05 * A -11.38 * B-21.53 * C-0.87 * A * B -12.43* A * C -34.83 * B * C -36.31 * A2+17.24 * B2 +25.29 * C2

Entrapment Efficiency =+67.58+10.76 * A-9.04 * B-2.27 * C+0.27 * A * B +5.99 * A * C-4.72 * B * C-8.22 * +7.95 * B2-4.86 * C2

Deformability = +13.50+2.16 * A -2.41 * B +0.13 * C+0.075 * A * B +1.20 * A * C -2.15 * B* C -2.24 * A2 +2.21 * B2 -0.36 * C2

Zeta Potential =+27.00+4.30 * A-3.81 * B -0.69 * C +0.10 * A * B+2.40 * A * C-2.27* B * C-3.49 * A2 +3.39 * B2-1.71 * C2

Vesicle size and morphology

Characterization of the transfersome formulation was done. Vesicle size, shape, entrapment effectiveness, deformability, number of vesicles per mm^3, viscosity, and pH are all factors in the vesicular system's characterization.[23] TEM was used to assess vesicle morphology. Multilamellar vesicles were discovered to be the vesicle shape of the formulation (Table 5).

The goal of interaction studies was to identify any interference and interactions between drugs and other formulation elements. Drug interaction with phospholipid, surfactant, and methanol in transfersome formulation. However, the medication was discovered to be comparatively stable and inert to the excipients utilized in Transfersomal gel in the interaction assays. According to the UV spectra, the formulation and pure drug solution had identical absorption maxima (λ max). Excipients for transfersome formulation were physically combined in vials and exposed to various temperatures for four weeks.

Drug-Excipients Compatibility Study

The results of drug-excipient compatibility study showed that EGCG was compatible with all excipients used to formulate transfersomes.[24]

Ex vivo studies on porcine skin

Permeation and retention studies on porcine skin were conducted using freshly cut pig ear skin (sourced from a nearby butcher). Pig ear skin was used for the investigation due to its similarities to human skin and widespread use in similar studies.[25]

DISCUSSION

The findings suggest, development and administration of EGCG-loaded transferosomes represent a promising for treatment of NMSC. EGCG, a bioactive compound with anticancer properties, has demonstrated efficacy in reducing cancer cell proliferation and inducing apoptosis in NMSC cell lines, such as A431. By incorporating EGCG into transfersomal nanocarriers, the stability, bioavailability, and skin penetration of EGCG can be significantly enhanced, addressing the limitations posed by traditional topical treatments. The ex vivo studies on

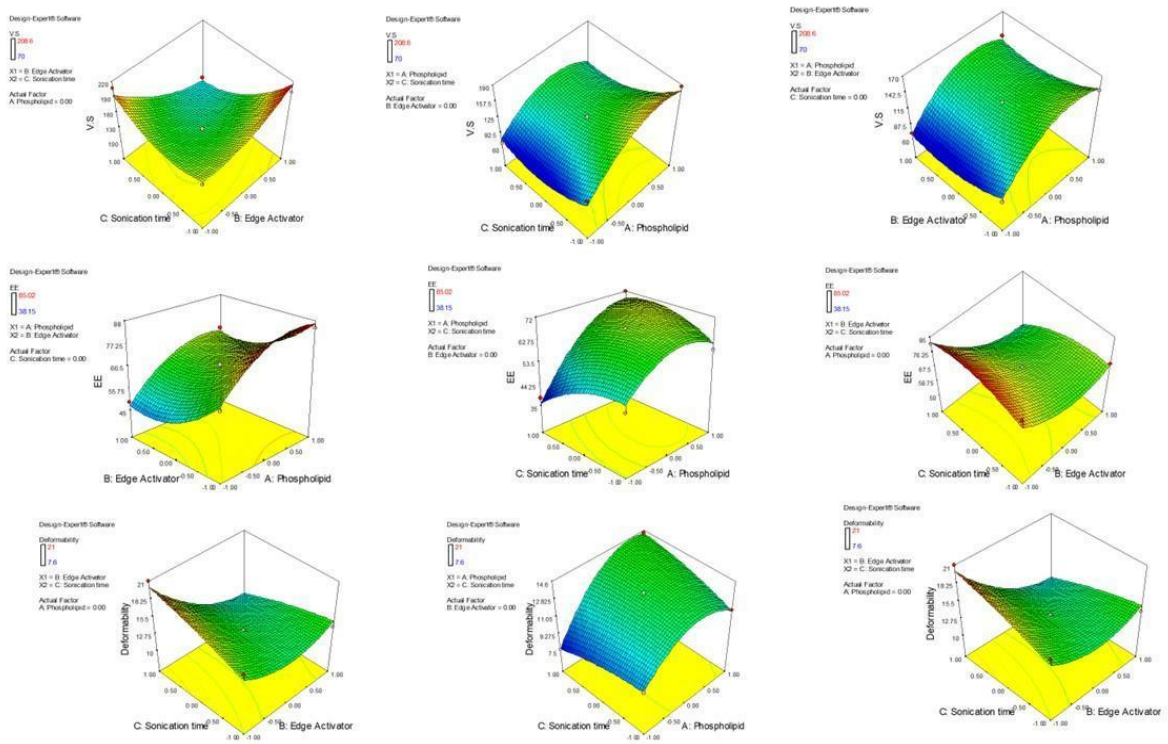


Figure 3: The drug-loaded transferosomes were optimized via Box-Behnken optimisation. Two dependent parameters were present along with three independent parameters. The amount of phospholipid, edge activator %, and sonication time were the independent variables. As the sonication period was extended, the size of the vesicles decreased because sonication assists in dissolving the larger vesicles to create smaller vesicles.

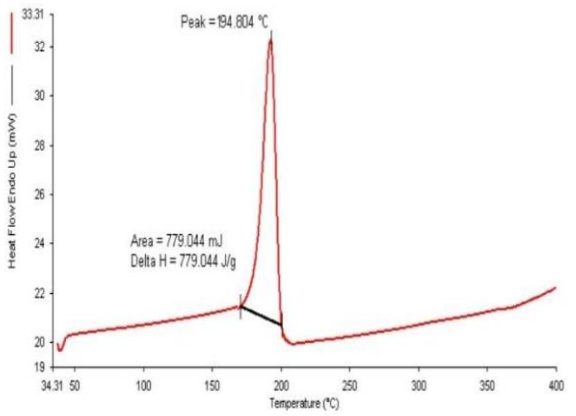


Figure 4: DSC Thermogram optimized formulation (TF-3)

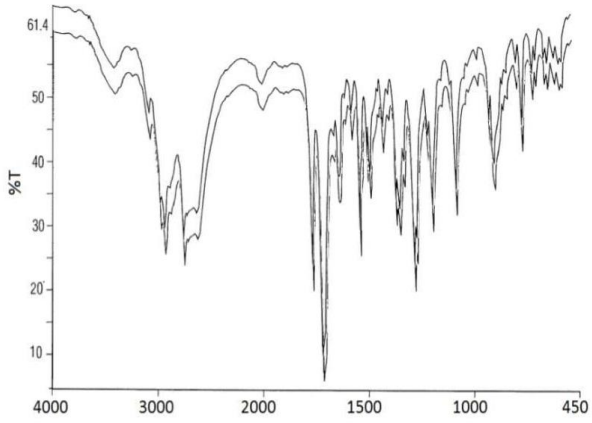


Figure. 5: FTIR Spectra of EGCG Loaded Transfersomes

porcine skin further demonstrated that the transfersomal gel can effectively penetrate the stratum corneum, reaching the viable epidermis, which is crucial for localized NMSC treatment. Importantly, this study also utilized a Box-Behnken Design for optimization, allowing for efficient development of a stable, high-performing formulation while minimizing resources and experimental variability.

CONCLUSIONS

This study highlights the potential of EGCG-loaded transfersomes as an innovative, effective approach for treating NMSC. The incorporation of EGCG into transfersomal carriers offers numerous advantages, including improved stability, enhanced penetration and targeted delivery, which are essential for addressing the limitations of current NMSC therapies. The promising results from molecular docking, cell line studies, and ex vivo porcine skin models provide a solid foundation for further exploration of EGCG transfersomes as a viable treatment option for NMSC. Given the prevalence of NMSC and the limitations of existing therapies, EGCG-loaded transfersomes could serve as an alternative or adjunctive therapeutic approach, potentially improving patient outcomes and quality of life. In conclusion, this research highlights the capacity of transfersomal gel systems in enhancing the transdermal delivery of bioactive compounds like EGCG. Overall, transfersomes of EGCG hold considerable promise in enhancing the treatment for

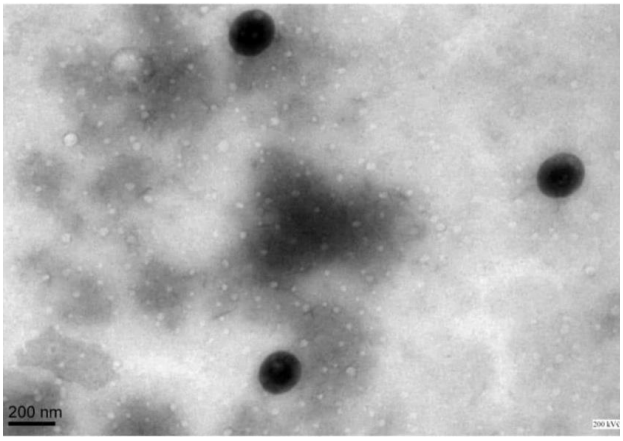


Figure. 6: TEM Image of EGCG Loaded Transfersomes

non-melanoma malignancy. They provide a stable, bioavailable, and targeted delivery method that enhances the therapeutic impact of EGCG while minimizing side effects and improving patient compliance.

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