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# Development and Evaluation of Nanocarrier for Delivery of Taxifolin Phytochemical.

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**KEYWORDS**

Niosomes, Taxifolin, Phytochemical, Solubility

**ABSTRACT:**

**Introduction**: The plant chemicals is called as phytochemicals which are used to prevent or suppress tumour, is known as chemoprevention. Many studies have been suggested and reported that numerous plant derived agents have anticancer potentials. As one such anticancer phytochemical Taxifolin which has several applications however that are limited due to its solubility.

**Objectives**: The aim of the present study was to design and evaluation of phytochemical based niosome of Taxifolin as an effective nanocarrier for novel drug delivery system.

**Methods**: Taxifolin loaded into niosomes to increase its solubility and hence efficacy. Taxifolin loaded niosomes was prepared by thin film hydration method followed by sonication. The particle size, PDI, zeta potential, drug content, entrapment effectiveness, invitro drug release, scanning electron microscopy (SEM), and transmission electron microscopy TEM) were used to characterize the Taxifolin niosomes.

**Results**: The F6 formulation was chosen as optimized formulation based on particle size, zeta potential, PDI and entrapment efficiency. The particle size (115.8± 11.61 nm), PDI (0.191±0.98), zeta potential (-27.7±2.37 mV), loading efficiency (89.78±3.14) were studied. In addition, the result of invitro release study indicated that cumulative release rate for pure Taxifolin and niosomes loaded Taxifolin were 71.18408 % and 96.85572 % after 24 hrs respectively.

**Conclusions**: The results demonstrated that niosomes increase the solubility of naturally derived hydrophobic phytochemicals and thus enhance their therapeutic effect.

## 1. Introduction

Plant chemicals, known as photochemical present in a number of fruits, vegetables, greens, herbs, and marine organisms, algae, seaweed, and sponge contain large amount of bioactive compounds/nutrients. They have various health benefits, including antioxidant, anti-cancer, antimicrobial, anti-inflammatory, anti-diabetic, and antibiotic properties. In current years there has been increasing interest in alternative therapies and therapeutics uses of natural materials and they have approved for the clinical treatment of various diseases. The phytochemicals have promising potential for maintaining and promoting health, as well as preventing and potentially treating some diseases without side effects. However, Phytochemicals have some drawback that decreases the patient compliance, such as penetrating smelling and nasty taste. Also plant extract are difficult to absorb into the body either in oral or topical dosage form because their multiple large ring size which cannot absorb by passive diffusion or due to their poor lipid solubility, severely limiting their ability to pass across the lipid rich biological membranes, resulting poor bioavailability. Because of numerous problem associated with phytochemicals, an assembled technological

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approach such as nanocarrier system is necessary. Nano-based drug-delivery systems have the potentials to address all these limitations. Nanocarriers can increase the stability and also improve the therapeutic efficiency of phytochemicals such as polyphenols, tannins, alkaloids, terpenoids and herbal extracts. These nanocarriers develop more efficient and stable formulation which show the good solubility and stability of phytochemicals, enhance their absorption, protect from premature degradation in the body and prolong their circulation time.

The nanoparticles used as carrier are designed to deliver the phytochemicals to the target site with enhanced bioefficacy. Nanoparticles used as nanocarriers are basically of two types inorganic and organic. Some of the most commonly used inorganic nanocarriers include Super Paramagnetic Iron-Oxide Nanoparticles (SPIONs), Mesoporous Silica Nanoparticles and Gold/Silver nanoparticles. The use of inorganic nanoparticles is very limited in drug delivery owing to their poor drug loading efficiency, high peripheral toxicity and health risks. The organic based nanocarriers are basically composed of lipids such as micelles, liposomes, niosomes, bilosomes, solid lipid nanoparticles (SLN) and archaeosomes.

Taxifolin (5,7,31,41-tetrahydroxyflavanol, dihydroquercetin) belongs to a member of the flavonoids family. Taxifolin was found from the leaves of Chamaecyparis obtuse (Cupressaceae) and also commonly extracted from Pseudotsuga taxifolia (Lamb.) Britt., Larix gmelinii (Rupr.) Kuzen, and Larix sibirica Ledeb. (Pinaceae). It was even obtained from fruits, vegetables, beverages, and so on. It elicits a wide range of pharmacological effects of anti-oxidation and anti-radiation. Furthermore, it also has anti-inflammation activity, anti-viral activity, anti-tumor activity, and protective postmenopausal osteoporosis activity. Due to its pharmacological diversity, its bioavailability and biological properties have raised a great interest in future studies. However Taxifolin having many applications in medical field, its delivery is a problematical challenges due to slightly solubility in water, poor permeability, low bioavailability and instability in biological systems.

Nanotechnology plays an important role in drug formation and its controlled delivery to the target site along with a controlled release. Thus, this technology provides numerous plausible benefits in treating chronic human diseases by site-specific, and target-oriented delivery of medicines. Niosomes is a non ionic surfactant vesicle, adding cholesterol to niosomal compositions imparts rigidity to the bilayer structure, which ultimately makes it less permeable and prevents leakage of the drug from the niosomal formulation. Niosomes have that much potential to deliver phytochemicals at targeted site and shown a sustain effect. Through this niosomes we can entrap both hydrophilic and hydrophobic drugs.

## 2. Objectives

The aim of the research work was to develop Taxifolin loaded niosomes for targeted drug delivery system to improve efficacy of a phytochemicals. The plant derived compounds have less toxicity as compared to chemical drugs, but their free consumption can decrease their efficacy because of their drawback. Although many studies proved that pharmacological applications of phytochemicals have been limited due to its poor water solubility, poor permeability, low bioavailability and low stability in biological systems. Formulating these phytochemicals in niosomes as Nano carrier to address these limitations effectively.

## 3. Material & methods

### Material

Taxifolin powder was obtained from Yucca Enterprises Mumbai, Cholesterol, Sorbitan Monostearate (Span 60) and Diacetyl Phosphate were obtained from Loba chemise, India. All other materials used in this study were of analytical grade.

### Method

For the preparation of niosomes, thin film hydration method followed by sonication was used as reported previously (5). The specific molar ratio of span 60, cholesterol and Taxifolin (4:4:1) were dissolved in to 250 ml round bottom flask which containing chloroform. After that chloroform was removed with the help of rotary evaporator (at 60 0c 100 rpm) for 30 min (Labline PBV 7D). To obtain niosomes formulations, the resulted lipid film was hydrated by 10 ml phosphate buffer Ph 7.4 at 60 0c for 30 min. The result, milky solution was obtained and further sonicated in an ultrasonic bath for 30 min at 50 0c to achieve niosomes with uniform size distribution. The formed niosomes formulations were

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centrifuged for 15 min at the speed of 10000 rpm, finally formulations were filtered.

**Table 1:** Span 60: Cholesterol: Taxifolin Ratio Selection

| Sr. NO. | FC | Span 60: Cholesterol; Taxifolin (% w/w/w) |
|---|---|---|
| 1. | F1 | 1:1:1 |
| 2. | F2 | 1:2:1 |
| 3. | F3 | 2:1:1 |
| 4. | F4 | 2:2:1 |
| 5. | F5 | 3:3:1 |
| 6 | F6 | 4::4:1 |

**Characterization of Taxifolin Loaded Niosomes**

The formulated niosomes of Taxifolin were studied by following parameters.

**Determination of Particle Size, Polydispersity Index and Zeta Potential**

The particle size, polydispersity index and zeta potential of vesicles were determined by dynamic light scattering technique. The developed formulation was diluted 100 µl with the appropriate volume of PBS (pH 7.4) and filled in cuvette and analyzed by Horiba SZ 100 particle size analyzer. The Zeta potential of the same sample was measured by using zeta potential cuvette. The result of particle size, PDI and zeta potential were reported in following table no. 02.

**Determination of EE**

The amount of encapsulated taxifolin in the niosomal vesicles was evaluated using the centrifugation method. Free drug can be removed by centrifugation. The niosomal dispersion were centrifuged at 12000 rpm for 30 min. The supernatant was collected and analyzed for free drug. The Concentration of the free drug in the supernatant was determined by measuring absorbance at specific wavelength with a UV spectrophotometer (Shimadzu, model UV 1650 PC, Kyoto, Japan). The percentage of drug entrapment in niosomes was calculated using the following formula.

$$\% \text{ Drug Entrapment} = \frac{\text{Total Drug} - \text{Drug in Supernatant}}{\text{Total Drug}} \times 100$$

**Fourier-Transform Infrared Spectroscopy Analysis**

Kbr were previously activated. The Taxifolin (1mg) was triturated with Kbr and pellet was formed. This pellet was then filled into die and analyzed by FTIR spectrometry in the range of 400- 4000 nm.

**Differential Scanning Calorimetry**

Differential Scanning Calorimetry instrument (821e Metler-Toledo GmbH) operating with STARe software version 9.1 with an intra cooler was used for the study. The instrument was calibrated by using indium. The sample (3–5 mg) was analyzed under dry nitrogen purge (50 mL/ min) in a sealed and pinhole Aluminum pan. The sample is heated from room temperature to five degrees (K) above the melting points for (Taxifolin)and held for 5 min, then the sample is cooled to 223 K (- 50 C) and held for 15 min, then the sample is again heated to five degrees (K) above the melting point of (Taxifolin). A constant heating and cooling rate of 10 C/min is used.

**X-ray diffraction study**

X-Ray diffraction is a useful tool to get the structural information of crystalline compounds. Each signal in XRD represents the plane of a crystal. The structural composition can be studied using X-ray diffraction method. Drug samples were ground to fine powder and spectra were recorded on Bruker D8 Powder XRD Instrument using the source Copper K alpha. X-ray Powder diffraction measurements is used to confirm the crystalline nature and glass formation of the sample. A XPERT-PRO diffractometer system with a rotating anode Cu Ka was used and scans are taken between 5 and 100.

**Transmission Electron Microscopy**

Transmission electron microscopy (TEM) (Jeol Model JM 2100) was used to examine the morphological characteristics of the optimized DTX niosomes. A drop of niosomal formulation was placed on a carbon-coated copper sheet, and the unwanted sample was wiped away using filter paper. The carbon grid was stained with a drop of staining factor (2%w/v solution for phosphotungstic acid) and left aside for 2 min. The

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excess staining agent was transferred to filter paper, and Transmission Electron Microscope was employed to observe the thin film of stained niosomes

**1. Scanning Electron Microscopy**

The shape and surface characteristics of the optimized formulation of niosomes were investigated and photographed with the help of scanning electron microscopy (JEOL and Tokyo, Japan JSM – 6360). The sample for SEM were prepared by mounting niosomes onto a double adhesive tapes stuck to an aluminum stub prior to coating, stubs were then coated with gold palladium under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electron microscope.

**In-vitro Release Study**

The cumulative in vitro release rates of pure Taxifolin and Taxifolin niosomes were determined by dialysis method. A formulation equivalent to 10 mg Taxifolin was placed into dialysis bag which was previously soaked overnight in water, then this bag placed into phosphate buffer ph 7.4 as a dissolution medium. The entire system was kept at 37 ± 0.5 $^{o}$c with continuous shaking at 100 rpm/min in bath. At selected time intervals, the sample was withdraw at predetermined time period and replaced with an equal volume of fresh medium in order to maintain sink condition. The absorbance of Taxifolin in the solution was determined using double beam UV-VIS spectrophotometer at 288 nm.

**Kinetic Release Study:**

The in vitro drug release data was subjected to kinetic treatment. The release kinetics of Taxifolin from niosomes was assayed by means of different kinetics models such as zero order, first order, Higuchi and Korsmeyer –Peppas (KP) models.

$Q_t = Q_0 + k_0 t$

$Q_t = Q_0 e^{-k1t}\ k_1/2.303$

$Q_t = k_H.t^{1/2}$

$M_t/M = k_p t^n$

Where $Q_t$ is the cumulative amount of released drug at time t, $M_t/M$ is the fraction of drug released, and $k_0$, $k_1$, $k_H$ and $k_p$ are the constant for zero, first, Higuchi and Peppas model respectively. Also $Q_0$ is the total concentration of loaded drug and n is diffusional exponent. The determination coefficient (r2) for all models was calculated to find the best fitting model.

**Result & Discussion**

**Characterization of Taxifolin**

The formulated niosomes of Taxifolin were studied and results are discussed above.

**Particle Size, PDI and Zeta Potential**

The particle size data for the various formulation codes (TF1 to TF 06) were analyzed. The diameter of niosomes was mainly in the range of 100.6± 10.57– 115.8± 11.61nm. After the loading of niosomes by Taxifolin, the spherical integrity of formulation did not significantly change. It is evident that TF6 stands out as the optimized batch in terms of particle size. With a particle size of 89.1nm, TF6 has the smallest particle size among all the formulations, indicating finer particles. This finer particle size can be advantageous in many applications where a specific particle size range is desired, such as in pharmaceuticals, cosmetics, or materials science. The optimization of TF6 suggests that it meets the desired criteria for particle size, making it a favorable choice for further development or use in applications where particle size is a critical parameter.

**PDI**

The homogeneity of the formulation was known as the polydispersity index (PDI). Small value of PDI < 0.1 indicate a homogeneous population, while a PDI > 0.3 indicates high heterogeneity. The PDI value of optimized niosome (TF6) was found to be 0.191±0.98 had satisfactory homogeneity and stability

**Zeta Potential**

The stability of niosomes formulation are dependent on the zeta potential. A zeta potential near ± 30 mv can guarantee a long –term stable formulation. Zeta potential for optimized batch was found to be -27.7±2.37 mV. High and negative zeta potential values are an indication of stable preparation and prevent aggregation phenomena. The loading of Taxifolin into niosomes resulted in more negative zeta values and hence more stable formulations.

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**Determination of EE**

The entrapment efficiency data for the various formulation codes (TF1 to TF 6) reveal that TF6 is the optimized batch with the highest entrapment efficiency. The EE of optimized formulation (TF6) was found to be 89.78±3.14. Many studies mentioned that hydrophobic drugs are entrapped into bilayers of niosomes through electrostatics interactions. High encapsulating efficiently of Taxifolin in niosomes is because of hydrophobic nature of Taxifolin that results in more affinity and thus more incorporation in niosomes bilayers. Such high drug loading will be beneficial for the systemic administrations and result in the release of a significant amount of Taxifolin at the site of action. Barani et al. (2018) prepared lawsone –loaded niosomes with a particle size of 300 nm and loading efficiency of 69%. The Taxifolin niosome prepared in this study had a higher loading efficiency and smaller particle size in comparison to the one mentioned above.

The EE of the formulated batches was determined and the results are recorded.

**DSC**

The DSC of Taxifolin was shown in fig no. 04. The melting point of Taxifolin found to be as 100.66°C. The Taxifolin DSC thermogram showed a high endothermic peak at 100.66°C that corresponds to the Taxifolin melting. The graph of Taxifolin revealed intense peaks, which indicates crystalline structure of powdered crude drug.

**FTIR**

The compatibility between Taxifolin and excipients were confirmed by IR spectrum. The IR spectrum of Taxifolin obtained on BRUKER FT-IR spectrophotometer. The spectra were scanned over the wave number range from 400-4000 cm -1 using KBr pellet.

IR spectrum indicated characteristics peaks due to vibration of principal functional groups at specific wave numbers. All characteristics peaks of niosomes carrier were seen in the physical mixture, no new peaks were observed. This shown that Taxifolin was compatible with vesicle components and no new chemical interaction happens between them.

**FT-IR spectra of Taxifolin** exhibit intense band at 3208.97 $cm^{-1}$ and 3421.1 $cm^{-1}$ represents –OH group, strong intense band at 1618.95 $cm^{-1}$ represents ketone C=O group and strong intense band at 1271.82 $cm^{-1}$ represents ether C-O group shown in fig. 05.

**FT-IR of physical mixture** (Taxifolin + cholesterol + span-40) exhibit strong intense band at 3423.03 $cm^{-1}$ represents –OH group, strong intense band at 1637.27 $cm^{-1}$ represents ketone C=O group, strong intense band at 2939.95 $cm^{-1}$ represents alkene =CH group, strong intense band at 1287.25 and 1170.58 $cm^{-1}$ represents ether C-O groups and strong intense band at 1471.42 $cm^{-1}$ represents alkene C=C group shown in fig. 06.

**XRD**

The X-ray diffraction pattern of Taxifolin exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of pure drug and showing similarity in the sharp, highly intense and less diffused peaks obtained with excipients, which confirms that there is no any interaction between the pure Taxifolin and excipients.

**Transmission Electron Microscopy**

The Transmission Electron Microscopy (TEM) micrograph confirming niosome formation and showing spherical or oval-shaped vesicular structures with a size of approximately above 100 nm is an important observation, especially in the context of niosomal drug delivery systems. The images showed in fig. 09 nanometer sizes, semi-spherical and homogenies from formulations. Moreover, the loading of niosomes did not cause any structural deformation, which confirmed high stability of formulations. It suggests the successful formation and characterization of niosomes for delivering the active compound, Taxifolin.

**Scanning Electron Microscopy**

The shape, size and morphology of niosomes were observed by SEM. Fig. 10 shown the SEM images of optimized Taxifolin niosomes formulation (TF6). SEM demonstrated nanometric niosomes with semi-spherical and closed vesicular structure without considerable aggregates.

**Drug Release Profile of Taxifolin Niosomes**

The release rate of drug is an important parameter which has to be critically evaluated. In vitro studies are performed at physiological conditions (37 0C and pH 7.4) which can give an idea of in vivo performance. The invitro drug release was performed here by the dialysis

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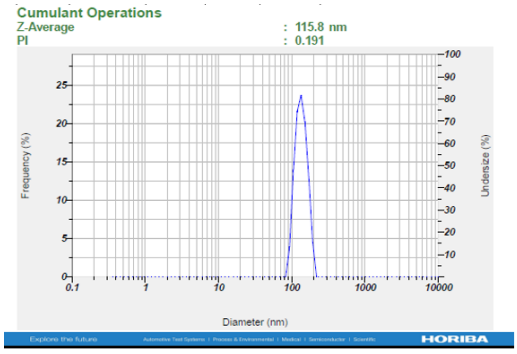
method. The sample were analyzed in specific time intervals by a UV-Visible spectrophotometer at 225 nm. The release profile is presented in fig. 11. Interestingly, the cumulative percentage release of free Taxifolin and Taxifolin niosomes significantly differed. Niosomes like other vesicular drug delivery systems showed a biphasic release, so that rapid drug release happened and then a steady state of release was obtained. The Taxifolin release rate in our formulation was significantly slower than the free Taxifolin. These findings that proved that niosomes have the capability of the sustainable and controlled release of Taxifolin. In fact, support studies working on other nanocarriers have concluded that niosome formulations can be applicable for delivering phytochemicals in a sustained and controllable manner.

**Kinetic Release Study:**

The drug release kinetics was evaluated using zero order, first order, Higuchi and KP kinetic models. Table No.5 Shows that the Higuchi Model best fitted the experimental data on the basis of the correlation coefficient ($R^2 > 0.98$).




. **Figure: 01** Particle size of TF6

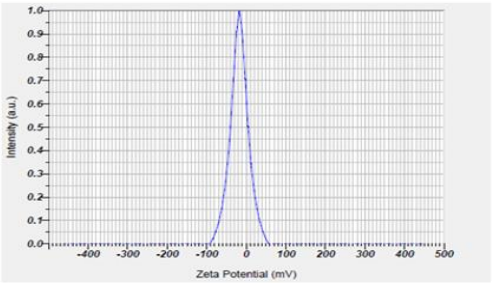




**Figure: 02** Zeta Potential of TF6

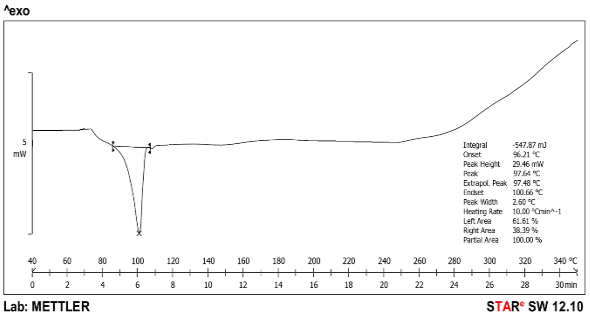



**Figure: 03** DSC Graph of Taxifolin

| Batches | Particle Size (nm) | PDI | Zeta Potential (mV) | EE (%) |
|---|---|---|---|---|
| TF1 | 106.5± 7.42 | 0.094 ± 0.083 | -23.8± 1.32 | 39.47.2 ± 2.14 |
| TF2 | 108.7 ± 11.84 | 0.103 ± 0.12 | -17.7 ± 1.74 | 48.51 ± 3.31 |
| TF3 | 105.2± 8.78 | 0.213 ± 0.086 | -18.4 ± 1.32 | 59.32 ± 3.73 |
| TF4 | 100.6± 10.57 | 0.420 ± 0.08 | -25 ± 2.74 | 68.68 ± 2.87 |
| TF5 | 112.1± 9.42 | 0. 226 ± 0.089 | -20.7 ± 1.46 | 77.34± 3.27 |
| TF6 | 115.8± 11.61 | 0.191±0.98 | - 27.7±2.37 | 89.78±3.14 |

**Table No: 02** Particle Size, PDI and Zeta Potential & EE% Taxifolin

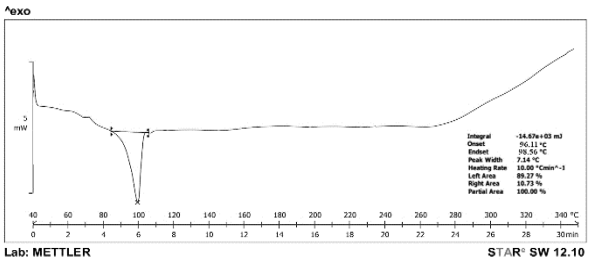



**Figure: 04** DSC of Taxifolin & Excipients

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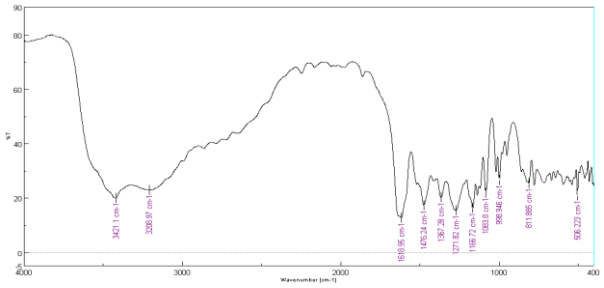

**Figure: 05** FTIR Spectra of Taxifolin

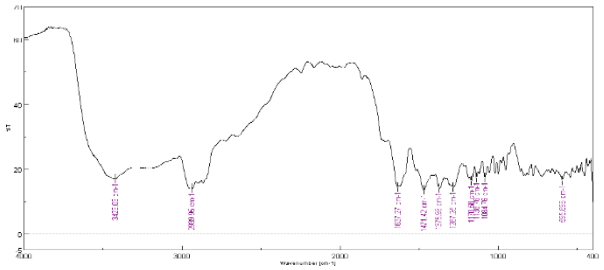

**Figure: 06** FTIR Spectra of Taxifolin & Excipients

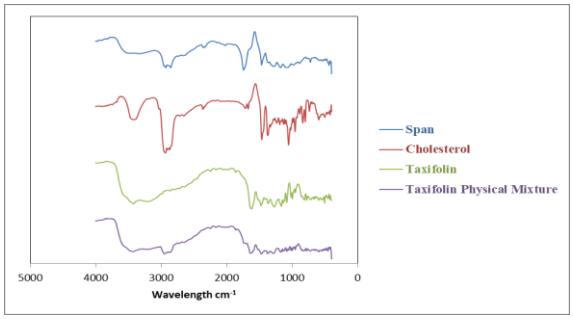


**Figure: 07** FTIR Overlay of Taxifolin and Excipients

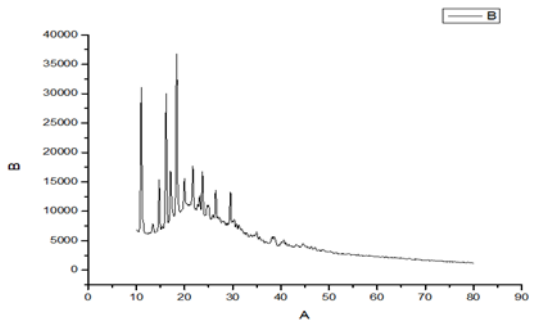


**Figure: 08** XRD Spectra of Taxifolin & Excipients

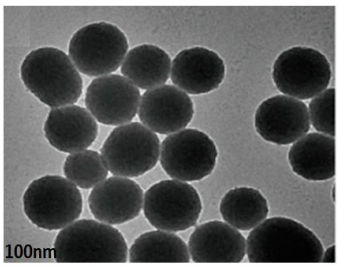


**Figure: 09** TEM of Optimized Formulation (TF6)

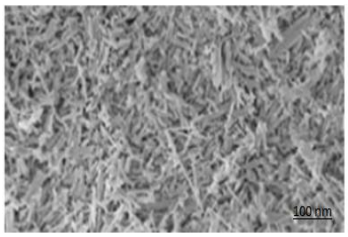


**Figure: 10** SEM of Optimized Formulation (TF6)

**Table No:** 03 Drug Release of Free Taxifolin

| Time | Abs | Con ug/ml | DF | %PD |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 0.214 | 3.207297 | 384.8756 | 19.24378 |
| 2 | 0.31 | 4.799337 | 575.9204 | 28.79602 |
| 3 | 0.348 | 5.429519 | 651.5423 | 32.57711 |
| 6 | 0.512 | 8.149254 | 977.9104 | 48.89552 |
| 9 | 0.596 | 9.542289 | 1145.075 | 57.25373 |
| 12 | 0.658 | 10.57048 | 1268.458 | 63.42289 |
| 24 | 0.736 | 11.86401 | 1423.682 | 71.18408 |

**Table No: 04** Drug Release of Niosomes Taxifolin

| Time | Abs | Con ug/ml | DF | %PD |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 0.234 | 3.538972 | 424.6766 | 25.23383085 |
| 2 | 0.605 | 9.691542 | 1162.985 | 34.14925373 |
| 3 | 0.666 | 10.70315 | 1284.378 | 43.21890547 |
| 6 | 0.811 | 13.10779 | 1572.935 | 58.64676617 |
| 9 | 0.938 | 15.21393 | 1825.672 | 66.28358209 |
| 12 | 0.981 | 15.92703 | 1911.244 | 78.56218905 |
| 24 | 0.994 | 16.14262 | 1937.114 | 98.85572139 |

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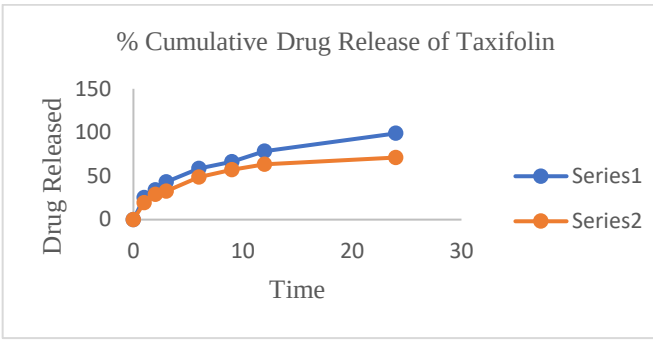


**Figure: 11** In vitro Release Profiles of Free Taxifolin (Series 2) and Taxifolin Niosomes (Series 1) in PBS 7.4 at 37 °C versus time

| Model | Equation | $R^2$ |
|---|---|---|
| Zero-Order | y = 3.6002x + 24.967 | $R^2$ = 0.8297 |
| First Order | y = -0.0759x + 2.0382 | $R^2$ = 0.9572 |
| Higuchi | y = 20.274x + 5.1062 | $R^2$ = 0.9868 |
| Kors-peppas | y = 0.2457x + 0.1107 | $R^2$ = 0.7431 |

**Table No: 05** Model, Equation, and Regressions of Taxifolin Release from Niosomes

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