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Research Article

# Formulation Development and Characterization of Pluronic Lecithin Organogel of Protein-Tyrosine Kinase Inhibitor Imatinib Mesylate

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## Abstract

Imatinib is a small molecule with antineoplastic effects. It functions as a specific inhibitor for a number of tyrosine kinase enzymes and acts by binding to the site of tyrosine kinase while preventing its activity, leading to apoptosis. The present research work was aimed at preparing reverse micelle based pluronic lecithin organogel for controlled delivery of imatinib mesylate for its application in skin cancer. Various batches of reverse micelles were prepared by varying the concentrations of lecithin (10%, 20% and 40%v/v) to obtain an optimal formulation with suitable thermodynamic stability transparency and particle size. The results show that formulation containing 10 %v/v of lecithin in isopropyl myristate (F1) was found to be optimum with particle size of 238.8 nm. Entrapment efficiency was found to be 47 %. The morphology of the reverse micelles was also confirmed by TEM. Imatinib mesylate loaded reverse micelle was converted in to organogel for topical delivery of drug using pluronic F127 as polymer. To prepare pluronic lecithin organogel, optimized reverse micelles containing imatinib mesylate was considered as oil phase and pluronic F127 dissolved in water as aqueous phase. Various concentration of pluronic F127 (30%w/v) was used to prepare organogel with suitable gelation. The optimized pluronic lecithin organogel was evaluated for organoleptic properties, pH, viscosity, bloom strength and spreadability. Pluronic lecithin organogel containing imatinib mesylate was found to be off white, homogenous and have pH value 6.6 which is non-irritant. Bloom strength and spreadability value indicates the formulated gel has suitable gel strength and easily spreadable. Drug content of the gel was found to be 90.83%. *In-vitro* diffusion study shows using phosphate buffer pH7.4 as medium which shows controlled release over a period of 8 hours. Therefore, from the above study it may be concluded that reverse micelles based pluronic lecithin organogel will be effective in topical delivery of imatinib mesylate.

**Keyword :** Imatinib mesylate, Micelle, Pluronic, Lecithin , organogel.

Introduction : Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. Organogels are bicontineous colloidal system that coexist as micro heterogeneous solid (i.e. Gelator) and organic liquid phase [1,2]

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In general, organogels formation is based in the spontaneous self assembly of individual gelator molecules into three-dimensional networks of randomly entangled fiber like structures. This three dimensional network holds micro domains of the liquid in a non flowing state mainly through surface tension. Lecithin organogels, the jelly like phases, consist of a 3-dimensional network of entangled reverse cylindrical (polymer-like) micelles, which immobilizes the continuous or macroscopic external organic phase, thus turning a liquid into a gel [3-7].The formation of transition at the micellar level in a low viscous newtonian liquid, consisting of lecithin reverse micelles in non polar organic liquid. However, these systems can also be called as polymer like micelles or wormlike or threadlike micelles [7,8]. Imatinib is a small molecule with antineoplastic effects. It functions as a specific inhibitor for a number of tyrosine kinase enzymes and acts by binding to the site of tyrosine kinase while preventing its activity, leading to apoptosis [9]. Imatinib mesylate (Gleevec, also known as STI–571), has been authorized to treat chronic myelogenous leukemia, gastrointestinal stromal tumors and is an important therapeutic period of breast cancer as well as some other types of cancer [10]. Its adverse effects include hair loss, diarrhea, nausea, loss of appetite, vomiting, dry skin, muscle cramps and swelling (especially in the legs or around the eyes) [11]. Imatinib is a 2-phenylaminopyrimidine derivative with a pKa value of 12.45 in acidic environment and 8.27 in basic environment [10]. It is soluble in conditions of less than pH 5.5 but is very slightly soluble to insoluble in neutral and alkaline aqueous buffers [10]. The present research work was aimed at preparing reverse micelle based pluronic lecithin organogel for controlled delivery of imatinib mesylate for its application in skin cancer.

## Materials and Methods

### Preparation of extracts:

Imatinib mesylate was obtained as a gift sample from Shreeji Pharma International, Baroda, India. Poloxamer (Pluronic F127); Soya Lecithin and sorbic acid were purchased from Qualigens Fine chemicals, New Delhi. Isopropyl myristate were procured from M/s Himedia labs Pvt. Ltd. Mumbai, India. All other chemical used were purchased from S.D Fine Chemical Limited, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

**Preformulation Studies**

**Melting point**

The melting point of the drug was determined by capillary tube method. Thin walled capillary melting point tubes are used to hold the samples. The tube was sealed at one end using Bunsen burner and the open end was filled with imatinib mesylate. The drug filled capillary tube was placed in the melting point apparatus and the temperature was raised gradually. The temperature at which drug started to melt was noted.

**Solubility study**

Saturation solubility of pure drug was tested in water, phosphate buffer pH 7.4 and isopropyl myristate. An excess amount of

drug was added to 10 ml of each solvent separately and shakenin a water bath shaker for 24 h at room temperature. The mixture was then filtered using 0.22 µm filter and the filtrate was suitably diluted. The absorbance of the solution was measured at 289 nm using a UV spectrophotometer (UV-1650 PC; Shimadzu Corporation) to determine the solubility of imatinib mesylate.

**Determination of lambda max**

***Preparation of stock solution A***

The imatinib mesylate stock solution A was prepared by dissolving 100 mg of drug in 100 ml of phosphate buffer pH 7.4 to obtain concentration of 1000 mcg/ml.

***Preparation of stock solution B***

From the above stock solution 10 ml was taken and diluted to 100 ml to prepare stock solution B of concentration 100 mcg/ml.

***Preparation of stock solution C***

From the above stock B, 1ml was taken and diluted to 10ml to prepare stock solution C of concentration 10mcg/ml.

**Determination of analytical wavelength**

Stock C solution was scanned using double beam UV-Visible spectrometer in the spectrum mode between the wavelength ranges of 200-400 nm.

**Standard curve of imatinib mesylate in phosphate buffer pH 7.4**

Standard stock solutions of imatinib mesylate were prepared by dissolving 100 mg of imatinib mesylate in 100 ml of phosphate buffer pH 7.4. 1 ml of this stock solution was diluted to 10 mlby using the same solvent to produce a concentration range of 100mcg/ml. From this stock solution (100 mcg/ml) further dilutions were made to produce 5, 10, 15, 20 and 25 mcg/ml. These solutions were analysed in the UV spectrometer at 289nm. A calibration curve was plotted with the concentration on the x-axis and the absorbance at y-axis. The regression coefficient was calculated.

**FT-IR spectroscopy**

To verify the possible interaction between drug and excipients, FT-IR study was conducted. FT-IR spectrum of pure drug (imatinib mesylate), surfactant (lecithin) and the mixture of drug and excipients were performed with FT-IR spectrophotometer using KBr pellets disc method.The sample were scanned over the range of 4000-400cm$^{-1}$

**Determination of CMC (critical micellar concentration)**

The CMC of the lecithin (surfactant) in isopropyl myristate was determined by drop count method using stalagmometer. The clean and dry stalagmometer is placed in the vertical position and held fixed. The number of drops between the uppermost (A) on the upper stem and lowermost (B) on the lower stem which fixes the volume (V) of the liquid is counted. The different concentration of stock solution 0.4% (v/v), 0.8% (v/v), 1.2% (v/v), 1.6% (v/v) and 2% (v/v) of lecithin in isopropyl myristate was prepared. The liquid was sucked above mark A and the number of drops of liquid falls between the marks A and B was counted. The surface tensionof different concentration was determined using the formula

$$\gamma_2 = \frac{n_2\rho_1 \times \gamma_1}{n_1\rho_2}$$

$\gamma_2$ = surface tension of the liquid to be determined,
$\gamma_1$ = surface tension of IPM
$n_1$= no of drops of IPM $n_2$ = no of drops of water
$\rho_1$ = density of IPM
$\rho_2$ = density of water A graph of concentration (%v/v) v/s surface tension (dynes/cm) was plotted and the critical micellar concentration of the surfactant was determined [12].

**Optimization of lecithin concentration**

Various concentrations of lecithin in isopropyl myristate above the CMC were considered for optimizing reverse micelles. Different concentrations [Listed in Table 1] were prepared by adding measured quantity of lecithin into IPM under continuous stirring. Measured quantity of distilled water was added into lecithin IPM solution and stirred for 1 hr and the temperature was maintained at 80°C throughout the process to obtain uniform and stable reverse micelles. Reverse micelles formed was confirmed when lecithin-isopropyl myristate solution is transparent, homogenous and stable [13].

**Preparation of imatinib mesylate loaded reverse micelles**

From the above optimization process, formulation containing 10% (v/v) lecithin in IPM was used to load the drug. 10 mg of imatinib mesylate was accurately weighed and dissolved in 0.3 ml of distilled water. This solution was added by means of microlitre syringe to the lecithin IPM solution and stirred for about 2 hrs to achieve complete micellar solubilization of the drug using magnetic stirrer. The temperature was maintained at 80°C throughout the process [14].

**Characterization of the imatinib mesylate loaded reverse micelles**

***Determination of morphology***

The morphology of the prepared imatinib mesylate loaded reverse micelles was studied by observing under Phase Contrast Microscopy. It is an optical microscopy technique that converts phase shifts in light passing through a transparent specimen to brightness changes in the image. The morphology of the prepared reverse micelles was determined by placing the samplein slide and focusing at 100X magnification.

***Particle size determination and polydispersity index (PDI) byzetasizer***

The mean particle size and PDI of the prepared reverse micelles was determined by Zetasizer (nano ZS90, Malvern instruments) at 25˚ C. The samples were kept in the polystyrene cuvetteand the readings were found out at the fixed angle.

***Drug encapsulation efficiency***

Encapsulation efficiency was determined by centrifugation method. Imatinib mesylate loaded reverse micelles were centrifuged at 13,000 rpm for 10 mins at controlled temperature using ultra centrifuge. The supernatant was recovered using micropipette and analyzed by UV Spectrophotometer at 289 nm.

***Transmission electron microscopy***

TEM provides morphologic, compositional and crystallographic information of the nanoparticles. The optimized formulation containing Imatinib mesylate loaded reverse micelles was analyzed for its surface morphology. One drop of imatinib mesylate loaded reverse micelles was deposited on a film-coated copper grid and it was stained with one drop of 2% (w/v) aqueous solution of phosphotungstic acid. Excess of solution was drained off with a filter paper and then grid was allowed to dry for contrast enhancement. The sample was then examined by transmission electron microscopy.

**Preparation of the pluronic lecithin organogel (PLO) optimization of concentration of pluronic F127**

The optimized imatinib mesylate loaded reverse micelle [F1] was converted in to organogel usingpluronic F127 as stabilizer.

Various concentration of pluronic F127 such as 10%.20% and 30% w/v was used to obtain gel with suitable characteristics. Weighed amount of pluronic F127 was dispersed in cold water and the mixture was kept overnight at 2-4°C in a refrigerator for the complete dissolution of pluronic F127. It was then observed for gelling behavior.

**Preparation of the pluronic lecithin organogel (PLO)**

PLO was prepared by mixing aqueous phase and oil phase. The optimized amount of pluronic F127 (30 % w/v) was considered as aqueous phase. Optimized imatinib mesylate loaded reverse micelles (F1) was considered as oil phase. 70% of aqueous phase [pluronic F127] was added drop by drop to 30% of oil phase with continuous stirring using mechanical stirrer [15].

**Characterization of prepared pluronic lecithin organogel (PLO)**

***Organoleptic examination***

The formulation was evaluated for its organoleptic properties i.e colour, odour, texture and phaseseparation as well as feels upon application (greasiness, stiffness and tackiness).

***Homogeneity test***

100 mg of the prepared organogel was pressed between the thumb and index finger in order tocheck if there are any coarse particles being attached or detached from the finger.

***Determination of pH***

The pH of the prepared PLO was measured by using pH meter (Systronics, pH system 361). The pH meter was calibrated using standard 7.4 phosphate buffer solution and the electrodes was immersed in organogel and the readings were recorded. The study was performed in triplicate and the average pH values were noted.

***Determination of viscosity***

Viscosities of the formulated pluronic lecithin organogel were determined using Brookfield Viscometer with Spindle no.7 at 25° with the spindle speed of 10 rpm. Viscosity measurement for gels was replicated three times and the mean values were recorded.

***Bloom strength***

The bloom strength of the prepared PLOs was determined by using Texture Analyser TA-XT Plus., equipped with 5kg load cell using a cylindrical probe 0.5" diameter as fixture. The sample in the container was placed centrally on the platform beneath the cylindrical probe. Aftercalibrating the height of the probe, the test was commenced. A trigger force of 10gm was usedfor the study.

**Spreadability**

The spreadability of the formulated PLOs was determined by Texture Analyser TA-XT Plus equipped with 5 kg load cell using spreadability rig as fixture. This fixture consists of a heavy duty platform, male cone and a female cone. The heavy duty platform was placed on the base of the machine and locked in the desired positioning by tightening the screws. An empty female cone sample holder was placed in the base holder. The male cone probe was attached above the female cone such that the male cone fits almost all the way to the female cone sample holder and proper care was taken to align the cones in this position. The height of the male cone was calibrated against the female cone so that the starting point was 25.0mm above the female cone (2mm form the tip of the male cone and the sample). After calibration the sample was placed on the female cone holder and the test was run. The values of firmness (g) and the work of shear (g/s) were noted down by running macros. (www.brookfieldengineering.com).

***Drug content***

Drug content for the optimized batch (PLO-3) was calculated by dissolving 100mg of gel in 100 ml of phosphate buffer pH 7.4 and filtered through 0.45µm. after filtration the drug content was found out by taking absorbance at 289 nm.

***In-vitro diffusion for pluronic lecithin organogel***

*In-vitro* diffusion studies were carried out through cellophane membrane. The one end of open cylinder *i.e* the donor compartment was tied with a semi-permeable membrane containing 2g of the formulation. The receptor compartment consisted of 50 ml of 7.4 phosphate buffers which was kept at continuous stirring using magnetic stirrer at room temperature for about 8 hrs. Sample was withdrawn at specified time intervals and replaced with fresh volume of buffer solution. It was then analyzed by UV spectrophotometer at 289 nm [16].

## Result and Discussion –

The melting point of imatinib mesylate (pure drug) was found to 129°C; it matches with the standard (226°C). Imatinib mesylate was freely soluble in water, partially soluble in 7.4 Phosphate Buffer and insoluble in isopropyl myristate. Lambda max for the diluted stock solutions of imatinib mesylate was scanned in the UV spectrometer region ranging from 200-400 nm. The maximum wavelength was seen at 289nm Figure 1. Drug-excipients compatibility was checked by comparing the IR spectra of pure drug, excipients and the physical mixture of the drug and excipients. FT-IR spectra of the drug excipient mixture retained the characteristic functional peaks of the drug and it was ensured that there was no interaction between the drug and the excipients Figure 2, 3**.** The CMC is the concentration of the surfactant in the bulk phase above which aggregates of molecules, so-called micelles, start to form. The CMC of various concentration of lecithin in isopropyl myristate such as 0.4%, 0.8%, 1.2%, 1.6% and 2% v/v was determined was drop countmethod. A graph of surface tension v/s concentration was plotted and the critical micellar concentration of the surfactant was found to be 1.6% Table 2. The concentration of the surfactant plays an important role in the formation of reverse micelles. Concentration above CMC such as 10%, 20% and 40% was used for preparing reverse micelles. Optimization of lecithin concentration was based on the parameters like transparency, physical stability, particle size and it was concluded that the formulation F1 showed best results when compared to the other. The results also indicate that when the concentration of the surfactant increases, there is increase in particle size and decrease in physical stability Table 3. Suitable formula for preparing drug loaded reverse micelles was selected from the optimization process considering physical stability, transparency, homogeneity and particle size as an evaluating factor. Formulation F1 containing 10% v/v of lecithin was considered ideal. To this 10 mg of imatinib Mesylate dissolved in 0.3 ml of distilled water was added by means of microlitre syringe under continuous stirring for about 2hrs using magnetic stirrer at a temperature of 80°C. The morphology of reverse micelles was observed using Phase Contrast Microscopy under the magnification of 100X. Fig 18 represents the morphology of reverse micelles which shows spherical shape Figure 4. The mean particle size of the prepared reverse micelles was determined by Dynamic Light Scattering (DLS) method. The average particle size of the optimized formulation F1 was 238.8 nm and PDI is 0.389 which shows that the prepared imatinib mesylate loaded reverse micelles are homogenous without any aggregates Figure 5. The encapsulation efficiency of the prepared imatinib mesylate loaded reverse micelles was carried

out by centrifuge method. The encapsulation efficiency is the characteristics of surfactant drug and water. The encapsulation efficiency of the optimized batch was found to be 47%. Various concentration of pluronic F127 such as 10 %(w/v),20%(w/v) and 30% w/v was used to obtain gel with suitable characteristics. Weighed amount of pluronic F127 was dispersed in cold water and the mixture was kept overnight at 2-4°C in a refrigerator for the complete dissolution of pluronic F127 Table 5. Suitable formulation for preparing pluronic lecithin organogel was selected from the optimization process considering gelation and homogeneity as an evaluating factor. Formulation PLO-3 containing 30 % w/v of pluronic F 127 was considered to be ideal with suitable characteristics of gel and it was used for further characterization. The prepared organogel was visually inspected for its organoleptic properties such as color, texture, appearance and phase separation. The results are tabulated in table 8 which indicates that formulated pluronic lecithin organogel has ideal characteristics of gel. No phase separation was observed after 72 hours which indicates the stability of the gel Table 6. Homogeneity test was performed to evaluate the ease of application of gel to the skin. The prepared pluronic lecithin organogel was evaluated for its homogeneity by pressing the gel between thumb and index finger. It shows that the gel is homogenous without any gritty particles. The pH of the organogel was determined by pH meter and the values are tabulated in table 9. The average pH value of pluronic lecithin organogel was found to be 6.6 which match with the skin pH. It shows that the formulated organogel is compatible and it may not produce any skin irritation. Viscosity is an important property of gel which describes its resistance to the flow. This rheological property helps in determining consistency and also the diffusion rate of the drug from gel. The measurement of viscosity of the prepared gel was done with Brookfield viscometer with spindle no 7 and the result was found to be 2548cps. This high viscosity may be due to the formation of 3D network upon the addition of polymer (Pluronic F127) to the reverse micelles. Bloom Strength is a measure of the ability of a colloidal dispersion to develop and retain a gel form. It is the force expressed in grams, necessary to depress by 4mm the surface of a gel with a standard 0.5" diameter cylinder probe. It is otherwise known as force required rupturing the gel. The bloom strength of gel indicates the resistance to penetration. For the formulated pluronic lecithin organogel, the value is 1.040kg. Since the bloom value was found to be high, therefore it was concluded that formulated pluronic lecithin organogel has good gel strength Table 7 & Figure 6. Spreadability of the formulated organogel was determined by using Texture analyzer. The firmness and work of shear obtained is mentioned in Table 8 .The values of spreadability indicate that gel is easily spreadable with small shear Figure 7. Drug content of the prepared organogel was determined by dissolving the gel in phosphate buffer pH7.4. The filtered sample was analyse sat 289 nm using spectrophotometer and the drugcontent was found to be 90.83%. *In-vitro* diffusion studies of formulated organogel was carried out through the cellophane membrane for about 8 hours using phosphate buffer pH 7.4 The values are tabulated in Table no and the graph was plotted by taking time on X- axis and percentage drug release on Y -axis. The results shows that formulated organogel shows sustained release (46.02 % for 8 hrs) Table 9.

## Conclusion

From the above study it may be concluded that reverse micelles based pluronic lecithin organogel will be effective in topical delivery of imatinib mesylate. Further in vitro cell line studies need to be conducted to confirm the above hypothesis.

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**Table 1: Optimization of Lecithin concentration**

| FORMULATION CODE | COMPOSITION | | |
|---|---|---|---|
| | IPM(ml) | Lecithin(ml) | WATER(ml) |
| F1 | 10 | 1 | 0.3 |
| F2 | 10 | 2 | 0.3 |
| F3 | 10 | 4 | 0.3 |

**Table 2: Determination of CMC**

| Concentration of lecithin in isopropylmyristate (%v/v) | Surface tension(dynes/cm) |
|---|---|
| **0** | **29.7** |
| **0.4** | **26.84** |
| **0.8** | **25.72** |
| **1.2** | **25.05** |
| **1.6** | **25.05** |
| **2.0** | **25.01** |

**Table 3: Optimization of lecithin concentration**

| Formulation code | Composition | | | | PARAMETERS | | | |
|---|---|---|---|---|---|---|---|---|
| | IPM (ml) | Lecithin (ml) | Water (ml) | IM (mg) | Homogeneity | Transparency | Physical stability | Particle Size (nm) |
| F1 | 10 | 1 | 0.3 | 10 | Homogenous | Transparent | Stable | 215.8 |
| F2 | 10 | 2 | 0.3 | 10 | Less Homogenous | Less Transparent | Less stable | 633 |
| F3 | 10 | 4 | 0.3 | 10 | Least Homogenous | Least Transparent | Least stable | 1125 |

**Table 4: Preparation of drug loaded reverse micelles**

| Formulation code | Composition | | | | PARAMETERS | | | |
|---|---|---|---|---|---|---|---|---|
| | IPM (ml) | Lecithin (ml) | Water (ml) | IM (mg) | homogeneity | transparency | Physical Stability | Particle Size (nm) |
| F1 | 10 | 1 | 0.3 | 10 | homogenous | transparent | Stable | 238.8 |

**Table 5: Optimization of Pluronic F127 concentration**

| Formulation Code | Concentration of Pluronic F127 (%W/V) | Parameters | |
|---|---|---|---|
| | | Gelation | HOMOGENEITY |
| PLO-1 | 10 | No gelation | Less homogenous |
| PLO-2 | 20 | Moderate gelation | Moderately homogenous |
| PLO-3 | 30 | Complete gelation | Homogenous |

**Table 6: Organoleptic evaluation of pluronic lecithin organogel**

| Formulation Code | Appearance | Color | Homogeneity | Phase Separation |
|---|---|---|---|---|
| PLO-3 | Opaque | Off white | Homogenous | No phase separation |

**Table 7: Bloom strength of pluronic lecithin organogel**

| Force (gm) | Value |
|---|---|
| 10 | 1.040 kg |

**Table 8: Spreadability of pluronic lecithin organogel**

| Firmness | Work of shear |
|---|---|
| 1849.56g | 1779.799g.sec |

**Table 9: *In-vitro* diffusion of pluronic lecithin organogel**

| Time (hours) | Percentage drug release (%) |
|---|---|
| 0 | 0 |
| 1 | 6.32 |
| 2 | 9.58 |
| 3 | 15.45 |
| 4 | 23.53 |
| 5 | 28.90 |
| 6 | 34.14 |
| 7 | 36.87 |
| 8 | 46.02 |

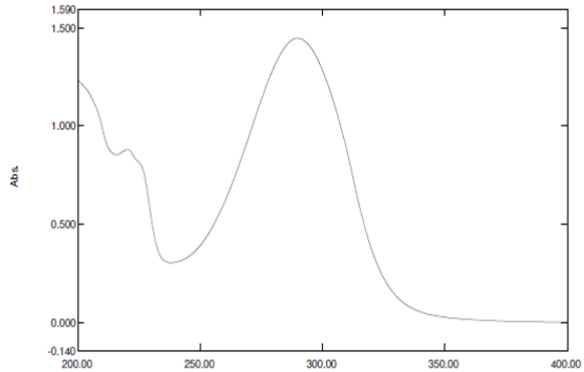


**Figure 1: Lambda max of imatinib mesylate**

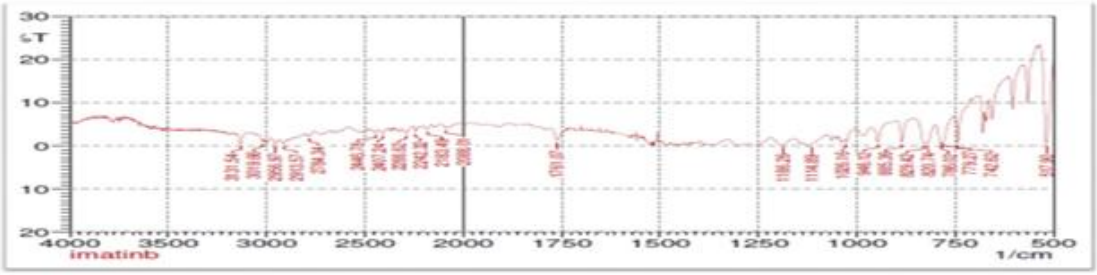


**Figure 2: FT-IR spectra of imatinib mesylate**

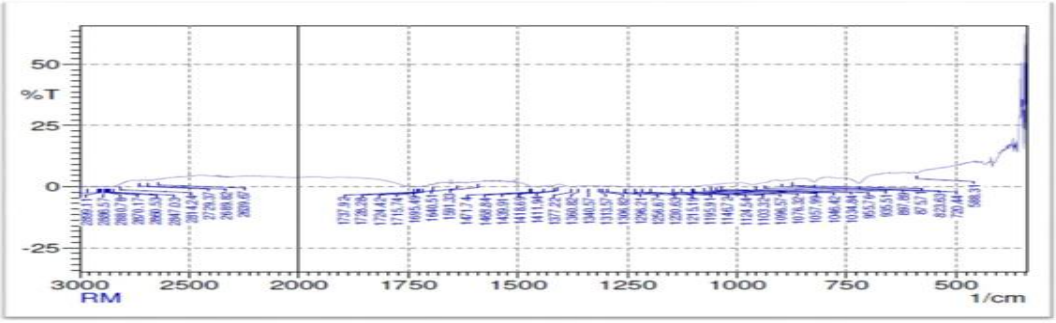


**Figure 3: FT-IR spectra of physical mixture**

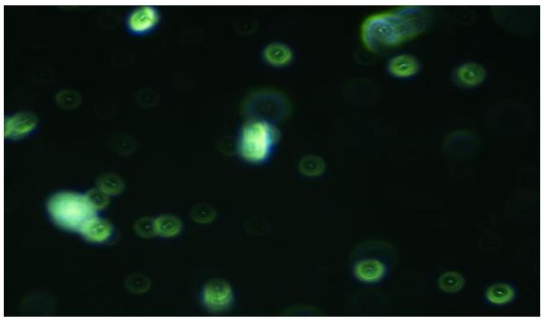

**Figure 4: Formulated imatinib mesylate loaded reverse micelle morphology by PCM**

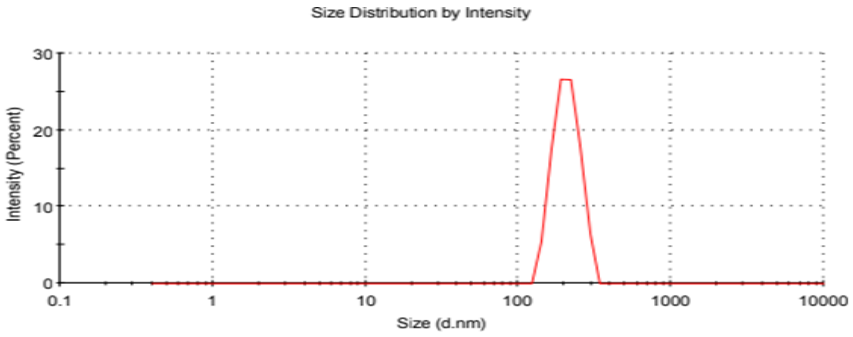


**Figure 5: Particle Size and PDI of imatinib Mesylate loaded reverse micelles**

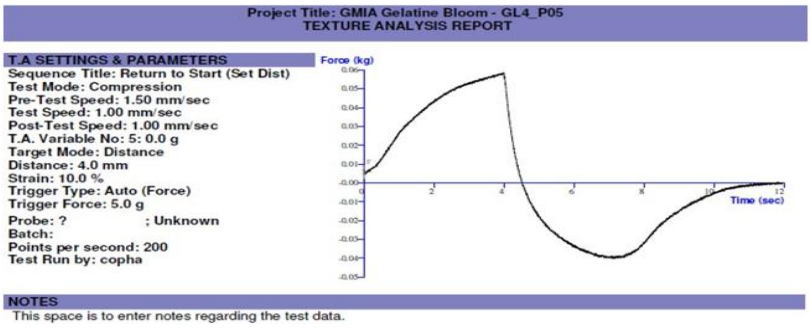


**Figure 6: Bloom strength of pluronic lecithin organogel**

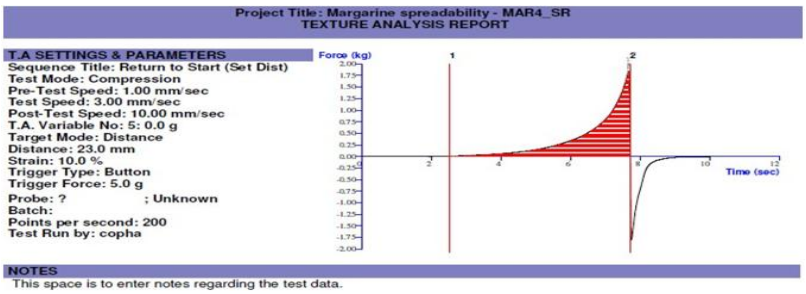


***Figure 7: Spreadability of pluronic lecithin organogel***