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Research Paper

Formulation and Evaluation of Allopurinol Loaded Transethosomal Gel

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ABSTRACT

The main aim of this research is formulate allopurinol loaded Transethosomal gel in which Transethosomes of allopurinol were composed of different concentration of soya lecithin, Cholesterol, tween-80 and solvent by using the cold method. Transethosomes were characterized of entrapment efficient, SEM (scanning electron microscopy), FTIR (Fourier transform infrared spectroscopy), In-vitro drug release as well as stability. Then the allopurinol Transethosomes were incorporated into the gel and evaluated for pH, wash ability, spread ability, Viscosity and stability. SEM studies showed that the Transethosomes are spherical in shape. FTIR result showed that there is no interaction of drug and excipients during the formulation of Transethosomes. The cumulative percentage of drug release of Transethosomes is 82.5 percent, entrapment efficiency is 85.2 percent the ph of the Transethosomal gel is 6.4, the viscosity of the Transethosomal gel is 3000cp. this rsearch result showed that the allopurinol loaded Transethosomal gel can be potentially used for transdermal delivery.

INTRODUCTION

Gout is caused due to the deposition of monosodium urate crystals and it is metabolic disorder caused due to the joint Pain and the inflammation in the joints[1]. Mainly caused due to the over production and deposition of the uric acid in the body and decrease the excretion of uric acid which are treated by decreasing the uric acid production and increase the excretion of the uric acid from the body[2]. Allopurinol is used as a first drug of choice in the treatment of chronic gout and competitive inhibitors of the Xanthine Oxidase inhibitors. It is slightly soluble in water[3]. It decreases the over production of uric acid in the body by increasing the excretion of uric acid from the body. The main objective of this research is to enhanced the bioavailability and increased the permeation of the deeper layer of the skin of the allopurinol which is slightly water-soluble drug. It is hypothesized that when we incorporate the

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Allopurinol in vescicular nanocarriers such as Transethosomes and then incorporated them into the Transethosomal gel it penetrate into the deeper layer of the stratum corneum and give the beneficial effect as compared to conventional drug delivery[4].

MATERIAL AND METHODS

2.1. Materials: - Allopurinol was kindly provided by the Indoco R&D Centre Maharashtra 400701. Cholesterol, soya lecithin, Tween 80, Ethanol, carbapol and Triethanolamine are all are used of analytical grade

Methods

2.2.1. Pre-formulation study was first done before developing and dosage form of the new substance. Pre-formulation study was done in order to collect all the necessary information about the drug Physiochemical Properties, Solubility, Melting Point, Bioavailability and flow properties in order to make safe and effective formulation[5].

2.2.1.1 Physical /morphological characterization of allopurinol

Physical and morphological characterization of allopurinol colour texture and odour was done by visual examination.

2.2.1.2. Determination of melting point

The melting point of a drug is the temperature at which it changes the state form solid to liquid at atmospheric pressure. The melting point of a substance depends upon the pressure which is usually termed as standard pressure. If we decrease the temperature at which solid particle remain then solid particles convert into the liquid only in some chemical compounds which is known as the freezing point. Melting point is an essential technique to determine the purity and identity of drug.

- Mix the solid substance into the fine powder
- Then take a capillary tube and sealed at one end and fill the substance into the capillary tube
- Then insert the capillary tube into the melting point apparatus and insert the thermometer.
- Note the temperature at which the drug start converting solid from liquid which is melting Point of the drug[6]

2.2.1.3. Determination of Solubility

One crucial physicochemical characteristic of medicinal substances that affects their systemic absorption and, consequently, their therapeutic efficiency is their water solubility. By gradually introducing solvent to a test tube that contained a set amount of solute, and vice versa, a semi-quantitative assessment of the solubility was made. The system is violently agitated and visually inspected for any remaining solute particles following each addition. The ratio of solute to solvent is used to express solubility[7].

2.2.1.4. Angle of repose

Angle of Repose is done in order to see the flow properties of the drug. High angle of repose shows poor flow of drug[8]. Angle of repose can be calculated by the following formula;

$$\tan \Theta = h/r$$

2.2.1.5. UV-Spectral analysis

Preparation of Standard stock solution

100mg of allopurinol was accurately weight through the electronic weighing balance and transferred into the 100ml volumetric flask. then 50ml Methanol was added into the volumetric flask and shake the volumetric flask to dissolve the drug. then 50ml of methanol was added to the volumetric flask to make the final volume of 1000/ml

Determination of Absorption maxima (λ max)

Determination of the absorbance maxima From the standard stock solution sample was taken and see the absorption from the UV – spectroscopy (Shmidazo) in the range of 200nm to 400nm.

Determination of calibration curve

10ml of stock solution (1000/ml) was taken into 100ml volumetric flask and volume was made upto100 ml with methanol to obtain solution in the

concentration 100/ml. from the stock solution 1 ml was pipette out(100/ml) and transferred into the 100ml volumetric flask then volume make was done to make the solution(10/ml). from this solution 1ml was taken into the10ml volumetric flask and volume make up done to make the solution (1/ml) in the same way different dilution done 2/ml, 3/ml, 4/ml,5/ml6/ml, 7/ml.the absorbance of each dilution was measured in triplicate from the selected wavelength using methanol as blank then calibration curve was plotted absorbance verses concentration[9].

2.2.1.6. Determination of Partition coefficient

In a Separating funnel 10mg Allopurinol was taken and 20ml(1:1) of Phosphate buffer and n-octanol was taken and mix then and keep for one hour for separating oil phase and aqueous phase after separating take the oil phase and aqueous phase and check the absorbance through the UV-spectrophotometer[10]**.**

The drug's partition coefficient was determined using a formula.

Partition Coefficient (*k*) =

$$\frac{\textit{Concentration of drug inorganic phase}}{\textit{Concentration of drug in aqueous phase}}$$

2.2.1.7. Drug and Excipient Compatability study

It ensures the quality and consistency of the formulation by confirming that the medicine and excipients stay chemically stable and unreacted. Through the analysis of the distinctive absorption peaks in the spectrum, FTIR enables you to identify every component in a physical mixture.

2.2.2. Methods of Preparation Of Transethosomes

Cold Method are used in the preparation of Transethosomes. In a Beaker Accurately weigh soya lecithin, cholesterol, drug and ethanol in specified amount and Put on the magnetic stirred with continuously stirring. Tween80 was dissolved in distilled water in the separate beaker. Then aqueous phase was added in the organic Phase though the syringe (guaze22) drop be drop. Stirring was done continuously through the magnetic stirrer for 30 minutes. After the stirring was done then the formulation was sonicated by the bath sonicator for 30 minutes and Transethosomes was Prepared[11].

2.2.2.1. Prepared of Transethosomal gel

Carbapol 934^{R} is used as a vehicle for the Transdermal delivery of allopurinol loaded Transethosomes. 2%(w/w) of carbapol is added into the distilled water and Placed one hours for swell. Then 10 g of Propylene glycol is added into the carbapol with gentle stirring for 60 min and the solution is neutralized by adding small amounts of Triethanolamine with gentle stirring. Allopurinol Transethosomes is added into the gel solution by stirring with homogenous. The formulation pH is maintained by adjusting the ph. Finally the allopurinol loaded Transethosomes gel are prepared[12].

2.2.3. Evaluation of Prepared Transethosomal gel

2.2.3.1. Entrapment efficiency

The ultracentrifugation method was used to determine the entrapment efficiency for each formulation. To separate the unentrapped, around 2 milliliters of the formulations were ultracentrifuged . for 60 minutes at 15,000 rpm and 4°C Transethosome pellets and free medication were found in the supernatant. In order to remove the unentrapped medication by centrifugation, transethosomal pellets were cleaned with PBS at a pH of 7.4. The combined supernatant was diluted with pH 7.4 PBS and measured using a UV spectrophotometer[13].

2.2.3.2.Drug release

A controlled diffusion technique is used in allopurinol transethosomal gel in vitro drug release using a dialysis membrane to evaluate the medication's release profile from the formulation. To ensure adequate hydration, a dialysis

membrane is first prepared and often soaked in distilled water for the whole night. A fixed amount of the gel formulation, usually 1-2 g, is placed inside the dialysis membrane, which is securely knotted at both ends to prevent leaks. The membrane containing the gel is then immersed in a receptor compartment containing a phosphate buffer solution (pH 7.4) maintained at 37 ± 0.5°C in order to mimic physiological conditions. The receptor medium is continuously swirled at a modest speed, typically between 50 and 100 rpm, to guarantee uniform distribution and prevent concentration gradients. Aliquots of the receptor medium are removed and replaced with an equivalent volume of fresh buffer at predetermined intervals (e.g., 0.5, 1, 2, 4, 6, 8, and 24 hours) in order to maintain sink conditions. A UV-visible spectrophotometer is used to analyze the extracted samples at the exact wavelength of allopurinol in order to determine the medicine concentration. The cumulative drug release is calculated and the findings are plotted against time to form the release profile[14].

2.2.3.3. Viscosity of Gel

The viscosity of gel is measured using a Brookfield viscometer. The spindle was continuously turned while the gel was held in the sample holder. The viscosity was then measured at 5, 10, 20, 30, 50, and 60 rpm[15].

2.2.3.4. Spreadability of gel

A glass slide containing 1 gram of gel was covered with another glass slide. After that, a 2 g weight was put on the slide, and the spreadability and diameter increase were calculated[16].

2.2.3.5. Ph of Gel

By combining 0.5 g of the gel with 20 ml of distilled water and stirring for 30 minutes with a magnetic stirrer, the pH of the Allopurinol-TELS gel formulation was ascertained. stirrer. Immersing the pH meter's probe into the distributed gel allowed for the measurement of the pH, which was then read on the digital display[17]

2.2.3.6 Scanning Electron microscopy (SEM)

To investigate the transethosomal vesicles' surface morphology, scanning electron microscopy, or SEM, was used. High-resolution images from SEM supported the homogeneity and structural integrity of the formulation by confirming the vesicles' spherical shape and smooth surface. Understanding the vesicles' physical properties, which have a direct impact on how well they distribute drugs, was made possible by this investigation[18].

2.2.3.7. Stability study

The Allopurinol-TELS gel formulation was kept in glass vials at 25±2°C/65±5% RH in a humidity control oven and at 4±2°C/65±5% RH in a refrigerator. The specimen was removed for visual inspection and drug content at 10, 20, and 30day intervals[19].

Formulation design for Allopurinol Transethosomes

Formulation code	Allopurinol	Phospholipid(mg)	Surfactant	Ethanol
F1	50	100	50	20
F2	75	100	50	20
F3	125	100	50	20
F4	100	100	50	20
F5	150	100	50	20
F6	100	120	50	20
F7	100	80	20	50

RESULT AND DISCUSSION

3.1. Physical/ morphological Characterisation

The allopurinol was white fine power and have odourless characteristic**.**

3.2. Melting Point

The Melting point of Allopurinol Is 350 ^{0}C

3.3. Solubility

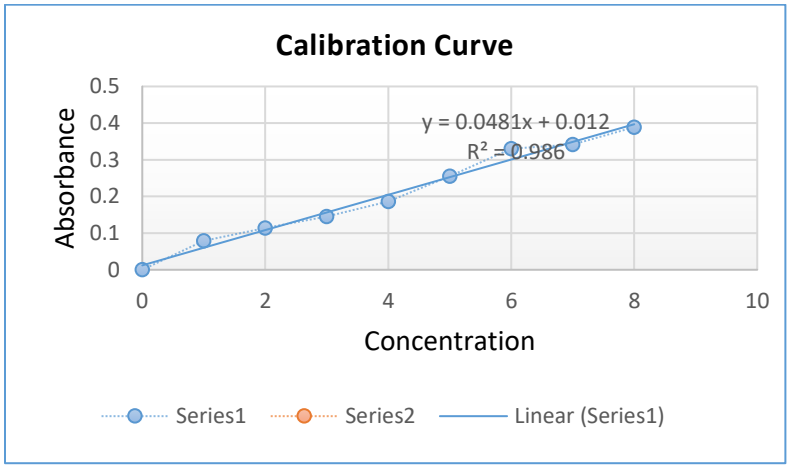
Allopurinol are slightly soluble in Methanol, and ethanol and insoluble in chloroform

3.4. Angle of Repose

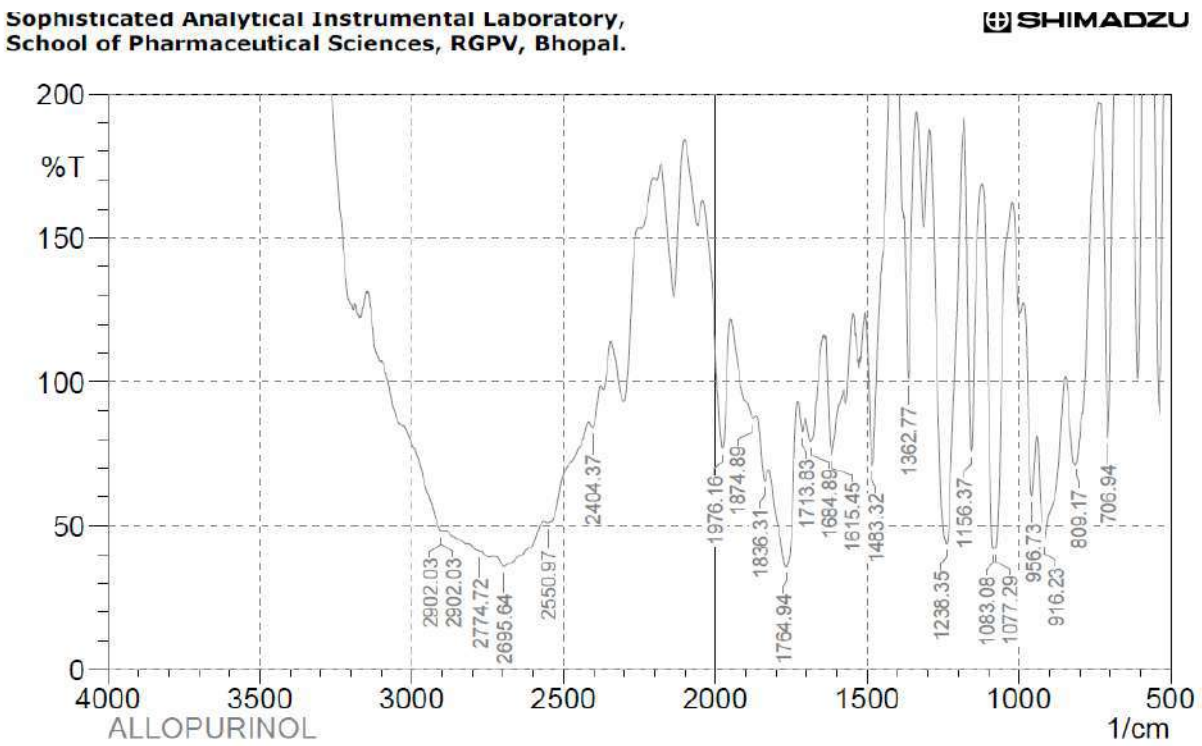
The angle of allopurinol is 37.5 which shows fair flow property**.**

3.5. Spectrum of Allopurinol

3.6. Calibration curve of Allopurinol

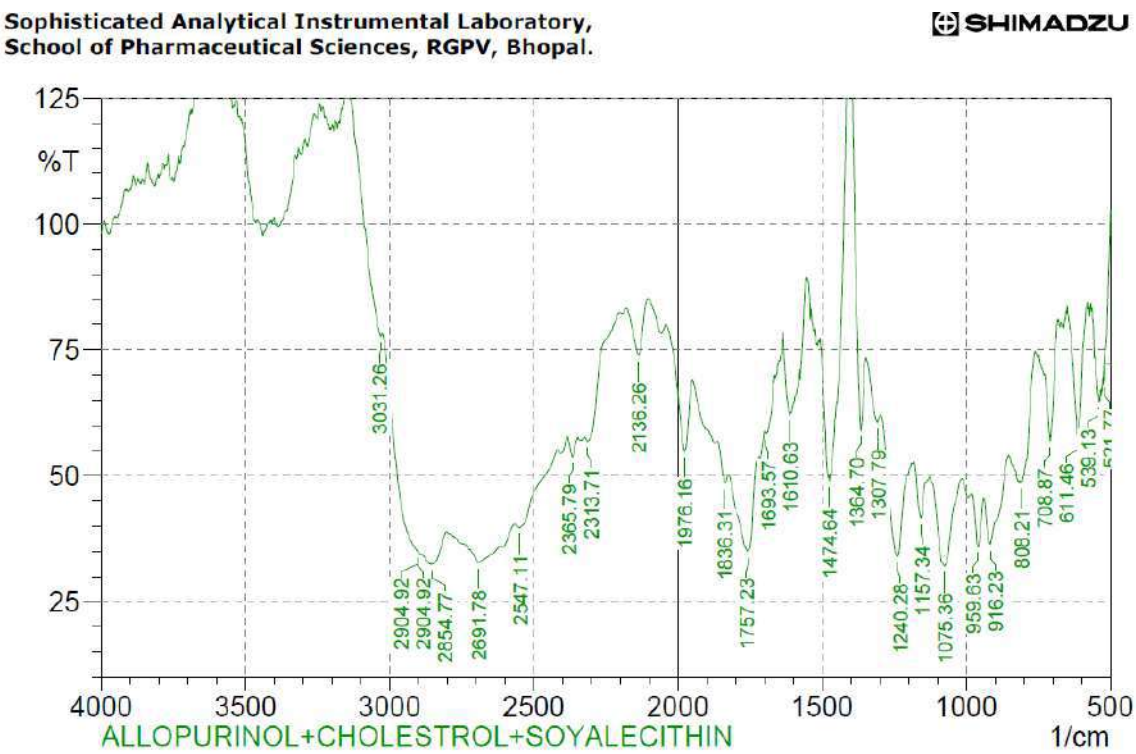


3.7. FTIR analysis of Pure drug



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	706.94	80.65	143.83	730.09	668.36	-12.19	10.23
2	809.17	71.78	0.91	810.14	791.81	1.73	0.04
3	916.23	45.04	41.25	939.37	847.75	18.57	14.8
4	956.73	60.24	38.02	984.7	940.34	3.53	3.84
5	1077.29	42.21	6.27	1080.18	1023.28	0.26	0.53
6	1083.08	41.94	6.75	1119.73	1081.15	1.8	0.54
7	1156.37	75.97	105.94	1180.49	1123.58	-5.98	8.51
8	1238.35	43.74	145.64	1293.33	1181.45	2.43	33.47
9	1362.77	100.96	69.56	1377.23	1336.73	-6.28	3.53
10	1483.32	70.69	59.48	1506.47	1455.35	0.49	6.44
11	1615.45	74.63	30.06	1634.74	1593.27	2.84	3.36
12	1684.89	79.18	16.95	1703.22	1644.39	2.22	2.42
13	1713.83	82.68	7.11	1726.36	1704.18	1.41	0.39
14	1764.94	35.78	48.09	1822.81	1727.33	26.99	18.04
15	1836.31	65.49	10.07	1862.35	1823.77	5.28	1.15
16	1874.89	87.19	2.7	1899.97	1863.32	1.78	0.23
17	1976.16	76.93	57.1	2040.77	1949.15	-4.98	8.69
18	2404.37	84.09	5.89	2416.91	2376.4	2.07	0.67
19	2550.97	51.1	3.73	2564.47	2417.87	26.42	1.42
20	2695.64	35.91	1.8	2721.68	2681.17	17.44	0.44
21	2774.72	41.15	0.2	2813.3	2772.79	15.16	0.12
22	2902.03	48.21	0.29	3027.41	2901.06	22.71	-1.82
23	2902.03	48.21	0.29	3027.41	2901.06	22.71	-1.82

3.8. FTIR analysis of Physical mixture



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	515.98	74.98	3.36	517.91	499.58	1.16	0.21
2	521.77	68.68	4.18	522.73	517.91	0.67	0.05
3	539.13	64.75	1.6	541.06	534.3	1.24	0.05
4	611.46	57.95	0.51	612.43	609.53	0.68	0.01
5	708.87	56.91	16.84	728.16	688.62	7.53	2.3
6	808.21	48.77	1.66	811.1	760.95	11.67	0.72
7	916.23	36.36	7.08	939.37	893.08	18.48	1.69
8	959.63	35.94	10.06	979.88	939.37	15.75	2.08
9	1075.36	32.11	1.09	1078.25	1014.6	24.84	-0.47
10	1157.34	41.59	8.79	1180.49	1141.91	13.01	1.64
11	1240.28	34	1.04	1295.26	1238.35	19.3	0.12
12	1307.79	60.59	4.26	1347.34	1295.26	9.66	0.78
13	1364.7	58.97	37.96	1405.2	1347.34	3.72	5.08
14	1474.64	49	2.19	1476.57	1448.6	7.2	0.38
15	1610.63	62.1	2.14	1634.74	1607.74	4.73	0.55
16	1693.57	58.47	0.35	1699.36	1689.72	2.24	0.02
17	1757.23	35.05	17.28	1825.7	1722.51	38.66	9.17
18	1836.31	48.65	3.49	1862.35	1825.7	10.52	0.54
19	1976.16	54.91	17.23	2041.74	1949.15	16.22	4.24
20	2136.26	73.86	10.47	2177.73	2103.46	7.52	1.98
21	2313.71	56.87	0.27	2321.43	2310.82	2.58	0.01
22	2365.79	53.79	3.94	2382.19	2346.51	9.07	0.55
23	2547.11	39.73	2.37	2564.47	2417.87	48.81	1
24	2691.78	32.8	1.54	2737.11	2672.49	30.12	0.57
25	2854.77	32.4	0.2	2859.59	2848.98	5.18	0.01
26	2904.92	35.08	0.69	3027.41	2902.99	38.2	3.3
27	2904.92	35.08	0.69	3027.41	2902.99	38.2	3.3
28	3031.26	77.68	1.6	3063.09	3027.41	3.16	0.24

3.9. Entrapment Efficiency

Transethosomal gel Formulation had encapsulation efficiency ranging from 72.5 percent to 85.2 percent. Table shows the entrapment efficiency of 7 Formulation**.**

Formulation code	Entrapment efficiency
F1	72.5
F2	78.3
F3	81.4
F4	85.2

F5	80.7
F6	68.9
F7	79.5

The F4 formulation's high EE of 85.2% suggests that it may work well as a transethosomal gel for the administration of allopurinol. A higher EE indicates that a larger percentage of the medication is contained and shielded by the vesicles, guaranteeing longer-lasting effects, improved skin permeability, and decreased drug loss. Furthermore, it might lessen the frequency of applications and the overall dosage needed, enhancing patient adherence and lowering adverse effects. Conversely, the F1 formulation's lower EE (72.5%) indicates less-than-ideal drug encapsulation, which may result in increased waste, accelerated drug release, and diminished therapeutic efficacy. This discrepancy emphasizes how crucial it is to optimize EE by optimizing formulation factors.

3.10. Partition coefficient

The allopurinol is hydrophilicity having K value -0.55

3.11 Drug Release

Time(hrs)	F1	F2	F3	F4	F5	F6	F7
1	12.4	15.0	14.1	17.5	15.8	10.3	13.8
2	25.6	26.0	27.2	32.5	29.1	18.5	27.0
4	41.5	45.2	42.0	50.2	44.6	42.0	42.2
6	58.3	61.1	60.3	69.0	59.6	48.5	62.2
8	71.0	74.0	69.4	80.1	74.6	62.3	72.1
12	80.2	73.0	65.5	**82.5**	55.3	52.3	80.3

The F4 formulation's excellent in vitro drug release (82.5%) demonstrates how well it delivers allopurinol. By guaranteeing that a sizable amount of the medication is available for absorption, this release profile improves therapeutic efficacy. The formulation's extended release feature may help lessen the need for frequent doses, increasing patient adherence. Furthermore, F4's optimal composition reduces drug waste and guarantees steady distribution throughout time. The lower drug release (52.3%) of the F6 formulation points to a less-than-optimal drug delivery strategy. For certain applications requiring prolonged drug retention, the progressive release may be beneficial, but it might not be the greatest choice for achieving the therapeutic levels necessary for allopurinol to function. The reduced release may be caused by larger vesicle sizes, excessive vesicle stiffness, or insufficient ethanol or surfactant levels; these problems need to be fixed for improved outcomes.

The F4 (82.5%) and F6 (52.3%) formulations of Allopurinol transethosomal gel were compared for in vitro drug release, highlighting the crucial impact that formulation parameters play in influencing drug release efficiency. F4's optimal composition, balanced phospholipid and surfactant ratios, suitable ethanol level, and vesicle properties that facilitate effective drug diffusion are all responsible for its exceptional performance. The reduced release of F6, on the other hand, indicates that further tuning is required to attain the intended therapeutic results. These results highlight how crucial careful formulation design and optimization are to creating transethosomal gels that deliver allopurinol effectively. Future attempts to improve the effectiveness of comparable drug delivery systems can be guided by the knowledge gathered from this study, which will ultimately improve patient outcomes and treatment success.

3.12. Viscosity

The viscosity of transethosmal gel at different rpm was found, 3000 cp,2000cp ,800cP,500cP and 450cP.

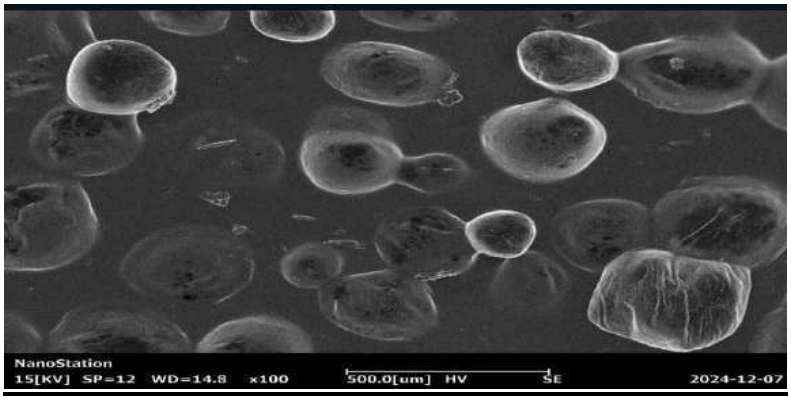
3.13. Spreadability

The Spreadability of the Transethosomal gel was found to be in the range of 6.3g/sec

3.14. pH of gel

The ph measurement of the Transethosomal gel carried out by using digital pH meter at room temperature. The pH value of the Transethosomal gel was found to be 6.4.

3.13. Scanning Electron microscopy (SEM)



Allopurinol transethosomal gel's well-optimized structural characteristics, such as spherical vesicles, nano-sized distribution, smooth surfaces, and strong matrix integration, are highlighted by the SEM examination. The formulation's excellent stability, improved drug distribution, and controlled release qualities are all a result of these characteristics taken together. The results confirm that the formulation is appropriate for transdermal administration of allopurinol and offer a solid basis for its use in clinical settings. The formulation can attain even higher therapeutic efficacy and patient acceptance by targeting small regions that require additional improvement.

SUMMARY AND CONCLUSION

An important development in topical medication delivery methods is the creation and assessment of allopurinol transethosomal gel. The formulation showed great promise in terms of therapeutic efficacy, stability, and penetration. This novel method offers focused therapy with little adverse effects, making it a competitive substitute for traditional oral formulations. Clinical trials could be the main focus of future studies to confirm the formulation's safety and effectiveness in human subjects. Furthermore, investigating the formulation's cost-effectiveness and scalability will be essential to its successful commercialization. All things considered, the study lays the groundwork for the application of transethosomal systems in systemic and dermatological therapy, opening the door for next-generation drug delivery methods

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