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FORMULATION AND CHARACTERIZATION OF ROSUVASTATIN LIPOSOMES FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The application of liposomal vesicles for the transdermal delivery of rosuvastatin sodium offers a promising approach to overcome limitations associated with its oral administration. Rosuvastatin, a hydrophilic HMG-CoA reductase inhibitor, suffers from low oral bioavailability (~20%) due to extensive first-pass hepatic metabolism, necessitating higher doses that increase the risk of adverse effects. Liposomal carriers, composed of amphiphilic phospholipid bilayers, improve dermal drug delivery by enhancing skin permeation and enabling controlled, sustained release. These vesicles interact with the stratum corneum, facilitating deeper penetration into dermal layers and providing a steady release profile, which minimizes systemic toxicity and peak plasma fluctuations. Encapsulation of rosuvastatin in liposomes has demonstrated improved bioavailability, prolonged therapeutic levels, and reduced dosing frequency. Key formulation parameters—such as vesicle size, lipid composition, and surface charge—significantly influence transdermal flux and drug retention. Both *in vitro and in vivo studies* support the enhanced pharmacokinetic profile of rosuvastatin through liposomal delivery systems. Despite these benefits, challenges such as long-term stability, batch-to-batch reproducibility, and large-scale manufacturing must be addressed. Future work should focus on formulation optimization and clinical validation to facilitate the translation of liposomal transdermal systems into viable alternatives for cardiovascular therapy.

INTRODUCTION

In recent years, the development of advanced drug delivery systems has focused extensively on enhancing the transdermal absorption of therapeutic agents, particularly for drugs exhibiting low oral bioavailability. Among the most promising platforms, liposomes have emerged as versatile nanocarriers owing to their structural resemblance to biological membranes, inherent biocompatibility, and capability to encapsulate both hydrophilic and lipophilic drugs. Structurally, liposomes are spherical vesicles composed of one or more concentric phospholipid bilayers, with an aqueous core that allows the entrapment of water-soluble drugs, while their lipid bilayers can accommodate lipophilic molecules. This unique dual-compartment nature facilitates the delivery of a broad spectrum of pharmacological agents. When applied topically, liposomes enhance skin penetration due to their amphiphilic composition, which allows them to interact favorably with the stratum corneum—the primary barrier to transdermal drug absorption. Their ability to

fuse with skin lipids enables deeper permeation into the epidermal and dermal layers, promoting localized drug deposition and sustained systemic absorption. Despite the barrier properties of the stratum corneum, liposomes, particularly those with nanometric sizes (preferably <600 nm), can penetrate effectively, especially when optimized with suitable excipients. Furthermore, skin appendages such as sweat glands and hair follicles, previously considered minor contributors to percutaneous absorption, are now recognized as potential pathways that facilitate the penetration of vesicular carriers into deeper layers of the skin. The reservoir effect created by liposomal systems enables prolonged drug residence time in the skin, resulting in sustained release profiles and improved therapeutic outcomes. This is particularly advantageous in conditions requiring long-term drug maintenance at the site of action or in systemic circulation. From a pharmacokinetic standpoint, transdermal liposomal drug delivery circumvents the hepatic first-pass metabolism,[1] a major drawback in conventional oral formulations. By avoiding the gastrointestinal tract, drugs are protected from enzymatic degradation and variable pH environments, leading to more consistent plasma drug levels and reduced dosing frequency. This not only improves the overall therapeutic index but also enhances patient compliance. Rosuvastatin sodium, a hydrophilic HMG-CoA reductase inhibitor used in hypercholesterolemia and cardiovascular disease management, is a prime candidate for such delivery systems. Its poor oral bioavailability (~20%) and extensive hepatic metabolism necessitate higher doses, increasing the risk of systemic side effects like myopathy, rhabdomyolysis, and hepatotoxicity. Transdermal liposomal formulations offer a promising alternative by enabling sustained drug release, enhancing absorption, and minimizing adverse effects associated with oral administration. Preclinical studies have demonstrated that liposomal formulations of rosuvastatin result in significantly improved skin permeability and prolonged drug retention in the dermis, leading to enhanced systemic availability and therapeutic efficacy. Additionally, co-formulation of liposomes with hydrogel matrices further augments the performance of the delivery system. Hydrogels provide a favorable rheological profile, improve skin adherence, and maintain a moist environment that facilitates drug absorption while minimizing irritation. These semi-solid systems also buffer environmental pH fluctuations, enhance patient comfort during application, and stabilize the encapsulated drug against physical and chemical degradation. The integration of liposomes within hydrogels helps overcome limitations related to liposomal instability and burst release, promoting a more controlled and sustained pharmacokinetic profile[2]. The physicochemical properties of liposomes—including particle size, surface charge (zeta potential), lipid composition, and lamellarity—play critical roles in determining their drug loading efficiency, release kinetics, and permeation behavior. Cholesterol is often added to formulations to modulate membrane fluidity, reduce leakage, and enhance the mechanical strength of vesicles. The inclusion of charge-inducing agents (e.g., stearylamine or dicetyl phosphate) can stabilize vesicles via electrostatic repulsion and improve their interaction with negatively charged skin components. Moreover, the dehydration-rehydration method, freeze-thaw cycling, and extrusion techniques are commonly employed during liposome preparation to optimize encapsulation efficiency and particle uniformity. Transdermal drug delivery systems (TDDS), including liposomal formulations, are designed to mimic the pharmacokinetics of continuous intravenous infusion by maintaining consistent plasma drug concentrations over extended periods. The delivery mechanism relies on passive diffusion, governed by Fick's law, where the drug moves from a higher concentration in the delivery vehicle (Cd) to a lower concentration in systemic circulation (Cr). The drug flux (dQ/dt) across the skin is proportional to the concentration gradient and the permeability coefficient (Ps), which is influenced by drug lipophilicity, molecular weight, formulation excipients, and the integrity of the stratum corneum. In vitro skin permeation studies using devices such as Franz diffusion cells or

Keshary-Chien diffusion chambers are employed to evaluate the rate and extent of drug permeation across human cadaver skin, animal skin models, or synthetic membranes. These studies provide critical data on flux, cumulative drug release, and retention, which inform formulation development and therapeutic dosing strategies. Different transdermal patch systems, including membrane-controlled, matrix-type, reservoir-type, and microreservoir designs, have been developed to facilitate regulated drug delivery[3]. In matrix-based patches, the drug is dispersed within a polymeric matrix, while reservoir systems compartmentalize the drug in a liquid or gel reservoir behind a rate-controlling membrane. Microreservoir systems combine the features of both, enabling both controlled and sustained release. The selection of an appropriate system depends on the physicochemical nature of the drug, target therapeutic window, and patient compliance requirements. Key considerations in the design of transdermal systems include drug solubility, diffusion coefficient, polymer-membrane interaction, hydration conditions, and the use of permeation enhancers such as surfactants, fatty acids, and terpenes. Despite the promising attributes of liposomal transdermal drug delivery, several formulation and manufacturing challenges must be addressed to enable their clinical and commercial translation. Liposomes are inherently prone to instability due to lipid oxidation, hydrolysis, and aggregation during storage. The scalability of production is constrained by batch-to-batch variability, complex processing steps, and the high cost of pharmaceutical-grade phospholipids. Furthermore, sterilization and packaging must preserve vesicle integrity without compromising encapsulated drug content. Emerging technologies such as microfluidics, high-pressure homogenization, and spray-drying are being explored to produce liposomes with controlled size distribution, high encapsulation efficiency, and scalable output. In conclusion, the integration of liposomes into transdermal delivery platforms represents a transformative approach in pharmaceutical formulation science. By improving drug permeation, bioavailability, and therapeutic targeting while minimizing systemic toxicity, liposomal vesicles offer a robust alternative to traditional delivery methods. When combined with hydrogel matrices or incorporated into patch-based TDDS, they provide enhanced patient adherence, controlled release, and clinical flexibility. While challenges remain regarding their long-term stability, regulatory approval, and industrial scalability, ongoing advancements in nanotechnology, material science, and formulation engineering continue to push the boundaries of liposome-based drug delivery. As such, liposomal systems hold immense promise for delivering a wide range of therapeutic agents, including cardiovascular drugs like rosuvastatin sodium, through minimally invasive, patient-friendly routes, thereby significantly improving treatment outcomes and quality of life[4].

2. MATERIALS: Simvastatin and Fluvastatin sodium were obtained from Dr. Reddy's Laboratories. Soya lecithin, sodium deoxycholate, and Triton X-100 were sourced from HiMedia Laboratories. Span 80 and Tween 80 were procured from Sigma-Aldrich. Carbopol was acquired from Yarrow Chem Products, while polyethylene glycol and triethanolamine were obtained from Qualigens Fine Chemicals, Mumbai.

3. METHODOLOGY:

3.1 Construction of calibration curve for Rosuvastatin: Accurately weighed 100 mg of Rosuvastatin was transferred to a 50 mL volumetric flask and dissolved in approximately 10 mL of phosphate buffer (pH 7.4). The solution was sonicated to ensure complete dissolution and then diluted to volume with the same buffer to obtain a primary stock solution with a concentration of 2000 µg/mL. From this stock, 1 mL was pipetted into a 10 mL volumetric flask and diluted to volume with phosphate buffer (pH 7.4) to prepare a working standard solution of 200 µg/mL. Aliquots of this working solution were further diluted with phosphate buffer to obtain final concentrations of 2, 4, 6, 8, and 10 µg/mL. The absorbance of each solution was measured at 238 nm using a UV-Visible spectrophotometer. A calibration curve was

constructed by plotting absorbance against drug concentration (µg/mL)[5].

3.2 Construction of calibration curve for Fluvastatin: Fluvastatin sodium was accurately dissolved in methanol to prepare a stock solution with a concentration of 1000 µg/mL. From this stock, aliquots were withdrawn and appropriately diluted with phosphate buffer (pH 7.4) to obtain working standard solutions in the concentration range of 2–10 µg/mL. The absorbance of these solutions was measured at 304 nm using a UV-Visible spectrophotometer. A calibration curve was subsequently constructed by plotting absorbance against concentration (µg/mL)[6].

3.3 Preparation of Rosuvastatin liposomes using Sol-Gel method: The liposomes were prepared by using thin film hydration method in which the soya lecithin and cholesterol are dissolved in chloroform-ethanol mixture along with Span 80 or Tween 80 in a round bottomed flask. Simvastatin or Fluvastatin sodium are highly lipophilic in nature and allowed to dissolve in the organic phase and added to the above mixture and subjected to rotary evaporation at a temperature of 60 ± 5℃ for the removal of the organic phase. This results in the formation of tin lipid film at the walls of the round bottomed flask. The dried film is hydrated with phosphate buffer media comprising polyethylene glycol and sodium deoxycholate under magnetic stirring to result in liposome formation. The liposomal suspension is subjected to ultrasonication at 100 kHz, 80 amps for 30 minutes at pulse on 30 seconds to result in the formation of unilamellar vesicles. The final pH (6.4) of the formulation is adjusted by adding prescribed quantities of triethanolamine (Table 1). The concentrations of the individual excipients are detailed in the formulation chart for reference[7].

3.3.1 Preparation of liposomal gels loaded with Rosuvastatin[8]: Carbopol (500mg) was taken as the gelling agent and dissolved in 5ml of water and allows to stand over night so that it leads to the formation of transparent gel with absence of air bubbles. The Rosuvastatin is incorporated to the above gel and mixed for 1hr for the formation of drug loaded gel. The resultant is added with methyl paraben and propyl paraben to preserve the stability of the dosage form and the final pH of the formulations are adjusted to 7.4 by adding 0.5% of triethanolamine and its final volume is adjusted to 10ml (Table 2).

3.4 Preparation of Rosuvastatin loaded liposomes using variable polymer concetrations[9]: Alternatively, the Rosuvastatin liposomes were prepared by thin film hydration method in which the lipid phase was prepared by dissolving the soya lecithin and tween 80 in 90:10 ration in chloroform: methanol mixture. Rosuvastatin is added to the above mixture and allowed to dissolve and the mixture is subjected to rotary evaporation at 45± 5℃ to from a thin layer at the sides of the round bottom flask. The round bottom flask is hydrated with phosphate buffer saline pH 7.4 with continuous stirring to result in multi lamellar vesicles. The liposomal suspension is subjected to ultrasonication at 100 kHz, 80 amp for 30 minutes at pulse on 30 seconds to result in the formation of unilamellar liposomes.

3.4 .1. Preparation of Rosuvastatin loaded liposomal gel: Individual gel bases were prepared by dispersing 500 mg each of methyl cellulose, sodium carboxymethyl cellulose, and hydroxypropyl methyl cellulose in 10 mL of distilled water. The dispersions were allowed to hydrate overnight at room temperature to form clear, homogeneous gels. To each gel base, 2717.94 mg of Rosuvastatin-loaded liposomes were incorporated under continuous magnetic stirring at 500 rpm for 45 minutes to ensure uniform distribution (Table 3). Subsequently, 100 mg of methyl paraben and 50 mg of propyl paraben, pre-dissolved in a minimal volume of distilled water, were added as preservatives. Finally, 1 mL of glycerin was added as a humectant, and the volume of each formulation was adjusted to 10 mL with distilled water to obtain the final liposomal gel preparations.

Table 1: Formulation chart comprising Rosuvastatin for the preparation of liposomes

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosuvastain (mg/ml)	10	10	10	10	10	10	10	10	10
Soya Lecithin (**%**)	95	92.5	90	95	92.5	90	95	92.5	90
Tween 80 **(%)**	5	7.5	10	-	-	-	-	-	-
Sodium deoxycholate **(%)**	-	-	-	5	7.5	10	-	-	-
Span 80 **(%)**	-	-	-	-	-	-	5	7.5	10

Table 2: Formulation chart for the preparation of Rosuvastatin loaded liposomal gel

S. No	Batch Code	Rosuvastatin (mg)	Carbopol (gm)
1	STG1	2960.68	10
2	STG2	2850.04	10
3	STG3	2717.94	10
4	STG4	3116.11	10
5	STG5	2996.02	10
6	STG6	2857.48	10
7	STG7	2823.00	10
8	STG8	2725.31	10
9	STG9	2631.86	10

Table 3: Formulation chart for the Rosuvastatin liposomes comprising variable polymer concentrations

Ingredients	STG 10	STG 11	STG 12
Rosuvastatin liposomes	2717.94	2717.94	2717.94
Methyl cellulose	500	-	-
Sodium carboxy methyl cellulose	-	500	-
Hydroxy propyl methyl cellulose	-	-	500
Methyl paraben	100	100	100
Propyl paraben	50	50	50
Glycerin (ml)	1	1	1
Distilled water (ml) up to	10	10	10

4. CHARACTERIZATION STUDIES:

4.1 FTIR Studies: The compatibility between Rosuvastatin and the excipients used in the preparation of liposomal gel are investigated using FTIR studies. The investigations are carried out using FTIR Spectrophotometer (SHIMADZU, Japan) between 4000 to 600 cm^{-1} [10]

4.2 Drug Content: A precisely weighed portion of the transdermal gel formulation, equivalent to 40 mg of Rosuvastatin, was quantitatively transferred to a 100 mL volumetric flask containing 50 mL of phosphate buffer (pH 7.4). The sample was sonicated for 30 minutes to facilitate complete extraction and solubilization of the Active pharmaceutical ingredient (API). The resulting solution was diluted to volume with the same buffer and subsequently filtered through Whatman No. 41 filter paper to obtain a clear filtrate. An appropriate aliquot was withdrawn and analyzed using UV-Visible spectrophotometry at a wavelength of 239 nm, employing phosphate buffer (pH 7.4) as the reference blank. The drug content was quantified by interpolating from a previously constructed Rosuvastatin calibration curve, and results were expressed as a percentage of the labeled claim[11].

4.3 Characterization studies for the Rate controlling membrane:

4.3.1 Physical appearance and Thickness uniformity: The physical characteristics of the gel, such as color, clarity, flexibility, and surface smoothness, were evaluated through visual inspection. The thickness of the rate-controlling membrane was measured using a

Vernier caliper, and the values were recorded for analysis.

4.3.2 Tensile Strength and Percentage of Elongation: Tensile strength and percent elongation at break were determined using a Universal Testing Machine (UTM) equipped with a 50 N load cell. Film specimens were clamped between two jaws set at a fixed distance, and force was applied at a constant rate until the point of rupture. Tensile strength (expressed in N/mm²) was calculated by dividing the maximum load applied by the cross-sectional area of the film, while percentage elongation was determined by measuring the increase in length at the breaking point relative to the original length. All measurements were performed at ambient conditions, and the results were averaged from three replicates to ensure accuracy and reproducibility[12].

4.3.3 Folding Endurance: Folding endurance was evaluated by repeatedly folding a uniformly cut 2×2 cm section of the film at the same point until visible breakage occurred. The number of folds sustained without tearing was recorded as the folding endurance, reflecting the film's mechanical strength and flexibility. A higher folding endurance indicates better durability and suitability for handling during application or packaging.

4.3.4 Water Vapor transmission rate: Water vapor transmission (WVT) was assessed using equal-diameter vials filled with 1.0 g of calcium chloride and sealed with polymeric films of 3.14 cm² surface area. The vials were initially weighed, then placed in a desiccator maintained at 80–90% relative humidity using a saturated potassium chloride solution. Weight measurements were taken at 18, 36, 54, and 72 hours. The WVT rate was calculated using the formula: **WVT rate = W × L / S,** Where *W* is the weight gain (g), *L* is the time (h), and *S* is the surface area of the film (cm²).

4.4 *In-vitro* diffusion studies [13]:

4.4.1 Membrane-moderated transdermal therapeutic system design: A silicone rubber ring with an inner diameter of 2.5 cm and a thickness of 3 mm was employed as the reservoir compartment for the study. A measured quantity of Rosuvastatin gel (40 mg) was placed within the ring, which was subsequently sealed with a cellulose acetate membrane to serve as the rate-controlling barrier for drug release. A double-sided adhesive strip was applied around the membrane's periphery to ensure secure attachment and structural integrity of the assembly.

4.4.2 Preparation of Mouse skin[14]: Swiss albino mice aged 6–8 weeks were humanely sacrificed using cervical dislocation, following ethical guidelines for animal handling. The abdominal region was shaved, and the epidermal skin was carefully excised. The excised skin was thoroughly rinsed with normal saline to remove adhering hair and debris. It was then trimmed into uniform 5 cm strips for experimental use. To preserve its physiological integrity, the skin was stored in normal saline at a controlled temperature of 5–8 °C and used within 24 hours for ex vivo permeation studies.

4.4.3 Using Franz Diffusion Cell[15]:

In vitro drug permeation studies were performed using a Franz diffusion cell apparatus to evaluate the transdermal delivery of membrane-moderated Simvastatin and Fluvastatin sodium formulations. The receptor compartment was filled with 15 mL of phosphate buffer (pH 7.4), maintained at a constant temperature of 32 ± 0.5 °C to mimic the skin surface temperature. A section of excised Swiss albino mouse epidermal skin was carefully mounted between the donor and receptor compartments, with the stratum corneum oriented toward the donor side. The transdermal systems containing the respective drug formulations were placed in the donor compartment. The receptor medium was continuously stirred using a magnetic stirrer at a speed of 50 rpm to ensure uniform mixing and sink conditions throughout the study. At predefined time intervals over a 24-hour period, 1 mL aliquots were withdrawn from the receptor compartment and immediately replaced with

an equal volume of fresh phosphate buffer to maintain volume consistency. The collected samples were analyzed for drug content using a UV-Visible spectrophotometer, with Rosuvastatin quantified at 239 nm and Fluvastatin sodium at 304 nm, using phosphate buffer (pH 7.4) as the blank. All experiments were performed in triplicate, and cumulative drug release was calculated and plotted as a function of time to determine the release kinetics.

4.5 Permeability Coefficient[16]: The permeability coefficient of the membrane-controlled transdermal drug delivery system was evaluated using a Franz diffusion cell apparatus. The receptor compartment was charged with 15 mL of phosphate buffer (pH 7.4) and maintained at a physiological skin temperature of 32 ± 0.5 °C. Excised mouse epidermal skin was carefully mounted between the donor and receptor compartments, ensuring the stratum corneum was oriented toward the donor chamber. The transdermal formulation was applied uniformly to the epidermal surface in the donor compartment. At predetermined time points over a 24-hour diffusion period, 1 mL samples were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh buffer to preserve sink conditions. The concentration of the permeated drug was quantified using a UV-Visible spectrophotometer at a wavelength of 239 nm for Rosuvastatin and 304 nm for Fluvastatin sodium. The permeability coefficient (Kp) was then determined using the equation = $\mathbf{Kp = J / C_0}$

where *J* is the steady-state flux (µg/cm²/h) and C_0 is the initial drug concentration in the donor compartment (µg/cm³)[17].

4.6 Diffusion flux: The transdermal diffusion flux (J) was quantitatively assessed employing a Franz diffusion cell system, wherein the receptor chamber was filled with phosphate buffer (pH 7.4) and thermostatically maintained at 32 ± 0.5 °C to simulate physiological skin conditions. Excised mouse epidermis was carefully positioned between the donor and receptor compartments, ensuring the stratum corneum faced the donor chamber. The drug-loaded formulation was topically applied to the donor surface. At defined time intervals over a 24-hour period, aliquots were withdrawn from the receptor compartment and replenished with an equivalent volume of fresh buffer to uphold sink conditions. Drug concentrations in the collected samples were determined spectrophotometrically using UV-Visible analysis at 239 nm for Rosuvastatin and 304 nm for Fluvastatin sodium. The cumulative amount of drug permeated per unit area (Q) was plotted against time, and the steady-state transdermal flux (J) was calculated from the slope of the linear portion of the permeation profile. The flux is calculated by using the following equation:

$$\mathbf{J = \frac{dm}{dt} \times \frac{1}{s}}$$

Where "dm/ dt" is referred to rate of permeation (µg/h) and "s" refers to surface area of the membrane (cm²).

4.7 Stability Studies[18]: Stability studies for the optimized formulations were systematically carried out over a period of three months under three distinct storage conditions: refrigerated (4 °C), ambient (25 ± 2 °C / 75 ± 5% RH), and accelerated (37 ± 2 °C / 75 ± 5% RH), in accordance with ICH stability testing guidelines. At predetermined intervals, samples were collected and subjected to a comprehensive set of physicochemical evaluations, including drug content, pH, viscosity, spreadability, physical appearance, extrudability, and degradation rate constant (K). These parameters were assessed to monitor any potential changes in the formulation's integrity, performance, and therapeutic efficacy over time. The data obtained were utilized to determine the formulation's stability profile and estimate its shelf life under various environmental stress conditions.

4.8 Skin Irritation Test[19]: A dermal irritation study was conducted in accordance with standard dermatological protocols to assess the biocompatibility of the liposomal formulations. Healthy albino rabbits

(weighing between 1.3–1.5 kg) were selected for the experiment. Polymeric films devoid of Rosuvastatin served as the control group. Prior to application, the dorsal abdominal region of each rabbit was carefully shaved and sterilized using rectified spirit to ensure a clean application site. The test formulations were affixed to the prepared skin area using hypoallergenic adhesive tape and left in place for a continuous exposure period of 24 hours. Following this exposure, the application sites were examined for signs of dermal reaction, including the presence of erythema (redness), edema (swelling), and any other indicators of irritation or inflammation. Observations were recorded and graded in accordance with established dermatological evaluation criteria to determine the skin tolerability of the tested formulations.

4.9 Preformulation characteristics: Preformulation studies were systematically conducted for the developed liposomal formulations to evaluate physicochemical compatibility, thermal behavior, and material handling characteristics essential for formulation development. The melting point was determined using a digital melting point apparatus to assess the thermal stability and purity of the drug substance. Moisture content was quantified through the loss on drying (LOD) method by subjecting the sample to a temperature of 105 °C until a constant weight was achieved. Bulk and tapped densities were measured using a graduated cylinder method, and the resulting values were utilized to calculate the Compressibility Index (Carr's Index) and Hausner's Ratio—key indicators of powder flowability and packing efficiency. The angle of repose was also determined to further characterize the flow properties of the powdered material. Additionally, solubility studies were carried out by equilibrating an excess amount of drug in various solvents, including water, ethanol, acetone, and chloroform, under controlled temperature conditions. After equilibrium was reached, the saturated supernatants were filtered and analyzed to establish the solubility profile in each solvent medium[20].

4.10 *In-vitro* Kinetic studies: In vitro drug diffusion studies were conducted using a Franz diffusion cell apparatus, wherein the receptor compartment was filled with phosphate buffer (pH 7.4) and thermostatically maintained at 35 ± 0.5 °C to simulate physiological skin conditions. The system was operated under continuous magnetic stirring to ensure homogenous distribution of the diffused drug throughout the receptor medium. A section of excised mouse abdominal skin was carefully mounted between the donor and receptor compartments, with the stratum corneum oriented toward the donor side. An accurately weighed quantity (1 g) of the liposomal gel formulation was applied to the donor compartment, which was subsequently sealed to prevent solvent evaporation. At predefined time intervals, 1 mL aliquots were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh buffer to maintain sink conditions. The drug concentration in the collected samples was quantified using UV-Visible spectrophotometry at 239 nm for Rosuvastatin and 304 nm for Fluvastatin sodium, based on a previously established calibration curve. The release data obtained were fitted into various mathematical kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The model exhibiting the highest correlation coefficient (R^2) was selected to best describe the release kinetics and the underlying drug release mechanism of the formulation.

5. RESULTS AND DISCUSSION:

5.1 Preformulation characteristics[21]: The melting point of Rosuvastatin was determined to be 134 °C, indicative of its high purity and inherent thermal stability. The loss on drying (LOD) was recorded at 0.21%, signifying low moisture content and suggesting favorable physical stability with minimal risk of hydrolytic degradation. Bulk and tapped densities were measured as 0.357 g/cm³ and 0.5 g/cm³, respectively, indicating that the powder is relatively light

and exhibits moderate compressibility. From these values, the Carr's Compressibility Index and Hausner's Ratio were calculated to be 34.5% and 1.4, respectively parameters that characterize the material as having poor flow properties and significant interparticulate friction. The angle of repose was measured at 42.78°, further supporting the conclusion that the powder exhibits suboptimal flow behavior, potentially necessitating the use of glidants or lubricants during processing. Solubility profiling revealed that Rosuvastatin is highly soluble in chloroform (209 mg/mL), moderately soluble in methanol (26 mg/mL), acetone (25 mg/mL), and ethanol (21 mg/mL), but practically insoluble in distilled water (0.0001 mg/mL). This pronounced hydrophobicity may adversely affect its aqueous solubility and bioavailability, thereby justifying the need for advanced formulation strategies such as lipid-based delivery systems or the incorporation of solubilizing agents to enhance systemic absorption.

5.2 FTIR Studies[22]: The Fourier Transform Infrared (FTIR) spectroscopic analysis of Rosuvastatin and its binary mixtures with various excipients elucidated critical insights into molecular interactions and formulation compatibility. The pure Rosuvastatin spectrum exhibited distinct absorption bands at 3431.57 cm^{-1} corresponding to O–H stretching vibrations, 2833.25 cm^{-1} for C–H asymmetric stretching, a prominent carbonyl (C=O) stretch at 1702.52 cm^{-1}, and characteristic ether linkages evidenced by asymmetric and symmetric C–O–C bending at 1276.74 cm^{-1} and 1047.24 cm^{-1}, respectively. Upon interaction with Soya Lecithin, an observable shift of the C=O stretching band to 1740.75 cm^{-1} and alterations in other vibrational modes suggest non-covalent interactions, most likely hydrogen bonding and possible entrapment within the lipid matrix. In the Rosuvastatin–Span 80 system, minimal perturbations in the spectral bands (e.g., C=O at 1708.52 cm^{-1}) denote weak Van der Waals or dipole–dipole interactions. Notably, the Rosuvastatin–Sodium Deoxycholate complex demonstrated a significant red shift in the carbonyl region (1640.92 cm^{-1}), indicative of strong electrostatic or hydrogen bonding, possibly due to ionic interactions with bile salt moieties. Other excipient combinations namely with Tween 80, Carbopol, HPMC, and Methyl Cellulose exhibited modest yet discernible shifts in the O–H and C=O bands. For instance, the Rosuvastatin–Methyl Cellulose blend showed an upfield shift of the C=O group to 1751.10 cm^{-1}, highlighting probable inter- and intramolecular hydrogen bonding or polymer-induced steric effects. These spectral modulations collectively affirm the absence of deleterious chemical incompatibilities and reinforce the existence of stabilizing physicochemical interactions, essential for enhancing the solubility, structural integrity, and bioavailability of Rosuvastatin within the transdermal delivery matrices[23].

5.3 Physiochemical characterization of Rosuvastatin loaded liposomal Carbopol gel: Gel-based formulations are gaining prominence among semisolid dosage forms due to their ease of application, patient compliance, and superior percutaneous absorption. Their ability to adapt to physiological movements such as skin flexion and mucociliary activity, while maintaining structural integrity makes them ideal for sustained, localized drug delivery. In this study, liposome-encapsulated drugs were incorporated into hydrogel matrices to act as drug reservoirs for controlled release. Physicochemical evaluation of the liposome-loaded gels included assessments of drug content, pH, viscosity, extrudability, and spreadability. Drug content ranged between 99.15% and 99.61%, indicating uniformity and formulation stability. The pH values (7.21–7.47) aligned with skin compatibility, minimizing irritation risk (Table 4). Rheological analysis confirmed plastic flow behavior, ensuring ease of application and structural resilience.

Table 4: Physiochemical parameters for the developed formulations

S. No	Batch Code	% Drug Content	pH	Viscosity (CPS)	Spreadability (g.cm/sec)	Extrudability
1	RSG1	99.41±0.12	7.21±0.03	3624±14	31.31±1.23	87.12±0.03
2	RSG2	99.46±0.16	7.32±0.05	3689±11	31.89±1.54	87.13±0.04
3	RSG3	99.15±0.18	7.39±0.09	3712±17	32.23±1.11	87.76±0.02
4	RSG4	99.23±0.27	7.43±0.06	3785±13	32.42±1.28	88.92±0.03
5	RSG5	99.30±0.12	7.26±0.06	3793±19	31.34±1.46	87.12±0.04
6	RSG6	99.37±0.21	7.34±0.09	3793±21	32.39±1.37	88.72±0.03
7	RSG7	99.61±0.11	7.41±0.07	3793±13	32.66±2.41	89.35±0.02
8	RSG8	99.42±0.17	7.45±0.09	3857±17	33.47±2.05	90.12±0.08
9	RSG9	99.57±0.31	7.29±0.07	3793±16	33.61±1.72	88.12±0.03

Table 5: Drug release kinetics for the developed liposomal gel formulations

Formulation	Correlation Coefficient Value				Diffusion Rate Constant, k_0 (mg/hr)	Exponential Coefficient (n)	T50 (hr)	T90 (hr)
	Zero Order	First Order	Matrix	Peppas				
RSG1	0.9915	0.8232	0.9532	0.9967	2.17	0.7585	9.2	16.5
RSG2	0.9949	0.7399	0.9460	0.9969	1.88	0.8022	10.3	18.5
RSG3	0.9996	0.8163	0.9272	0.9996	1.74	0.9668	11.4	20.4

5.4 *In-vitro* Kinetic studies[27-29]: The in vitro drug release kinetics of the formulated liposomal gels were analyzed using multiple mathematical models, including zero-order, first-order, Higuchi matrix, and Korsmeyer–Peppas equations, to elucidate the underlying release mechanism and rate-controlling dynamics. Among the tested models, the highest correlation coefficients were observed for both the zero-order (R^2 = 0.9996) and Korsmeyer–Peppas (R^2 = 0.9996) models in the case of formulation RSG3. This dual fitting suggests that RSG3 follows a concentration-independent, controlled release profile consistent with a Peppas-type anomalous diffusion mechanism[30]. The calculated diffusion rate constants (k_0) spanned from 1.74 to 2.17 mg/hr, with RSG1 exhibiting the highest release rate. The release exponent (n) values, ranging from 0.7585 to 0.9668,

Indicated a non-Fickian (anomalous) transport mechanism, reflecting a combined influence of drug diffusion and polymer matrix relaxation. RSG3 demonstrated the most prolonged release characteristics, with T values of 11.4 hours and 20.4 hours, respectively, confirming its suitability for sustained transdermal delivery (Table 5). Collectively, the kinetic modeling results affirm that RSG3 exhibits the most favorable controlled release behavior, attributed to its optimized formulation matrix and effective drug entrapment, making it a strong candidate for advanced transdermal therapeutic systems.

CONCLUSION:

The exploration of liposomal vesicles for transdermal delivery of rosuvastatin sodium presents a promising strategy to address the drawbacks of conventional oral administration. As a hydrophilic HMG-CoA reductase inhibitor, rosuvastatin sodium suffers from poor oral bioavailability (20%) primarily due to extensive first-pass hepatic metabolism, which necessitates higher doses and contributes to adverse effects such as myopathy and hepatotoxicity. Liposomes,

with their amphiphilic phospholipid bilayer structure, act as efficient nanocarriers capable of encapsulating hydrophilic drugs, enhancing transdermal permeation, and enabling sustained, controlled release. This mode of delivery improves systemic bioavailability, ensures steady plasma drug concentrations, and minimizes toxicity associated with peak levels. Preclinical studies have demonstrated that rosuvastatin-loaded liposomes significantly enhance skin penetration, maintain prolonged therapeutic levels, and lower the risk of dose-dependent side effects. However, key challenges such as liposome stability during storage and scalability of production remain. Addressing these through optimized formulation design and advanced manufacturing approaches is essential for successful clinical translation, potentially establishing liposomal transdermal delivery as a safer, more effective alternative for long-term rosuvastatin therapy.

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REFERENCES:

1. Biju SS, Talegaonkar S, Mishra PR and Khar K.R.; Vesicular System: An overview I.J.P.S, 2009; 71(4): 421-427
2. Jin. YS et al. Self-Assembled Drug Delivery SystemsProperties and In Vitro –In Vivo Behaviour of Acyclovir Self-Assembled Nanoparticles (san). Int J Pharm, 2006; 309(1– 2): 199-207.
3. Vaizoglu MO and Speiser PP. Pharmacosomes--A Novel Drug Delivery System. Acta Pharmacetica Suecica, 1986; 23: 163 – 172.
4. Goldberg. E P. Eds. In; Targeted Drugs, 2nd edition, Wiley, New york, 1983; 312.
5. Gregoriadis. G. Nature, 1977; 265-407.
6. Poste G, Krisch R and Koestler T. Liposome Technology. Vol 3, CRC Press Inc, Banco Raton, F1, 1983; 29.
7. Saraf Swarnlata, Rathirahul, Kaur Chanchal Deep and Saraf Shailendra. Colloidosomes: an Advanced vesicular system in drug delivery. Asian Journal of Scientific Research, 2011; 4: 1-15.
8. Annakula Deepthi, Rao Madhukar, Jukanti Raju, Bandari Suresh, Reddy Prabhakar Reddy Veera. Provesicular drug delivery systems: An overview and appraisal. Scholars Research Library, 2010; 2: 135-146.
9. Keservani Raj K, Sharma Anil K, Ayaz MD, Kesharwani Rajesh K. Review Novel drug delivery system for the vesicular delivery of drug by the niosomes. International Journal of Research in Controlled Release, 2011; 1: 1-8.
10. Gupta Stuti, Singh Ravindra Pal, Lokwani Priyanka, Yadav Sudhir, Gupta Shivjee K. Vesicular System As Targeted Drug Delivery System: An Overview. International Journal of Pharmacy & Technology, 2011; 3: 1021.
11. Doijad Rajendra C, Bhambere Deepak S, Manvi Fakirappa V and Deshmukh Narendra V. Formulation And Characterization Of Vesicular Drug Delivery System For Anti-HIV Drug. Journal of Global Pharma Technology, 2009; 1: 94-100.
12. Prajapati SK, Kumar S, Sahu VK, Prakash G. Proniosomal Gel of Flurbiprofen: Formulation and Evaluation. Journal of Drug Delivery & Therapeutics, 2012; 2: 105-114.
13. Gangwar Mayank, Singh Ranigi, Goel RK, Nath Gopal: Recent

Advances In Various Emerging Vesicular Systems: An Overview. Asian Pacific Journal of Tropical Biomedicine, 2011; 33: 848.
14. Polanski. M.J and Juliano. R.L. Pharmacol. Rev, 1983; 36: 27.
15. Bangham AD, Standish MM and Watkins JG. The action of steroids and streptolysin S onthe permeability of phospholipid structures to cations. J. Mol. Biol, 1965; 13: 238.
16. Ogihara Umedai, Sasaki T, Toyama H, Odak, Sneha M, Nishigori H. Cancer Detect Prev,1997; 21(6): 490.
17. Kavitha D, Naga Sowjanya J, Shanker Panaganti. Pharmacosomes: An Emerging Vesicular System. International Journal Of Pharmaceutical Sciences Review And Research, 2010; 5(3):168-171.
18. Anwekar H., Patel S., Singhai A.K., Liposome-As Drug Carrier, International Journal of Pharmacy and Life Sciences, 2011; 2(7): 945-951.
19. Wagner A., Uhl K.V., Liposome Technology for Industrial Purposes, Journal of Drug Delivery, 2011; 2010: 1-9.
20. Cevc G., Schatlein A.,Blume G., Transdermal Drug Carriers: Basic Properties, Optimization and Transfer Efficiency in the case of Epicutaneous Applied Peptides, Journal of Controlled Release, 1995; 36: 3-16.
21. Jain S., Jaio N., Bhadra D., Tivari A.K., Jain N.K., Transdermal Delivery of an Analgesic Agent using Elastic Liposomes: Preparation, Characterization and Performance Evaluation. Current Drug Delivery, 2005; 2(3): 223-233.
22. Ali N., Harikumar S.L., Kaur A., Niosomes: An Excellent Tool for Drug Delivery, International Journal of Research in Pharmacy and Chemistry, 2012; 2(2): 479-487.
23. Khan A., Sharma P.K., Visht S., Malviya R., Niosomes as Colloidal Drug Delivery System: A Review, Journal of Chronotherapy and Drug Delivery, 2011; 2(1): 15-21.
24. Jadhav S.M., Morey P., Karpe M., Kadam V., Novel Vesicular System: An Overview, Journal of Applied Pharmaceutical Sciences, 2012; 02(01): 193-202.
25. Tarekegn A., Joseph N.M., Palani S., Zacharia A., Ayenew Z., Niosomes in Targeted Drug Delivery, International Journal of Pharmaceutical Sciences and Research, 2010; 1(9): 1-8
26. De Pintu kumar, De Arnab. Pharmacosomes: A potential vesicular drug delivery system. I R J P, 2012; 3(3): 102-105.
27. Kaur and Kanwar M. Ocular Preparations: The Formulation Approach. Drug Dev. Ind. Pharm, 2002; 28 (5): 473–493.
28. Semalty A, Semalty Mona, Rawat BS, Singh D, and Rawat SM. Development and Evaluation of Pharmacosomes of Aceclofenac. Indian Journal Pharmaceutical Sciences, 2010;5: 576-581.
29. Semalty A., Semalty M, Singh D Development and Characterization of AspirinPhospholipid Complex for Improved Drug Delivery. International Journal of Pharmaceutical Sciences and Nanotechnology, 2010; 3(2): 940-947