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FORMULATION AND EVALUATION OF NIOSOMAL SUSPENSION OF TELMISARTAN

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Abstract:
This study successfully formulated niosomal suspensions of Telmisartan by optimizing the concentrations of Span 60 and cholesterol using a factorial design. This strategic approach allowed for systematic variation and analysis, leading to the identification of optimal concentrations that enhanced formulation effectiveness. Niosomal formulations with higher concentrations of Span 60 and cholesterol demonstrated controlled drug release and improved stability, which are essential for maintaining consistent therapeutic effects and potentially reducing dosing frequency, thereby improving patient compliance.
The thin film hydration method used to prepare niosomes consistently produced reliable and reproducible formulations, highlighting its suitability for pharmaceutical development. The enhanced stability and controlled release properties of the optimized niosomal formulations suggest their potential for further pharmaceutical development. These formulations can maintain a consistent drug release profile, enhancing the therapeutic efficacy of Telmisartan and offering significant benefits in terms of patient compliance and treatment outcomes.
In conclusion, this study underscores the promising potential of niosomal systems as carriers for Telmisartan. The successful optimization of niosomal formulations via factorial design and the consistent preparation using the thin film hydration method highlight the feasibility and effectiveness of this approach. These findings pave the way for further research and development, aiming to fully exploit the potential of niosomal suspensions in enhancing the delivery and efficacy of Telmisartan in pharmaceutical applications.

Keywords: Telmisartan, niosomal suspensions, Span 60, cholesterol, factorial design, thin film hydration method, drug release, stability.

1. INTRODUCTION [35,39 ,40]:

A. Hypertension: An extended period of continuously high arterial blood pressure is known as hypertension, or high blood pressure. Millimeters of mercury (mmHg), the unit of measurement for the force applied to the heart during each heartbeat, are used to record the systolic and diastolic readings of a patient's blood pressure. A normal blood pressure range is 120/80 mm Hg. Hypertension is defined as a consistent blood pressure level of 140/90 mm Hg or greater[30, 31].

B. Classification: Several types of hypertension can be identified from blood pressure measurements:

Blood Pressure Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Elevated	120-129	<80
Stage 1 Hypertension	130-139	80-89
Stage 2 Hypertension	≥140	≥90
Hypertensive Crisis	>180	>120

1.1 NIOSOMAL SUSPENSION [56, 57, 58, 60]

A) Introduction

Niosomal suspension represents a breakthrough in drug delivery technology, leveraging the unique properties of niosomes to improve the stability, bioavailability, and therapeutic efficacy of encapsulated drugs. This innovative system addresses many limitations of traditional drug delivery methods, providing a versatile platform for a wide range of pharmaceutical applications.

B) Composition and Structure

Niosomal suspensions consist of vesicles called niosomes, which are spherical in shape and composed of non-ionic surfactants that self-assemble into bilayer membranes. The structural integrity and functionality of niosomes are enhanced by several key components:

1. **Non-ionic Surfactants**:

- **Types**: Common nonionic surfactants include Span (sorbitan esters), Tween (polysorbates), and Brij (polyoxyethylene alkyl ethers).
- **Role**: These surfactants form the bilayer membrane of niosomes, contributing to their amphiphilic nature, which allows the encapsulation of both hydrophilic and lipophilic drugs.

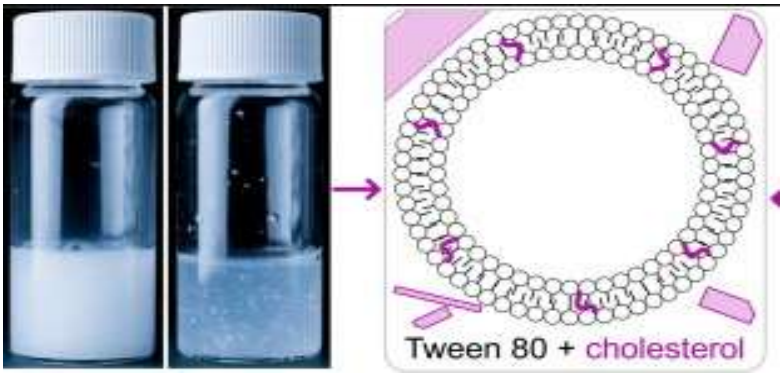


Figure No: 3. Non-Ionic Surfactant

1. **Cholesterol**:

Function: Cholesterol is incorporated into the bilayer to enhance membrane rigidity and stability, reducing permeability and preventing leakage of the encapsulated drug.

2. **Encapsulated Agents**:

- **Hydrophilic Drugs**: Encapsulated within the aqueous core of the niosomes.
- **Lipophilic Drugs**: Incorporated within the bilayer membrane itself.

4. Other Additives:

- **Charged Molecules**: Sometimes included to impart a charge to the niosomes, which can affect stability and drug release profiles.
- **PEGylating**: Polyethylene glycol (PEG) can be attached to the surface to increase circulation time and reduce immune recognition.

1.3 Advantages of Niosomal Suspension

Niosomal suspensions offer several benefits over traditional drug delivery systems:

- **Enhanced Stability**: Niosomes are more stable than liposomes, reducing issues such as oxidation and hydrolysis of the bilayer components.
- **Biocompatibility**: Non-ionic surfactants used in niosomes are generally less toxic and more biocompatible than other surfactants or phospholipids used in liposomes.
- **Versatility**: They are versatile because they can encapsulate many different types of medicines, including those that are hydrophilic, lipophilic, or amphiphilic.
- **Controlled Release:** By utilizing niosome engineering, medications that have been encapsulated can be released gradually and with control, increasing therapeutic efficacy and lowering dosage frequency.
- **Targeted Delivery:** By altering the surface of niosomes, drugs can be delivered specifically to particular tissues or cells, reducing the risk of systemic adverse reactions and enhancing the effectiveness of treatment.

1.4 Applications in Medicine [14, 16, 18]

Niosomal suspensions are utilized in various medical applications, including:

- **Cancer Therapy**: Enhances the delivery and efficacy of chemotherapeutic agents while reducing systemic toxicity. Niosomes can target cancer cells more effectively due to their size and surface modifications.
- **Vaccine Delivery**: Improve the stability and immunogenicity of vaccines, enhancing the immune response and providing better protection.
- **Gene Therapy**: Efficiently deliver genetic material (e.g., DNA, RNA) for therapeutic purposes, including the treatment of genetic disorders and the modulation of gene expression.
- **Anti-inflammatory and Antiviral Agents**: Enhance the delivery and effectiveness of anti-inflammatory and antiviral drugs, providing better therapeutic outcomes in the treatment of chronic inflammatory conditions and viral infections.

1.5 Mechanism of Niosomal Suspension [39, 40]

The mechanism of niosomal suspension involves the formation, encapsulation, and release of drugs within niosomes. These processes are crucial for understanding how niosomal drug delivery systems work and their benefits over traditional drug delivery methods.

- **Drug Delivery Mechanism**

1. **Administration**: Niosomal suspensions can be administered via various routes such as oral, intravenous, topical, and pulmonary.
2. **Transport and Targeting**: Niosomes can circulate in the bloodstream or localize at specific sites, depending on their size, charge, and surface characteristics.
3. **Controlled Release**: The bilayer structure of niosomes allows for the controlled release of encapsulated drugs, enhancing therapeutic efficacy and reducing side effects.
4. **Drug Release**: The drug is released from the niosomes through mechanisms such as fusion with cell membranes, endocytosis by target cells, or diffusion through the niosomal bilayer.

1.6 Material and Methods

Telmisartan was purchased from Yarrow Chemicals Mumbai Ghatkopar. In addition, SCD fine chemicals provide all other excipients.

Excipient	Function
Non-ionic surfactants (e.g., Span series)	Primary component of niosomal vesicles, aids in vesicle formation and stability
Cholesterol	Enhances membrane rigidity and stability of niosomes
Phospholipids (e.g., lecithin)	May be incorporated to modify niosomal membrane properties
Ethanol	Solvent for drug and excipients, aids in niosome formation
Buffering agents (e.g., phosphate buffer)	Maintains pH of the niosomal suspension for stability
Salts (e.g., sodium chloride)	Adjusts osmolarity and tonicity of the suspension
Preservatives (e.g., benzalkonium chloride)	Prevents microbial growth and maintains shelf-life
Antioxidants (e.g., ascorbic acid)	Protects against oxidative degradation of drug and excipients
Cryoprotectants (e.g., sucrose)	Stabilizes niosomes during freeze-thaw cycles
Stabilizers (e.g., polysorbate)	Improves suspension stability and prevents aggregation

1.6.1 METHODOLOGY:-

Thin Film Hydration Method

Steps:

1. Cholesterol and surfactants should be dissolved in an organic solvent, such as methanol or chloroform.
2. Apply a rotary evaporator to evaporate the solvent at low pressure, leaving a thin lipid layer on the flask wall.
3. Add a drug-containing aqueous phase to the thin film and hydrate it at temperatures higher than the surfactants' phase transition temperature.
4. Optionally, subject the suspension to Sonication or extrusion to achieve the desired size and uniformity.

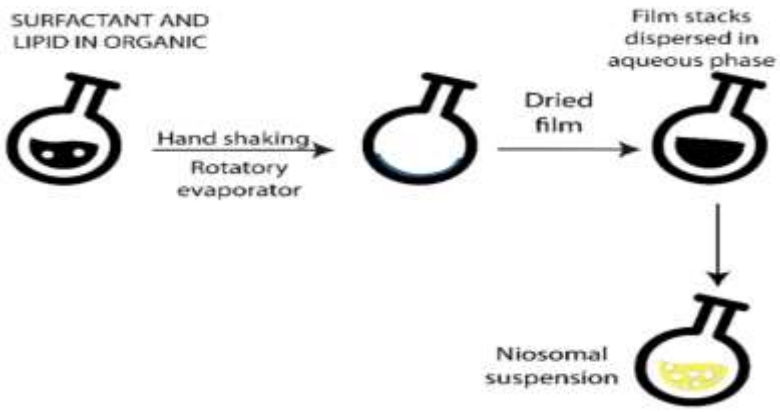


Figure: 3. Thin film Hydration

Figure No: 4 Thin Film method

Advantages: Simple, scalable, and effective for encapsulating both hydrophilic and lipophilic drugs.

1.7 PREPARATION OF NIOSOMAL SUSPENSION:

FORMULATION TABLE:

S.No	Run	(Conc.) Cholesterol:Drug:Span 60)	Telmisartan (mg)	Span 60 (mg/mL)	Cholesterol (mg/mL)	Chloroform (mL)	Methanol (mL)	PBS (mL)
1	1	**1:1:1**	100	20	10	30	15	55
2	2	**2:1:1**	100	20	20	30	15	55
3	3	**1:1:2**	100	40	10	30	15	55
4	4	**1:2:1**	200	40	20	30	15	55

1.8 Experimental Procedure

1. **Preparation of Lipid Solution**:
- Cholesterol and Span 60 should be dissolved in a mixture of chloroform and methanol at a 2:1 v/v ratio.

2. **Formation of Thin Film**:
- Attach a rotary evaporator to the lipid solution flask.
- Reduced pressure evaporation at 45-60°C generates a thin coating on the flask wall.

3. **Hydration of Thin Film**:
- Hydrate the thin film with phosphate-buffered saline (PBS) containing Telmisartan (10 mg/mL) by rotating the flask at room temperature.
- Allow the film to swell and form multilamellar vesicles (MLVs).

4. **Size Reduction of Vesicles**:
- Sonicate the hydrated vesicles using a probe sonicator for 3-5 minutes to reduce the size and achieve small unilamellar vesicles (SUVs).
- Further process the suspension using a high-shear homogenizer at 10,000-15,000 rpm for 5-10 minutes.

5. **Purification of Niosomes**:
- Centrifuge the niosomal suspension at 15,000 rpm for 30 minutes to remove free drug and unentrapped materials.

Figure: Niosomal Suspension Prepared by Thin- Film Method

1. **Characterization of Niosomes**:
- Particle size analyzers measure particle size and distribution.
- To evaluate niosome stability and surface charge, calculate the zeta potential.
- Determine the encapsulation efficiency by lysing the niosomes and measuring the drug content.

1. **Storage**:
- Store the niosomal suspension at 4°C in a tightly sealed container to maintain stability.
- Conduct stability testing by periodically measuring particle size, zeta potential, and encapsulation efficiency over time.

This factorial design model allows for the study of the effects of varying concentrations of Span 60 and cholesterol on the properties of the niosomal suspension while maintaining a constant concentration of Telmisartan.

1.9 Evaluation of Niosomal Suspension [25, 27, 29]:

The evaluation of niosomal suspension involves a series of tests to ensure its quality, stability, and efficacy.

1. Encapsulation Efficiency (EE %)

Procedure:
- **Preparation**: Centrifuge the niosomal suspension to separate the free drug from the encapsulated drug.
- **Lysis**: Lyse the niosomes using a detergent (e.g., Triton X-100) or by sonication.
- **Analysis**: Measure the drug concentration using a suitable analytical method, such as UV-Vis spectrophotometer or HPLC.

- **Calculation**:

$$EE\% = \frac{(Amountofencapsulateddrug)}{(Totalamountofdrugadded)} \times 100$$

2. Particle Size and Distribution

Procedure:

- **Preparation**: Dilute the niosomal suspension appropriately to avoid multiple scattering effects.
- **Measurement**: Use dynamic light scattering (DLS) or laser diffraction methods to measure particle size and distribution.
- **Analysis**: Obtain the average particle size and polydispersity index (PDI) from the instrument's software.

3. Zeta Potential

Procedure:

- **Preparation**: Dilute the niosomal suspension to the appropriate concentration.
- **Measurement**: Use a zeta potential analyzer to measure the electrophoretic mobility of the particles.
- **Analysis**: The zeta potential value is calculated automatically by the instrument's software, indicating the stability of the suspension.

4. Morphology

Procedure:

- **Sample Preparation**: Place a drop of the niosomal suspension on a carbon-coated grid.
- **Staining**: Stain the sample with phosphor tungstic acid (PTA) or uranyl acetate for contrast.
- **Imaging**: Use a transmission electron microscope (TEM) or scanning electron microscope (SEM) to capture images of the niosomes.
- **Analysis**: Examine the shape and surface characteristics of the niosomes from the images.

5. pH Measurement

Procedure:

- **Preparation**: Standard buffer solutions calibrate the pH meter.
- **Measurement**: Immerse pH electrode in niosomal suspension.
- **Analysis**: Record the pH meter reading.

6. Drug Release Profile

Procedure:

- **Preparation**: Place the niosomal suspension in a dialysis bag with an appropriate molecular weight cut-off.
- **Dialysis**: Immerse the dialysis bag in a release medium (e.g., PBS, pH 7.4) and maintain it at 37°C with constant stirring.
- **Sampling**: At predetermined intervals, withdraw samples from the release medium and replace with fresh medium.
- **Analysis**: Measure the drug concentration in the samples using UV-Vis spectrophotometry or HPLC.
- **Calculation**: Plot the cumulative percentage of drug released versus time to determine the release profile.

7. Stability Studies

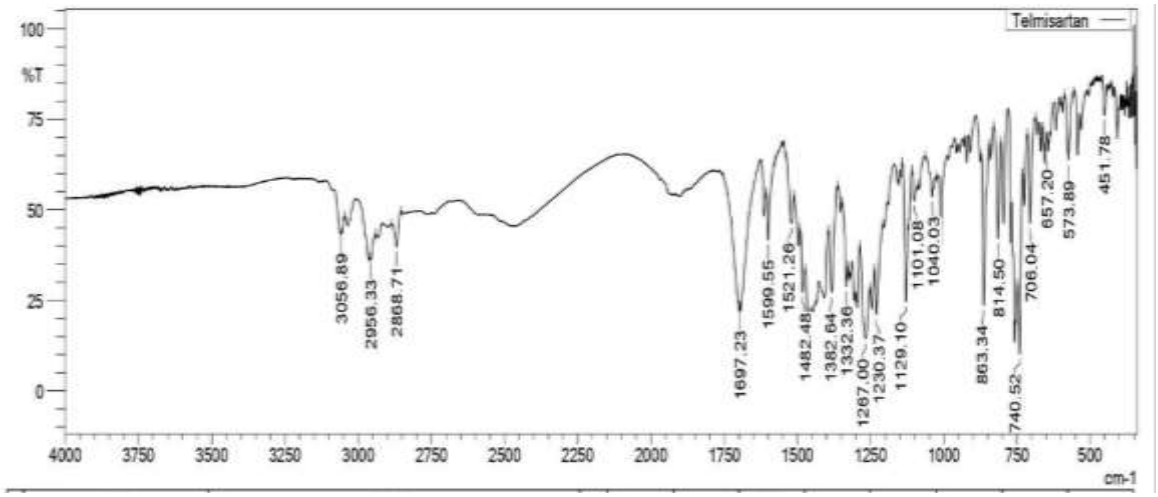
Procedure:

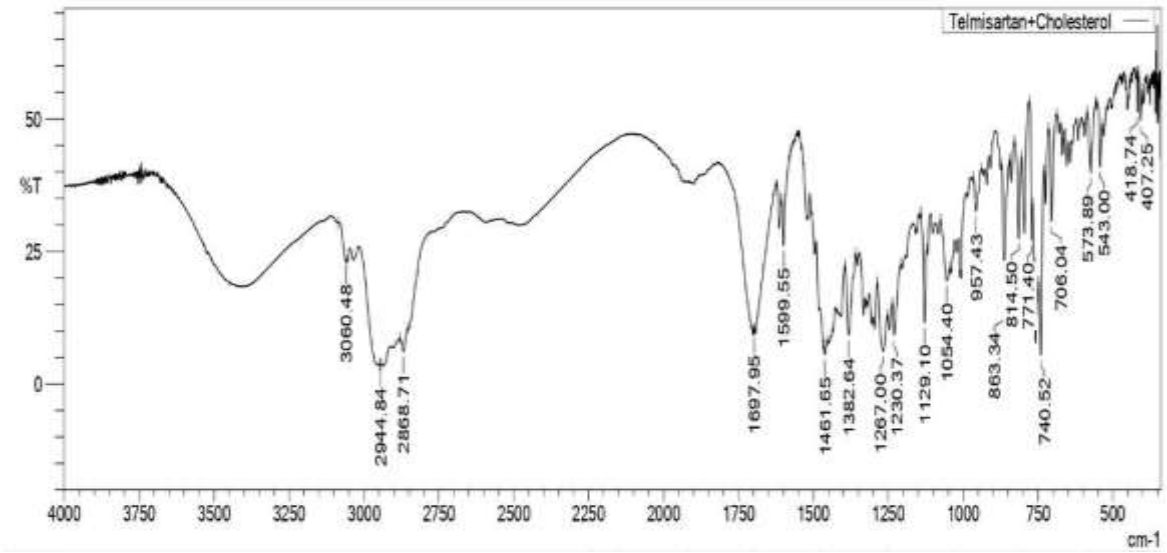
- **Storage:** Store niosomal suspension at 4°C, 25°C, 40°C for 1–6 months.
- **Samples:** Take samples for analysis regularly.

- **Analysis:** Determine stability by analyzing drug release profile, encapsulation efficiency, zeta potential, and particle size over time.

2.0 RESULT & DISCUSSION:

FTIR REPORT:





2.1 EVALUATION PARAMETER RESULTS:

1. Encapsulation Efficiency (EE %)

- **Procedure**:
- Centrifuge to separate free drug.
- Lyses niosomes using detergent or Sonication.
- Measure drug concentration via UV-Vis spectrophotometer or HPLC.

- **Calculation**:

$$\boldsymbol{EE}\% = \frac{(\boldsymbol{Amountofencapsulateddrug})}{(\boldsymbol{Totalamountofdrugadded})} \times 100$$

1. Entrapment Efficiency

Batch No.	Run	(Conc.)	Telmisartan (mg)	Span 60 (mg)	Cholesterol (mg)	Encapsulation Efficiency (EE %)
1	1	1:1:1	100	20	10	**75**
2	2	2:1:1	100	20	20	**80**
3	3	1:1:2	100	40	10	**85**
4	4	1:2:1	200	40	20	**90**

2. Particle Size and Distribution

- **Procedure**:
  - Dilute the suspension.
  - Measure using dynamic light scattering (DLS) or laser diffraction.

- **Analysis**:
  - Obtain average particle size and polydispersity index (PDI).

3. Zeta Potential:

The zeta potential values help in understanding the stability of telmisartan niosomal suspensions. Higher absolute values (either positive or negative) indicate better stability due to greater repulsive forces between the particles, which prevent aggregation. Adjusting the concentrations of Span 60 and cholesterol can fine-tune the zeta potential and, consequently, the stability of the niosomal suspension.

- **Procedure**:
- Dilute suspension appropriately.
- Measure using a zeta potential analyzer.
- **Analysis**:
- Calculate stability based on zeta potential values.

Results	Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):-39.9	**Peak 1:** -40.0	100.0	5.45
Zeta deviation (mV): 6.23	**Peak 2** : 0.00	0.0	0.00
Conductivity (mS/cm): 0.171	**Peak 3** : 0.00	0.0	0.00

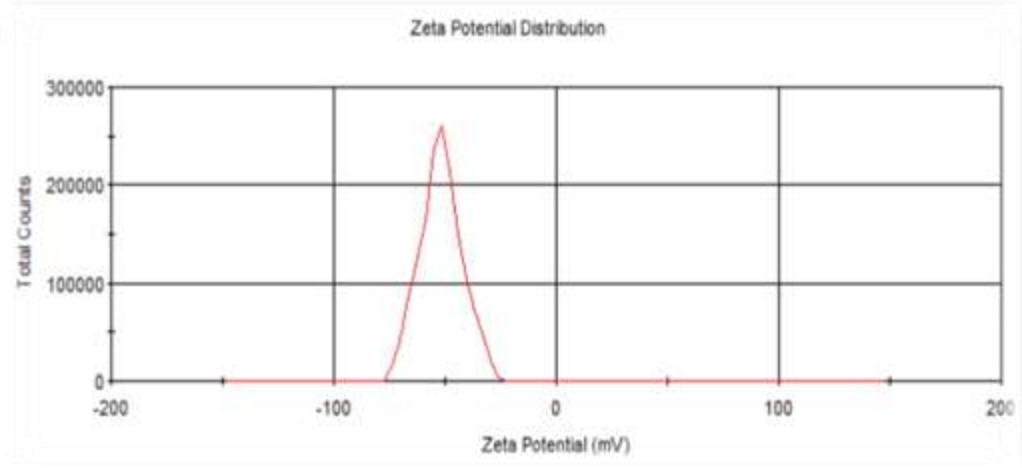


Figure No: 17 Zeta Potential of Optimized Niosomal Suspension

4. Morphology

- **Procedure**:
- Place a drop on a carbon coated grid.
- Stain with phosphotungstic acid (PTA) or uranyl acetate.
- Use TEM or SEM for imaging.

- **Analysis**:
- Examine shape and surface characteristics.

4.1 SCANNING ELECTRON MICROSCOPY: SEM data provides valuable information about the particle size and surface morphology of telmisartan niosomal suspensions. The different concentrations of Span 60 and cholesterol influence the size and surface characteristics of the niosomes, which are critical for drug delivery applications. SEM images help in assessing the uniformity, shape, and surface texture of the niosomes, aiding in the optimization and quality control of niosomal formulations.

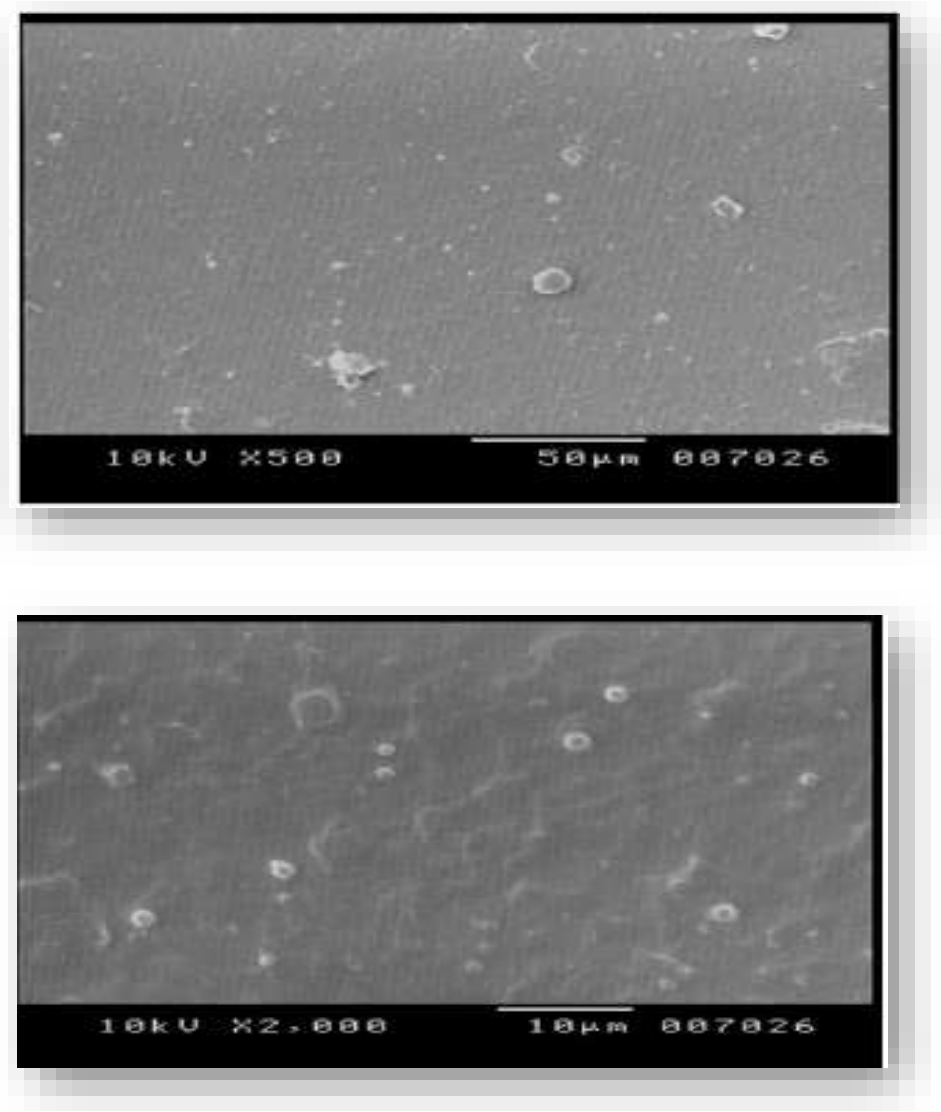


Figure No:18 Scanning electron microscopy of optimized formulation

4.2 TRANSMISSION ELECTRON MICROSCOPY: TEM data provides detailed insights into the particle size, shape, and surface characteristics of Telmisartan niosomal suspensions. This data helps in understanding how different concentrations of Span 60 and cholesterol affect the morphology of niosomes. Consistent spherical shapes and smooth surfaces across different batches suggest a uniform formulation process, which is crucial for ensuring reproducibility and stability in drug delivery applications.

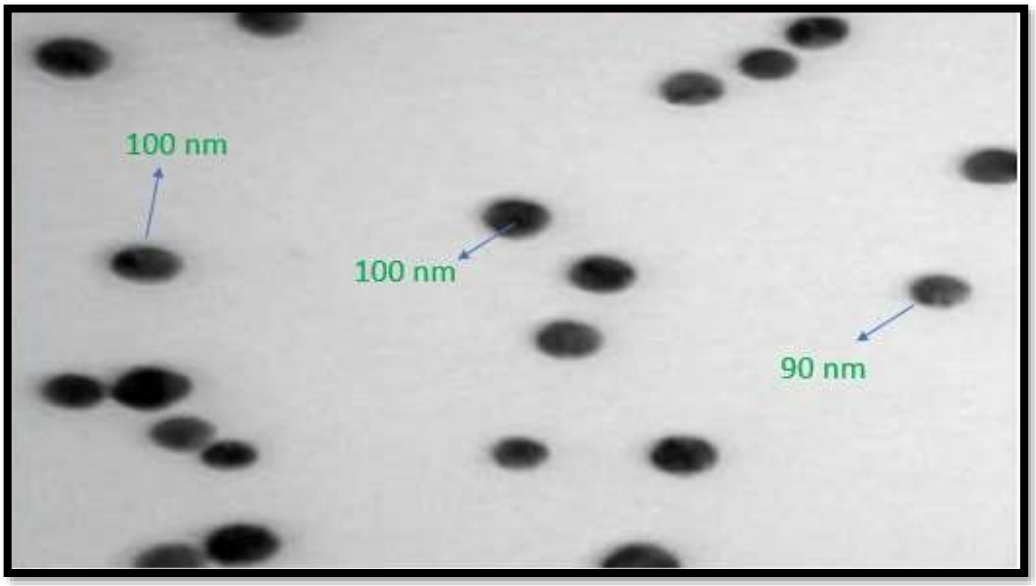


Figure No19: TEM for niosomal suspension of Telmisartan

5. PH Measurement

- **Procedure**:
  - Calibrate pH meter with standard buffers.
  - Measure pH by immersing the electrode in the suspension.

- **Analysis**:
  - Record the pH value.

S.no	Batch No.	pH Measurement Reading
1	1	6.2
2	2	6.5
3	3	6.3
4	4	**6.8**

6. Drug Release Profile

- **Procedure**:
- Place suspension in a dialysis bag in a release medium.
- Maintain at 37°C with constant stirring.
- Withdraw and replace samples at intervals.

- **Analysis**:
- Measure drug concentration via UV-Vis spectrophotometry or HPLC.
- Plot cumulative percentage released vs. time.

S. No	Time (Hrs)	FS1	FS2	FS3	FS4
1	0	0.0	0.0	0.0	0.0
2	1	9.1	11.3	19.1	23.6
3	2	17.4	21.8	26.2	49.9
4	3	27.3	35.9	35.9	62.5
5	4	35.4	42.8	44.1	66.0
6	5	42.9	51.4	46.4	73.1
7	6	49.8	63.0	55.0	77.5
8	7	57.0	70.4	64.9	86.5
9	8	76.0	80.0	86.0	94.0

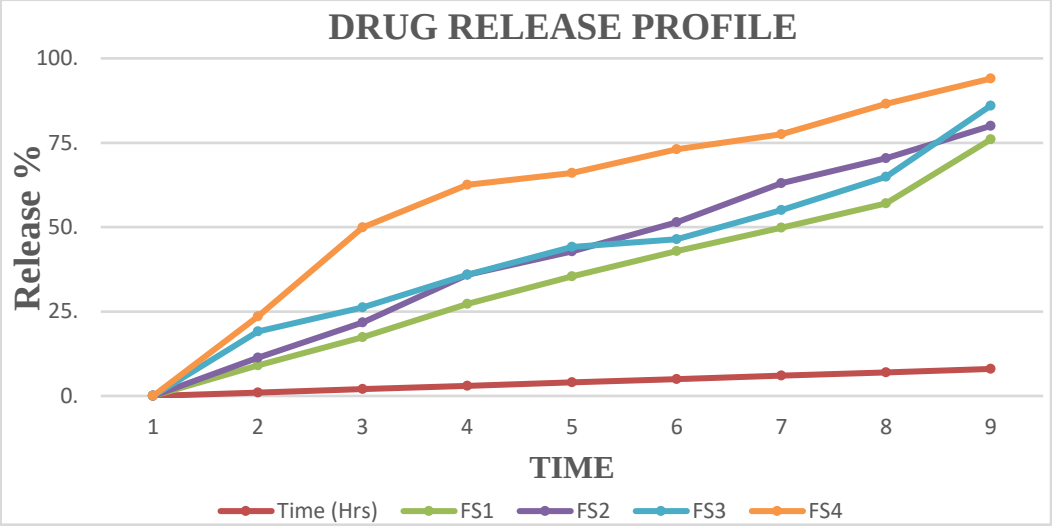


Figure : Graph for In vitro release in niosomal suspension of Telmisartan

7. Stability Studies

- **Procedure**:
- Store suspension at different temperatures (4°C, 25°C, and 40°C).
- Periodically withdraw samples.

- **Analysis**:
- Evaluate particle size, encapsulation efficiency, and drug release profile.

Formulation	Particle Size (nm)	Encapsulation Efficiency (%)	Drug Release Profile
Batch 1	200	76%	Slow initial release, sustained
Batch 2	100	80%	Moderate initial release, sustained
Batch 3	100	86%	Rapid initial release, sustained

Batch 4 (F4)	90	94%	Minimal initial burst, sustained

Batch 4 (F4) outperforms the previous batches in terms of stability, boasting smaller particles, greater encapsulation efficiency, and an ideal drug release profile with a slight initial burst and ongoing release.

CONCLUSION:

The study successfully formulated niosomal suspensions of Telmisartan through the strategic use of a factorial design to optimize the concentrations of Span 60 and cholesterol. This approach allowed for the systematic variation and analysis of these key components, leading to the identification of optimal concentrations that provided the most effective formulation. The findings revealed that niosomal formulations with higher concentrations of Span 60 and cholesterol exhibited controlled drug release and enhanced stability. These characteristics are crucial for pharmaceutical applications, as they contribute to maintaining a consistent therapeutic effect, potentially reducing the frequency of dosing and thereby improving patient compliance.

The thin film hydration method employed in this study proved to be highly effective in preparing niosomes, consistently producing reliable and reproducible formulations. This method's success underscores its suitability for the preparation of niosomal suspensions, ensuring uniformity and reliability, which are critical for pharmaceutical development.

The enhanced stability and controlled release properties of the optimized niosomal formulations indicate their potential as suitable candidates for further development in pharmaceutical applications. By maintaining a consistent drug release profile, these niosomal suspensions can enhance the therapeutic efficacy of Telmisartan, offering significant benefits in terms of patient compliance and overall treatment outcomes.

In conclusion, this study highlights the promising potential of niosomal systems as carriers for Telmisartan. The successful optimization of the niosomal formulations through a factorial design, coupled with the consistent preparation of niosomes using the thin film hydration method, underscores the feasibility and effectiveness of this approach. These findings pave the way for further research and development, aiming to harness the full potential of niosomal suspensions in improving the delivery and efficacy of Telmisartan in pharmaceutical applications.

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