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A RESEARCH ARTICLE ON FORMULATION AND CHARACTERIZATION OF HYDROQUINONE LIPOSOME BASED HYDEROGEL

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ABSTRACT

This study explores the development of a hydrogel formulation for the effective topical delivery of hydroquinone (HQ) for the treatment of hyperpigmentation. Hydroquinone, a widely used skin-lightening agent, works by inhibiting tyrosinase, thus reducing melanin production. However, conventional topical formulations such as creams and gels face challenges, including stability issues, stickiness, and uncontrolled drug release. To overcome these limitations, hydrogels, particularly liposomal hydrogels, are being investigated. Liposomes enhance the local retention of drugs, ensuring sustained release and reducing systemic absorption. In this formulation, hydrogels provide a moisture barrier, promoting wound healing and reducing bacterial contamination. The controlled release of HQ from liposomal hydrogels offers potential advantages over traditional delivery systems, including increased skin concentration and prolonged therapeutic action. The study focuses on evaluating the stability of HQ in hydrogel dispersion, aiming to improve its efficacy in treating conditions such as melasma, freckles, and post-inflammatory hyperpigmentation. By using appropriate liposomal formulations and optimizing the hydrogel matrix, this approach offers a promising strategy for targeted, controlled, and effective treatment of hyperpigmentation with reduced side effects.

KEY WORDS: *Hydroquinone, Hyperpigmentation, Liposomal Hydrogels, Melasma.*

INTRODUCTION

One of the human body's largest and easiest organs to access is the skin. An adult's skin has a surface area of around 3000 inches and gets one-third of the blood that circulates throughout the body. It is tough, elastic, and, in normal physiological circumstances, self-regenerating to the thickness of a half millimetre.

INFRAORBITAL DARK CIRCLE DISEASE

Periorbital aesthetics is preferred when determining an individual's age and level of weariness. Social judgments across cultures are similar in that periorbital dark circles are associated with fatigue. For example, a woman in the United States spends $15,000 (USD) on cosmetics and cosmeceuticals over the course of her lifetime, with under-eye concealers accounting for a significant portion of this amount.

ATIOLOGY OF INFRAORBITAL DARK CIRCLES

Comprehending anatomy in great detail is essential to accurately determine the cause of infraorbital dark circles. A number of anatomical factors, such as the bony structure, the prominence of the orbicularis oculi muscle and vasculature, the thin skin of the eyelids with little to no subcutaneous tissue, and the facial legamentous architecture, can all contribute to the appearance of periocular circles.

UNDERLYING LIGAMENT AND BONE STRUCTURE

The facial soft tissue is supported by the underlying facial ligament and bone structure, which also affects the overall appearance of the face. The principal structural divisions of the facial fat compartments are comprised of the osseo-cutaneous facial ligaments.

MIDFACE SOFT TISSUE CONTRIBUTION

The orbicularis oculi muscle and the strong subcutaneous vascular network that underlie the prominence of the midface soft tissue are not well camouflaged by the thin and rather translucent skin of the eyelids. The skin appears darker as a result of this. The infraorbital soft tissue area may see an accumulation of infraorbital eyelid fluid, which would further accentuate the area's aged and darker appearance.

NOVEL DRUG DELIVERY SYSTEM

Since the dawn of time, a variety of compounds have been applied to human skin for use as cosmetics and therapeutic agents; but, in the twentieth century, the skin has evolved into a pathway for long-term delivery. By reducing the medicine's degree of action

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and the side effects connected with oral therapy, transdermal drug administration offers a way to maintain drug release. When developing transdermal drug delivery systems (TDDS), factors such as medication pharmacokinetics and clinical requirements selection are crucial.

LIPOSOMES

Liposomes are merely small vesicles with a completely lipid-based membrane enclosing an aqueous volume. Liposomes are structurally defined as concentric bilayer vesicles with a completely membranous lipid bilayer, primarily made of synthetic or natural phospholipids, enclosing an aqueous volume. Greek terms "liposome" and "some's" denote "fat" and "body," respectively. Alec D. Bangham created the first liposome in England in 1961.

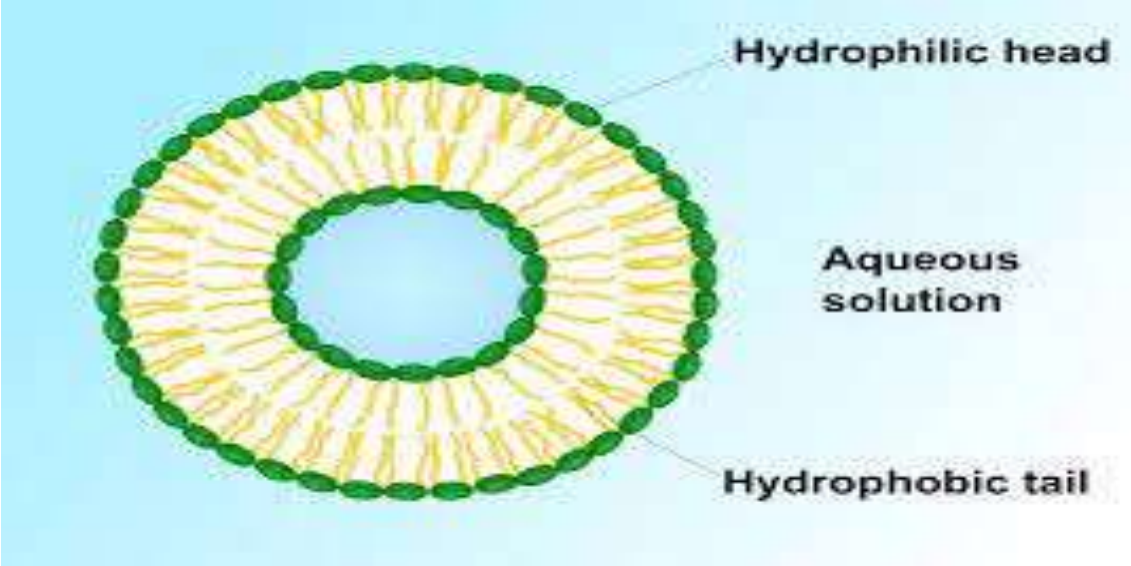


Fig. 1: Scheme of a liposome formed by phospholipids in an aqueous solution

Types of Liposomes

- 1 Based on Structural Parameter
- 2 Based on Method of Liposome Preparation
- 3 Based Upon Composition and Applications

Advantages

- Liposomes increased efficacy
- Facilitation of transport across membranes.
- Liposomes increased stability via encapsulation.

HYDROQUINONE

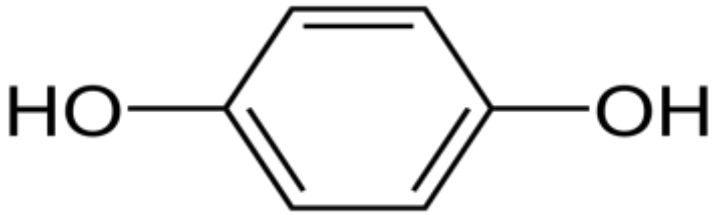


Fig. 2: Structure of Hydroquinone

Hydroquinone, also known as **benzene-1,4-diol** or **quinol**, is an aromatic organic compound that is a type of phenol, a derivative of benzene, having the chemical formula $C_6H_4(OH)_2$. It has two hydroxyl groups bonded to a benzene ring in a para position. It is a white granular solid. Substituted derivatives of this parent compound are also referred to as hydroquinone. The name "hydroquinone" was coined by Friedrich Wöhler in 1843. In 2021, it was the 282nd most commonly prescribed medication in the United States, with more than 800,000 prescriptions.

USES

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Hydroquinone has a variety of uses principally associated with its action as a reducing agent that is soluble in water. It is a major component in most black and white photographic developers for film and paper where, with the compound metol, it reduces silver halides to elemental silver.

MATERIALS AND METHODS

Table 1: List of materials used

Materials	Source
Hydroquinone	Ranchem Lab, India.
Phospholipon 90 H	Ranchem Lab, India.
Cholesterol	Ranchem Lab, India.
Lecithin	Ranchem Lab, India.
Sodium alginate	Ranchem Lab, India.
Potassium di hydrogen ortho Phosphate	Ranchem Lab, India.
Sodium hydroxide	Ranchem Lab, India.
Methanol	Ranchem Lab, India.
Sodium periodate	Ranchem Lab, India.
Sodium chloride	Ranchem Lab, India.

Table 2: List of instruments and equipment used

Equipment/Instruments	Model/ Manufacturer
Electronic balance	AW120 Shimadzu, Japan.
FT-IR Spectrophotometer	FTIR-8400SShimadzu, Japan.
Orbital shaking incubator	CIS24BL, Remi, Mumbai, India.
UV-Visible Spectrophotometer	UV1800, Shimadzu, Japan
Magnetic stirrer	Remi, Mumbai.
Centrifuge	Remi, Cooling centrifuge.
Viscometer	Brookfield DVII+ viscometer, HBD
Digital pH meter	Elico-LI120 pH(type003), Hyderabad.
Sonicator	MU1000:RC system.
Zetasizer3000	Malvern Instruments, UK.
Trinocular Microscope	Hl10 Coslab115
Stability Chamber	Thermo lab humidity chambers, India.

METHODS

PREFORMULATION EVALUATION

DETERMINATION OF □MAX OF HYDROQUINONE IN PHOSPHATE BUFFER PH 7.4

Stock solution of 100 mg/ 100ml hydroquinone solution was prepared by dissolving 100 mg of pure drug in 10 ml of ethanol and made up to 100 ml with phosphate buffer pH 7.4. This is designated as stock solution A(1 mg/ml). From the stock solution A, 5 ml was taken and diluted to 100 ml with phosphate buffer pH 7.4 to give the concentration 50 µg/ml (stock solution B). The above solution was scanned between 200-400 nm. The sample showed a λ_{max} of 228 nm shown in Figure 6 and was used for further analysis.

STANDARD PLOT OF HYDROQUINONE

From the above stock solution B‟, aliquots of 1, 2, 3, 4, and 5 ml were transferred to 10 ml volumetric flasks and made up to the mark with methanol to get concentrations of 5, 10, 15, 20, and 25 µg/ml. The absorbance of these solutions was measured at 228 nm and a graph of concentration versus absorbance was plotted.

COMPATIBILITY STUDIES

Done by Fourier transform infrared spectroscopy. FT-IR analysis was carried out for pure drug and drug with polymers, using KBr pellet method on FTIR spectrophotometer (FTIR-8400S, Shimadzu, Japan). The pure drug was mixed with KBr in the ratio of 1:3 and punched in a hydraulic press at 5-6 ton load. The prepared pellets were scanned from 4000 to 400 cm-1 using FT-IR spectrophotometer. The FT-IR spectra of the physical mixture were compared with the spectra of pure drug.

PERCENTAGE DRUG CONTENT

Liposomes (100 mg) was taken in a 50 ml volumetric flask, the volume was made up to 50 ml using methanol. 5 ml of this solution was further diluted to 25 ml with methanol. Then drug concentration was determined by measuring the absorbance at 228 nm using

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UV-Vis. spectrophotometer.

PREPARATION OF HYDROQUINONE LIPOSOMAL HYDROGELS

Preparation of hydrogels and incorporation of optimize hydroquinone liposomes: Gels were prepared by using a double syringe fibrin glue applicator, in which one syringe was filled with the solution of oxidized alginate in 0.1M borax and the other with equal volume of gelatin in water along with optimized hydroquinone liposomal hydrogels. The applicator was fitted with a 20G needle. The mixing of the polymer solutions inside the hypodermic needle on pushing the plunger in the applicator led to gelation and cross-linking in a few seconds with the incorporation of optimized liposomes and subsequent formation of the liposomal hydrogel. The liposomes added into the hydrogel contained 2% w/w hydroquinone

a. EVALUATION

Gelling time: About 1 ml of oxidized alginate in 0.1M borax was reacted with 1 ml of gelatin solution in glass vials of 15 ml capacity (diameter 20mm) under magnetic stirring using a teflon-coated stir bar (diameter 5mm, length 10mm) at 37 °C. The time required for the stir bar to stop was noted as gelling time. The gelling time was studied by varying the concentration of oxidized alginate and gelatin[39].

Swelling index: The swelling ability of hydrogels was determined by a conventional gravimetric method, hydrogels were partially hydrated, then equilibrated in air at room temperature, after which, each hydrogel formulation was immersed in distilled water at room temperature (37ºC) and its increase in weight with time was noted. The water content (WC) was calculated[110].

$$\text{Equilibrium fluid content (\%)} = \frac{w_s - w_d}{ws} \times 100$$

Where W_s and W_d represent the weight of swollen and dry sample, respectively

In vitro drug release studies: In vitro release studies were carried out using modified Franz diffusion cell. Dialysis membrane (Hi Media molecular weight 5000) was placed between receptor and donor compartments. The liposomal hydrogel was placed in the donor compartment and the receptor compartment was filled with 25 ml of phosphate buffer (pH 7.4) maintained at 37±0.5°C with constant stirring. Aliquots were withdrawn at specific time intervals from receiver compartment through side tube and the medium were replaced with fresh PBS to maintain a constant volume. The amount of drug released was determined by using UV-Visible Spectrophotometer.

Viscosity: Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield Engineering Laboratories, Inc, Middleboro) was used to determine the viscosity of different formulations at 25 ± 1.0°C.

Spreadability: Spreadability was determined by wooden block and glass slide apparatus. A ground glass slide was fixed on the block and an excess formulation (2 g) was placed between two glass slides and 100 g weight was placed on the upper glass slide for 5 min to compress the formulation to uniform thickness. Weight (100 g) was added to the pan. The time in seconds required to separate the two slides was taken as a measure of spreadability.

Percentage drug content: Liposomal hydrogel (1 g) was taken in a 50 ml volumetric flask. The volume was made up to 50 ml using methanol. 5 ml of this solution was diluted to 25 ml with methanol. Then drug content was determined by measuring the absorbance of solution at 223 nm using UV-Vis. spectrophotometer.

pH: The pH of each liposomal hydrogel was measured using previously calibrated pH meter. The measurements were made in triplicate.

Scanning electron microscopy (SEM): SEM photographs were taken with a scanning electron microscope (Hitachi S3400, Tokyo, Japan) at the required magnification at room temperature. The liposomal hydrogels were placed on a glass disc applied on a metallic stub and subjected to evaporation under a vacuum overnight. The samples were metallized under an argon atmosphere with a 10-nm gold palladium thickness.

Kinetics of drug release: To study the drug release mechanism from the liposomal hydrogels, the release data was fitted into various mathematical models. The parameters like „n“ the time exponent, „k“ the release rate constant and “R“ the regression co-efficient were determined to know the release mechanisms.

Stability studies: The optimized formulation was packed in a screw capped bottle and studies were carried out for 12 months by keeping at:

- 25±2°C and 60 ± 5% RH
- 30± 2°C and 65 ± 5% RH

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And for 6 months for accelerated storage condition at

- 40± 2°C and 75 ± 5% RH

Samples were withdrawn on 0, 3, 6 and 12 months for long term storage condition and 0, 3 and 6 months for accelerated storage condition and checked for changes in physical appearance and drug content.

RESULT AND DISSCUSSION

UV spectroscopic analysis

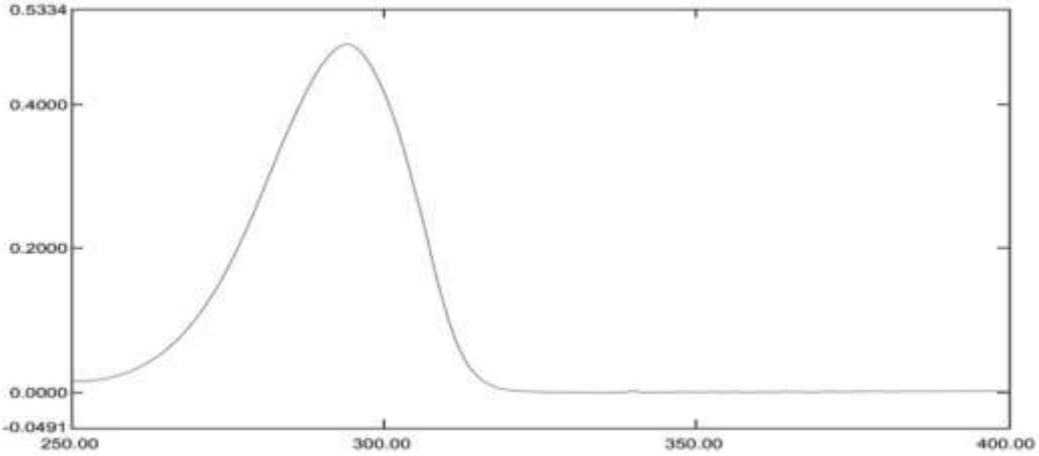


Fig. 3: λ_{max} of hydroquinone in phosphate buffer pH 7.4

Table 3: Calibration curve of Hydroquinone in phosphate buffer pH 7.4

S. No.	Concentration	Absorbance
1.	0	0
2.	5	0.173
3.	10	0.367
4.	15	0.592
5.	20	0.753
6.	25	0.985

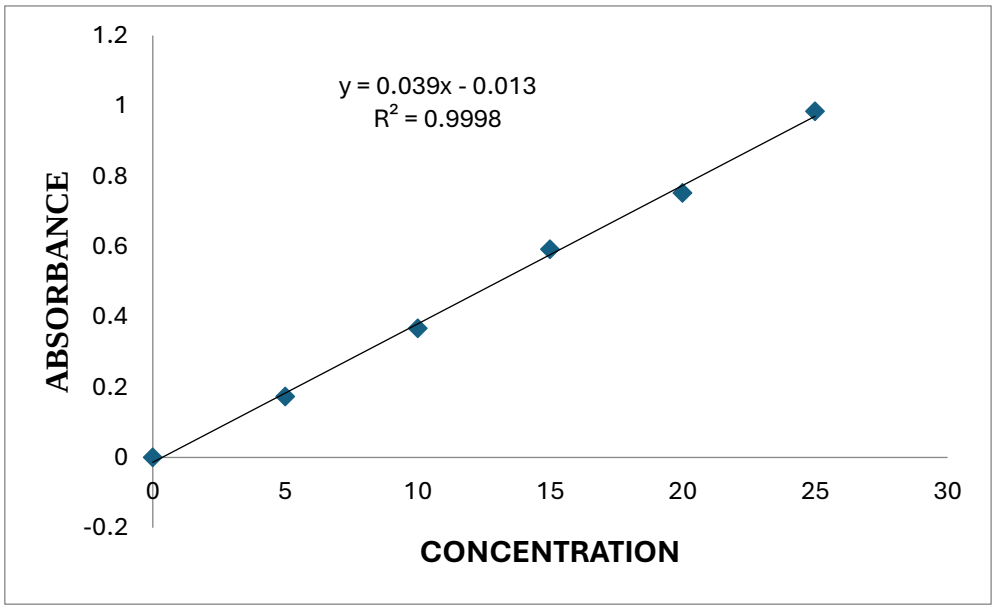


Fig. 4: Calibration curve of hydroquinone in phosphate buffer pH7.4.

Compatibility Studies: FT-IR studies are used to determine the possible interaction between the drug and excipients used. The existence of an interaction is detected by the alteration, shift or disappearance of a functional group peak of the drug. The FT-IR spectra of Hydroquinone and its physical mixture with polymer are shown in Figure 8. There were no significant differences in the characteristic peaks position of Hydroquinone (3481 and3308 cm^{-1} due to O-H group, peaks at 1729 and 1712 cm^{-1} corresponding

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to the C=O group and peaks at 1232 and 1222 cm^{-1} corresponding to C-O group) compared to its physical mixture with the polymers. Hence Hydroquinone was compatible with excipients.

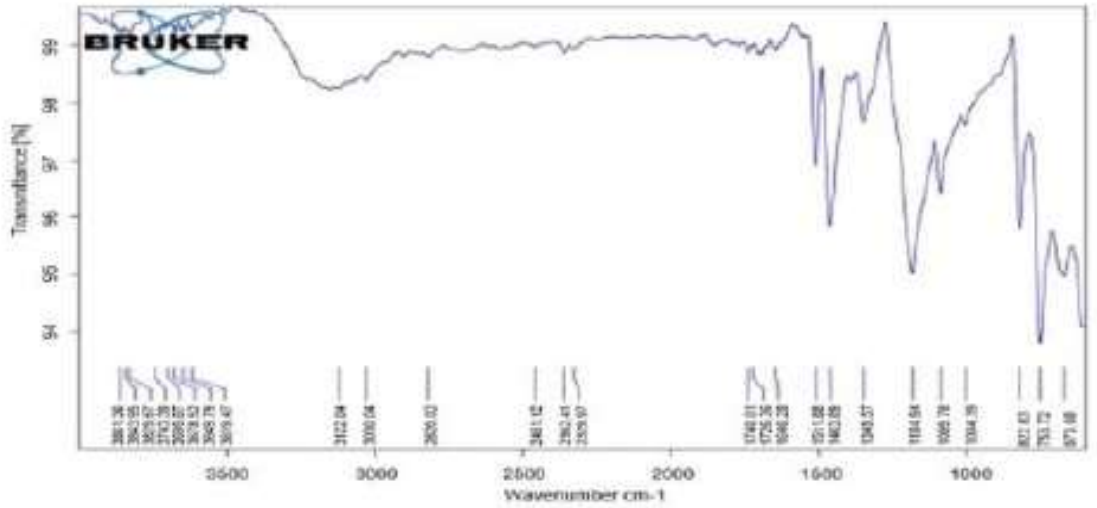


Fig. 5: FTIR Spectrum of Hydroquinone

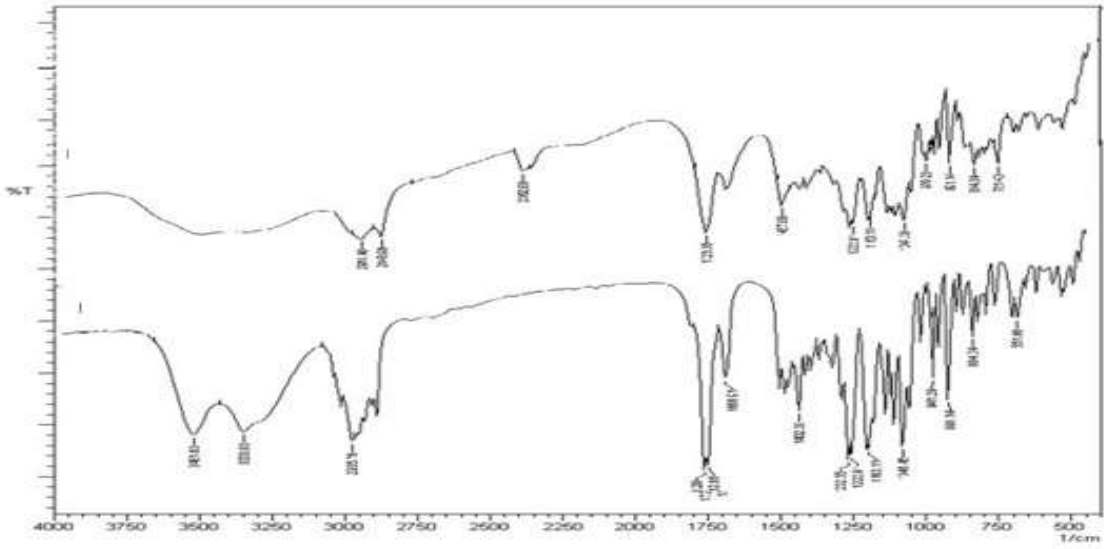


Fig. 6: FT-IR spectra of Hydroquinone and physical mixture of polymers.

Table: 4 FTIR Interpretation of Hydroquinone

WAVE NUMBER	INTERFERENCE
3829.67	O-H Str.
3122.04	=CH str. (Aromatic)
1511.88	C=C Aromatic

PREPARATION OF LIPOSOMES

Table: 5 Composition of liposomes

Formulation	Lecithin (mg)	Cholesterol (mg)	Rotation speed (rpm)
H1	**100**	**20**	**200**
H2	**100**	**50**	**200**
H3	**200**	**20**	**100**
H4	**200**	**20**	**200**
H5	**200**	**50**	**200**
H6	**100**	**20**	**100**
H7	**100**	**50**	**100**
H8	**200**	**50**	**100**

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Table 6. Percentage yield, particle size and polydispersity index of hydroquinone liposomes.

Formulations	% Yield	Particle size (nm)	Polydispersity index
H1	70.45±0.56	364.40	0.387
H2	76.67±0.77	165.51	0.210
H3	74.14±0.61	265.30	0.253
H4	71.71±0.98	237.60	0.300
H5	72.19±0.44	391.41	0.370
H6	77.11±0.54	149.17	0.233
H7	68.03±0.82	314.63	0.470
H8	68.28±0.68	205.11	0.371
H9	70.66±0.48	115.30	0.320

Table 7. Encapsulation efficiency and drug content of hydroquinone liposomes.

Formulations	Encapsulation efficiency (%)	Drug content (%)
H1	55.21±0.52	97.61±0.56
H2	65.85±0.34	96.55±0.48
H3	62.25±0.52	98.11±0.13
H4	62.25±0.52	98.36±0.66
H5	59.89±0.34	98.52±0.16
H6	57.46±0.73	97.23±0.32
H7	69.14±0.35	98.14±0.28
H8	52.73±0.66	98.76±0.23
H9	62.33±0.36	97.45±0.33

Standard deviation, n=3

Table 8. Particle size with polydispersity index of hydroquinone liposomes.

Formulation	Particle size (nm)	Polydispersity index (PDI)
H6	**264.30**	**0.233**

Table 9. Invitro dissolution data of optimized hydroquinone liposomes in phosphate buffer pH 7.4.

Time	Cumulative % drug release
0	0
1	10.65±0.24
2	19.89±0.81
3	26.75±0.52
4	35.59±0.41
5	44.85±0.78
6	53.78±0.51
7	61.97±0.45
8	72.84±0.79
9	81.75±0.51
10	87.59±0.23
11	92.84±0.78
12	95.43±0.22

Standard deviation, n=3

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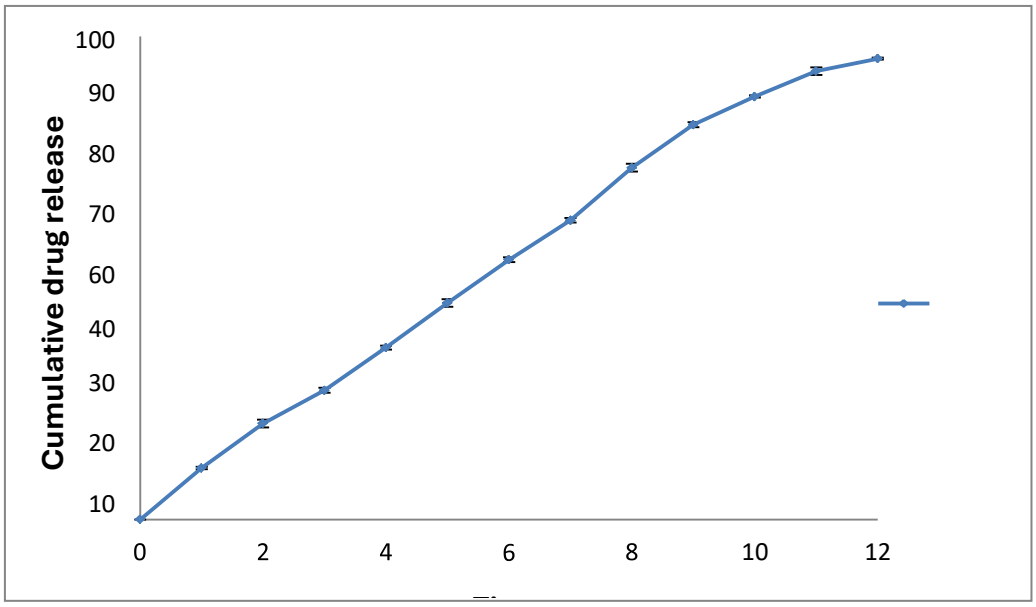


Fig. 7: Invitro drug release profile of optimized hydroquinone liposomes in phosphate buffer pH 7.4.

Shape of liposomes: The shapes of most of the hydroquinone loaded liposomes were spherical in shape.

Scanning electron microscopy (SEM): Liposomes surface morphology and shape were investigated by SEM analysis. The Hydroquinone loaded liposomes have vesicular structure and were spherical in shape.

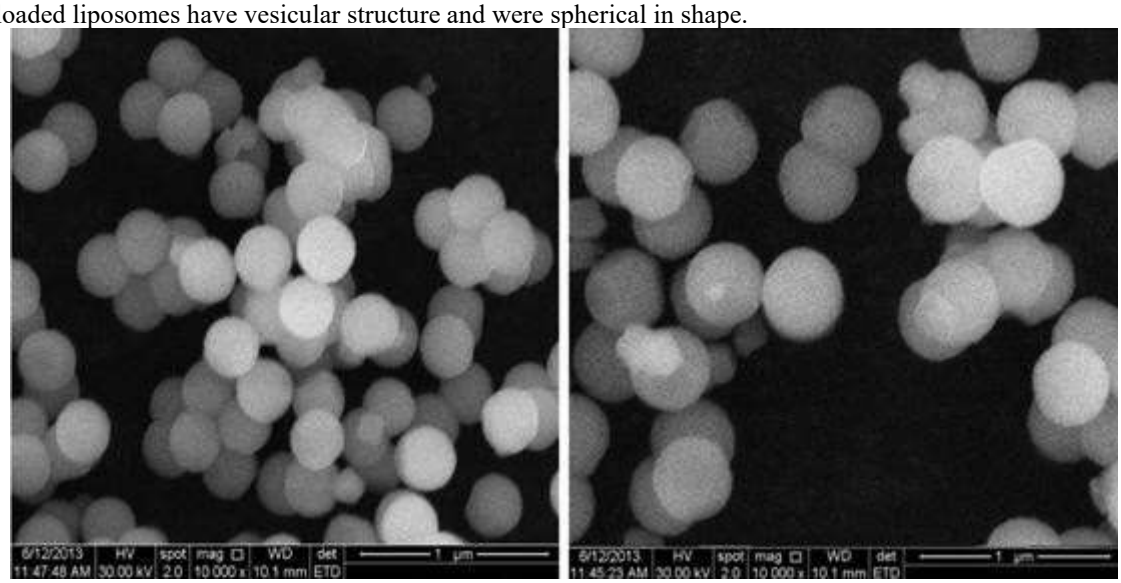


Fig. 8: SEM images of optimized hydroquinone liposomes.

Stability Studies: The optimized formulation was packed in a screw capped bottle and studies were carried out for 12 months by keeping at 25±2°C and 60 ± 5% RH and 30± 2°C and 65 ± 5% RH And for 6 months for accelerated storage condition at 40± 2°C and 75 ± 5% RH Samples were withdrawn on 0, 3, 6 and 12 months for long term storage condition and 0, 3 and 6 months for accelerated storage condition and checked for changes in physical appearance and drug content. After checking it was found that optimized formulation was stable and not any changes appear on formulation it means optimized formulation is stable.

SUMMARY AND CONCLUSION

Aim of the research work was to develop and evaluate the Hydroquinone liposomal hydrogels for skin diseases such as black spot. The prepared liposomal were evaluated for percentage yield, particle size, polydispersity index, drug content, and in vitro drug release studies. The liposomal hydrogels were evaluated for drug content, viscosity and in vitro drug release studies. Hydroquinone was compatible with excipients chosen for study as indicated by FT-IR. The optimized hydroquinone liposomes showed yield of 77.11%, particle size 149.17 nm and polydispersity index 0.233. Hydroquinone was uniformly distributed in liposomes. The drug content was in the range of 97.23±0.32-98.76±0.23%. In vitro release drug of the optimized hydroquinone liposomes was

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Volume: 10 | Issue: 1 | January 2025 - Peer Reviewed Journal

95.43±0.22% at the end of 12 h. The release kinetics studies revealed that the hydroquinone was released from liposomes by a diffusion-controlled mechanism.

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