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DEVELOPMENT, EVALUATION AND TARGETING OF IMATINIB MESYLATE LOADED SOLID LIPID NANOPARTICLES TO THE LYMPHATIC SYSTEM

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Keywords:

Imatinib mesylate, Solid Lipid Nanoparticle, Pharmacokinetics, Lymphatic delivery, Hot homogenization

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ABSTRACT: For a formulation scientist, the delivery of therapeutic agents to the diseased organ has been a challenging problem. It is expected to improve the therapeutic index and reduce side effects of a drug by good delivery strategy to diseased organ. The objective of this investigation is to evaluate the targeting potential of solid lipid nanoparticle (SLN) formulation of imatinib mesylate to the lymphatic system using response surface methodology of design of experiment. Box-Behnken DOE was constructed using imatinib mesylate, compritol 888 ATO (X1) and pluronic F68 (X2) as independent factors and particle size (Y1) and entrapment efficiency (Y2) as dependant factors. The SLN formulation was prepared by hot homogenization followed by ultrasonication. Prepared SLN were analyzed by FTIR, DSC, DLS, PXRD and SEM. The optimized particle size and entrapment efficiency of the imatinib mesylate loaded solid lipid nanoparticle was found to be 190 nm and 62.5% respectively, which are sufficient to reach lymphatic system. FTIR revealed no interaction between imatinib mesylate and compritol 888 ATO. Compritol 888 ATO retained its crystalline nature in the imatinib mesylate loaded SLN formulation revealed by DSC study. The results showed that pharmacokinetic parameters such as area under the whole blood concentration- time curve, Cmax, Tmax were significantly different ($P<0.05$) compared with standard imatinib mesylate oral suspension and the targeting efficiency of both imatinib mesylate loaded SLN and the standard suspension at the mesenteric lymph node significantly increased ($P<0.05$).

INTRODUCTION: Now-a- days, for a formulation scientist, the delivery of therapeutic agents to the diseased organ or tissue has been a challenging problem. It is expected to improve the therapeutic index and reduce the side effects of a drug by a good delivery strategy to the diseased organ. The traditional methods with conventional dosage forms are ineffective as it is associated with severe side effects.

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One of the primary objectives of a formulator is the controlled delivery of a pharmacological agent to the site of action at a therapeutically optimal rate and dosage regimen. The site specific or targeted delivery combined with delivery at an optimal rate would not only improve the efficacy of a drug, also improving the therapeutic index. Among the most promising systems to achieve this goal are colloidal drug delivery systems [32, 33, 35].

In recent decades solid lipid nanoparticles (SLN) has gained much importance in the field of medicine. Solid lipid nanoparticles combines the merits of colloidal drug carriers like liposomes, polymeric nanoparticles and emulsions but at the same time avoid or minimize their drawbacks.

Many naturally occurring or synthetically prepared biocompatible, biodegradable polymers are used for the formulation of SLN. Glycerol palmito-stearate (Precirol ATO 5), glyceryl behenate (Compritol 888 ATO), cetyl palmitate, witepsol cetyl palmitate *etc*. are used in general. Surfactants commonly used are pluronic F68, pluronic F127, soya lecithine, polysorbates and polyvinyl alcohol (PVA) (Barwal *et al*., 2013; Han *et al*., 2008) [23, 24, 25]. The purpose of this research is improved chemotherapy of cancer associated with the lymph using solid lipid nanoparticles (SLN).

Several problems frequently encountered with anticancer drugs, such as normal tissue toxicity, poor specificity, poor stability and a high incidence of drug resistant tumour cells are promising [1, 49, 51]. These problems can be overcome by formulating the anticancer agents as SLN which bypass several uptake mechanisms such as reticulo-endothelial system (RES), opsonization and several efflux transporters [2]. Fatty substances are broken down into monoglycerides and triglycerides by the enzyme intestinal lipase and they reassemble in presence of bile inside the enterocytes and forms colloidal lipoproteins. These lipoproteins are taken up through the lymph capillaries into lymph vessel and reach the circulation *via* inferior venacava [3, 4, 5].

Imatinib mesylate is an anti-neoplastic agent for the treatment of acute lymphoblastic leukemia/ lymphoma, acts by inhibiting the protein tyrosine kinase, responsible for the proliferation of lymphocytes. The compritol 888 ATO in the SLN is a triglyceride which carries the drug to the lymphatic system and thus the targeting potential increases. The surfactants such as pluronic F68 and pluronic F127, hydrophilic tri block copolymer which has been proved to impart *in-vivo* stability to orally administered nanoparticles. Pluronic F68 bypasses the efflux transporters such as P glyco-protein and improves the targeting potential towards lymphatic system [6, 50, 46].

The relationship between variables affecting the formulation and response (output) of that formulation can be determined by design of experiment (DOE), the statistical way of testing large number of formulations and process variables in a minimum number of experiment run. Response surface model is commonly used to estimate the main effect, their interaction, the quadratic effects and shape of response surface. The Box-Behnken design is an independent quadratic design which does not contain an embedded factorial or fractional factorial design [7]. The treatment combinations in this design are at the midpoints of edges of the process space and at the centre. These designs are rotatable and require three levels of each factor. The Box-Behnken design is advantageous over central composite design because it needs only minimum experimental run when the number of factors investigated is three [8, 36, 37].

The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles, it shows the electrical potential of colloidal particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticle with a zeta potential ± 30 mV has been shown to be stable, as the surface charge prevents aggregation of the particles [21, 22, 34]. The quality of a drug substance is influenced by the environmental factors such as temperature, humidity and light, stability studies are performed to access these effect and to predict the shelf life and storage conditions of the formulation. The Accelerated stability testing should be done for at least six months according to ICH guidelines and it suggests sampling intervals of 0, 3, 6 months [38, 39, 40].

MATERIALS AND METHOD:

Materials: Imatinib mesylate was obtained from Cipla Pharmaceutical Pvt Ltd., Mumbai, Compritol 888 ATO was obtained from Gattefosse Mumbai, India and Pluronic F68 was obtained from Research lab, Mumbai, India. Methanol and Acetonitrile were obtained from CDH Chemicals, New Delhi, India. Nylon 66 membrane filter was purchased from Himedia, New Delhi, India.

Methods:

Design of Experiments: Box- Behnken DOE was constructed to optimize the solid lipid nanoparticle formulation using the software design expert [9]. In this design the treatment combinations are at the midpoints of edges of the process space and at the center. These designs are rotatable or near rotatable and require 3 levels of each factor. The quadratic equation of the model is described as:

$$Y= \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{23}X_2X_3 + \beta_{11}X_1^2 + \beta_{22}X_2^2 + \beta_{33}X_3^2$$

Where Y is the measured response obtained from each factor level combinations; β_0 is the intercept and β_1 to β_{33} are the regression coefficient computed from the response Y; X_1, X_2, X_3 are independent factors. The contour plot for particle size and response surface plot for particle size and entrapment efficiency are found out [18, 19, 20].

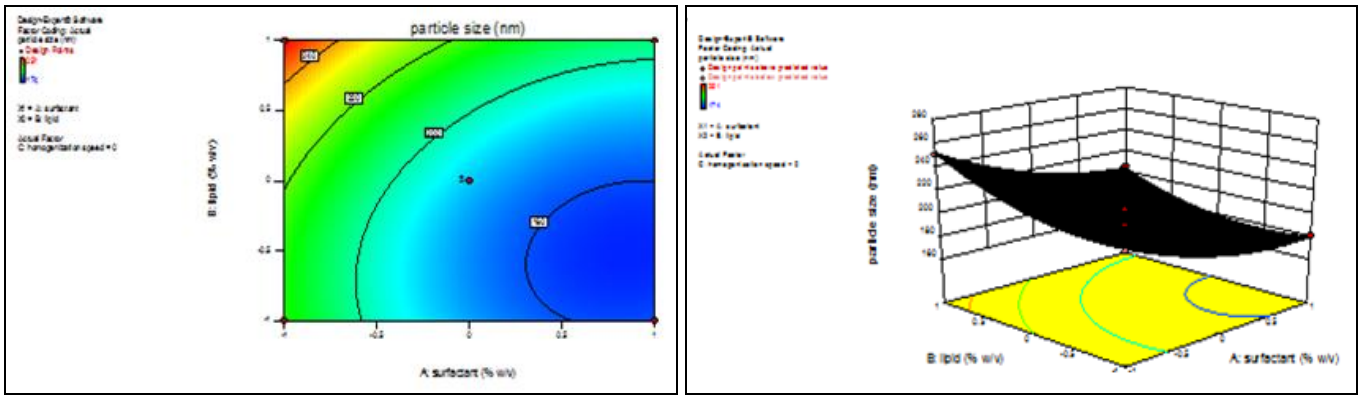

FIG. 1: CONTOUR PLOT AND RESPONSE SURFACE PLOT OF PARTICLE SIZE DISTRIBUTION

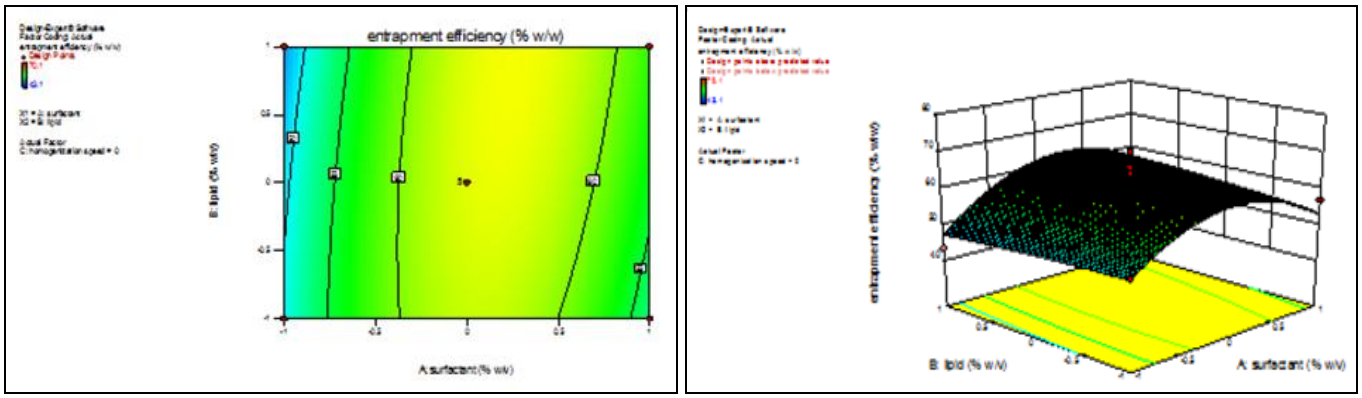

FIG. 2: COUNTER PLOT AND RESPONSE SURFACE PLOT OF ENTRAPMENT EFFICIENCY

Preparation of Imatinib Mesylate Loaded Solid Lipid Nanoparticles: Solid lipid nanoparticles loaded with imatinib mesylate was prepared using hot homogenization method followed by ultra-sonication. Accurately weighed the required amount of compritol 888 ATO and was melted at 75 ºC; 100mg imatinib mesylate was weighed accurately and was dispersed in the lipid melt. The required amount of pluronic F 68 was dissolved in distilled water and was heated to 75 ºC.

When clear homogenous phase was obtained hot aqueous phase was added to the lipid melt and homogenized at 10000 rpm for 2 min using a high speed homogenizer (Heidolph, Bangalore, India); the temperature was maintained at 75 ºC during the homogenization time, the hot primary emulsion formed was then ultrasonified using a probe sonicator (M Sonics vibra cell, sonics vcx 750, NT, USA) for 3minutes at an amplitude of 40% and 30/10 second pulse ON/OFF [9, 26, 27]. In order to prevent the recrystallization and precipitation during sonication the temperature was set 4 - 5 ºC above the melting point of the lipid (74ºC). The obtained nanoemulsion was cooled in an ice bath to form nanoparticles which was diluted to 100 mL. The dilute dispersion was then filtered using stirred ultra filtration unit (Millipore stirred cell UF 8050, Bangalore, India). Nylon 66 membrane of pore size 0.4µ is used as the filtration medium; a positive nitrogen pressure of 3 Kg/cm^2 was applied to facilitate filtration.

The filtrate was collected and again filtered through another membrane of 0.05µ pore size (polycarbonate membrane filter) and the residue on the membrane was washed thrice with distilled water and was retrieved from the filter unit. The nanoparticulate suspension was then transferred to glass vials and was prefreezed to -80 ºC, the prefreezed samples were then freeze dried using (Subzero lab instruments, Chennai) at -80 ºC for 24 h. The freeze dried nanoparticles were collected and was stored in the refrigerator [28, 29, 30].

Entrapment Efficiency and Drug Loading: 50mg of the freeze dried nanoparticles were vortexed with 5 mL of distilled water for 1h and was filtered through 0.22 µm membrane filter. Then the drug content in the filtrate was analyzed by ultraviolet (UV) spectrophotometer at 258 nm against dummy nanoparticles, which had also been prepared as reagent blanks and treated similarly to the drug-loaded nanoparticles [10, 31, 41]. The percent encapsulation, a measure of encapsulation efficiency, was calculated as the ratio of the drug content in the freeze dried powder to the initial drug amount added.

Loading efficiency = weight of drug in nanoparticles / weight of nanoparticles

Entrapment efficiency = practical drug loading / theoretical drug loading

HPLC Analysis: HPLC analysis of imatinib mesylate was done using Shimadzu prominence (UFLC, LC 20 AD, Kyoto, Japan) apparatus with manual sampler injector connected to UV detector. C 18G (250 mm × 4.6 mm × 5 µm) was used as analytical column and mobile phase was a mixture of methanol: acetonitrile in the ratio of 40:60 (v/v). The mobile phase flow rate was adjusted to be 1.0 mL/min and the total run time was 8 min [11]. The volume of injection was 20 µL. The λ_{max} for detection of imatinib mesylate was 254 nm. The column temperature was maintained at 25 ºC [42].

***In-vitro* Release Study:** The drug release from imatinib mesylate loaded SLN was performed in phosphate-buffer (PB) solution (pH 6.8), using the dialysis bag method. Dialysis membrane with a molecular weight cut off 100kDa was used. The membrane was sealed in PB solution for 12 h prior usage. The dispersion was placed in a dialysis bag and sealed at both ends. The dialysis bag was placed in a beaker containing 100 mL of dissolution medium phosphate buffer (PB, pH 6.8) at 37 ± 2 ºC and magnetically stirred at 100 rpm.

Samples were withdrawn at predetermined time intervals and sink condition was maintained by replacing with fresh pre warmed PB solution at same temperature [12, 43, 44]. The content of imatinib mesylate in the samples was determined by UV spectro-photometer (1700, Shimadzu, Japan) at λ_{max} 258nm. The drug release study of SLN was also performed in 0.1N HCl and drug content was determined at λ_{max} 258 nm.

Particle Size and Zeta Potential: The particle size distribution and zeta potential (ZP) of the prepared nanoparticles were analyzed by Zetasizer (ZS, nanoseries, Malvern Navi Mumbai, India). It is a general rule that an absolute value of ZP above 60 mV yields excellent stability, while 30, 20 and less than 5 mV generally results in good acceptable short term stability [13]. But nanoparticles made of large molecular weight polymer shows low zeta potential, despite having good stability in suspension because of steric stabilization performed by the polymer used [45, 47, 48].

Morphological Characterization: The particle shape and size was observed by scanning electron microscopy (model: JEOL JSM-6390). The freeze dried nanoparticles were mounted on a platinum ribbon supported on a disc and was coated with platinum using platinum sputter module (JFC-1100, JEOL Ltd) in a higher vacuum evaporator for 5 min at 20 mA. The particles were then viewed at different magnifications and images were taken.

Fourier Transforms Infrared Spectroscopy (FTIR): KBr disc was made and FTIR spectrum was recorded using Perkin Elmer spectra 400 analyzer and reported in wave number (cm^{-1}). The scanning range was 400 - 4000 cm^{-1}. The FTIR spectra of pure components, physical mixture and nanoparticle formulation were measured by ATR-FTIR.

Differential Scanning Calorimetry (DSC): DSC was carried out using DSC Q 200 instrument. Samples of imatinib (8.3 mg) was accurately weighed and sealed in an aluminum pan and was equilibrated to room temperature. DSC analysis was then run over the temperature range of 50 to 200 ºC for heating rate of 0.5 ºC/min.

Powder X-ray Diffraction (PXRD): PXRD analysis was performed by X- ray diffractometer (X pert PRO, Haryana, India) using Cu K α radiation. The diffraction patterns were recorded from 0º to 80º at a diffraction angle of 2θ.

Determination of Imatinib Mesylate in Blood Plasma and Intestinal Lymph Fluid: The blood

plasma and lymph fluid concentration of imatinib mesylate was determined by HPLC analysis. The stock solutions of Imatinib mesylate were prepared at 1 mg/mL in HPLC grade methanol and acetonitrile in the ratio 40:60 and stored at 4 ºC. Calibration standards of the rat blood plasma and lymph fluid were prepared at concentrations of 10, 20, 30, 50 and 100 µg/mL in a 100 µL drug free pooled blood plasma and 20 µL lymph fluid. The calibration curves were obtained by plotting the peak area versus concentration of imatinib mesylate.

After 1h from the administration of formulated SLN and standard solution of imatinib mesylate, 100 µL lymph fluid was taken and dissolves in 200 µL HPLC grade methanol to extract the drug and in 200 µL HPLC grade acetonitrile to precipitate the proteins of the sample. Centrifuge the sample at 5000 rpm to settle down the precipitate and supernatant was collected. The solution was then passed through 0.2 µ pore size syringe filter and was used for HPLC analysis.

The lymph fluid was taken at an interval of 1, 2, 4, 6 h and the above procedure followed for HPLC analysis [14]. For calculating the oral bioavailability of imatinib mesylate, 200µL plasma was separated from the blood of rat which was taken at an interval of 0.5, 1.5, 3, 6, 9, 24 h. After centrifugation, supernatant was collected and filtered using 0.2 µ syringe filter and was used for HPLC analysis [15, 52].

Pharmacokinetic Analysis and Evaluation of Lymphatic Targeting Efficiency: The pharmacokinetic parameters associated with oral administration of 50 mg/kg drug were estimated by one compartmental model [16]. The pharmacokinetic parameters such as C_{max}, T_{max} were calculated from the graph and area under the whole blood concentration (AUC) was calculated by trapezoidal rule with time extrapolated to infinity.

Furthermore, the targeting efficiency of imatinib mesylate to the lymphatic system was calculated by comparing the rate of transport of drug from SLN formulation and standard solution to the lymph fluid [17].

Accelerated Stability Studies: The accelerated stability study was carried out according to ICH (International Conference on Harmonization) Q1A guidelines with optimized solid lipid nanoparticles. Sealed vials of freshly prepared solid lipid nanoparticles loaded with imatinib mesylate were placed in stability chamber maintained at 25 ºC ±2 ºC/60% RH ± 5% RH. The nanoparticles subjected to stability tests were analyzed over 3 month's period for particle size and drug content.

Statistical Evaluation: All data were analyzed for statistical significance by the Student's *t*-test ($P<0.05$). The whole calculated values were expressed as the mean ± SD.

RESULTS AND DISCUSSION:

Preparation of Imatinib Loaded Solid Lipid Nanoparticles: Optimization of pluronic F68, compritol 888 ATO and homogenization speed the lipid percentage was varied from 1-5 % of aqueous phase and the particle size of the prepared particles was measured. The formulation which contained 1% compritol 888 ATO; phase separation occurred within few hours after formulation so the formulation was discarded. The formulation which contained 5 % lipid was thicker and has a creamy appearance. The particle size of the formulation at 2 % w/v lipid was not statistically significant with particle size at 3 % w/v lipid.

Hence comparing the particle size of the formulations, the lipid concentration (%w/v) of 2 was discarded and 3 % w/v of lipid was arbitrarily fixed for the optimization of other parameters. Optimization of surfactant concentration is of prime importance since it governs the size and drug entrapment. During preoptimization studies the surfactant concentration was varied from 0.5-4% of aqueous solution and the particle size was measured. High and stable foam was formed in the formulation contained 4% surfactant concentration and as the temperature was increased to 80ºC the precipitation of the pluronic F68 surfactant as thin film was occurred.

The particle size of the formulation at 2% w/v surfactant was statistically significant ($P<0.05$) with the particle size at 3% w/v surfactant. Hence comparing the particle size of the formulation, the surfactant concentration (% w/v) of 3 was discarded and 2 % w/v surfactant was arbitrarily fixed for the optimization of other parameters. Homogenization

speed was optimized as 10000 rpm. At 8000 rpm creaming of the emulsion was occurred and at 14000 rpm, heat generated in the system resulted in the separation of pluronic F 68 surfactant. The sonication time was optimized as 3 minutes and 40 % amplitude; above this the temperature exceeds 100 ºC. The factors and the levels obtained from the preoptimization study applied on the Box-Behnken design. The responses such as particle size (Y1) and entrapment efficiency (Y2) added on the design and their contour plots and response surface graphs are obtained. Based on the statistical evaluations the software gave 43 solutions for the optimization of the batches and selected one optimum batch.

Zeta Potential of Imatinib Mesylate Loaded Solid Lipid Nanoparticle: The formulation showed a negative zeta potential, it might be due to the negativity of the polymer glyceryl behenate. The average zeta potential of the formulation was found to be -30.1 ± 2.27 mV.

Morphological Characterization: In the SEM observation (**Fig. 3**), the prepared imatinib mesylate loaded SLN were about 200n m in size and had a spherical shape with a smooth surface. The result showed that imatinib mesylate loaded SLN about 200 nm in size and ideal morphology were successfully prepared by the hot homogenization method.

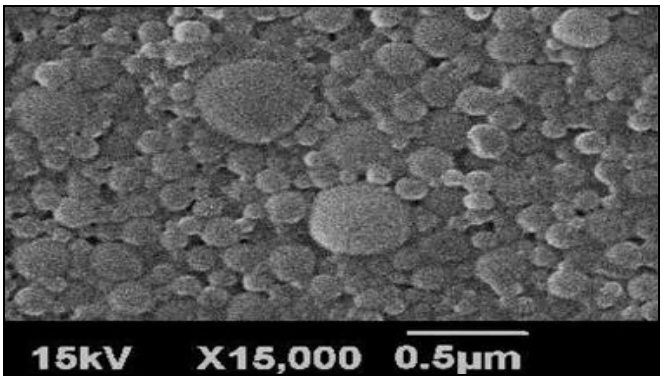

FIG. 3: SEM ANALYSIS OF FORMULATED SLN

DSC and PXRD Analysis: DSC studies were performed to characterize drug status inside the SLN and the melting point of the compounds. DSC of the drug, polymer, physical mixture, lyophilized solid lipid nanoparticle is shown in the **Fig. 4**. The DSC thermogram of the lyophilized SLN showed two peaks, one sharp peak around 73ºC indicating the endothermic peak of the polymer compritol 888 ATO and a small peak around 108ºC indicating imatinib mesylate endothermic peak. The reduction in the peak intensity of the endothermic peak of imatinib mesylate was viewed owing to the molecular inclusion of imatinib mesylate in the lipid matrix.

This suggests that imatinib mesylate exists in the amorphous state in the lyophilized solid lipid nanoparticles. The change in the crystallinity improves the bio-availability of the drug from the formulation. In PXRD studies, the sharp peaks found at 2θ scattered angle at 17, 20.2, 21.5 and other low intensity peaks indicated the crystalline nature of the drug. The compritol 888 ATO showed peaks at 20.77º and 23.47º also showed its crystalline nature.

The lyophilized solid lipid nanoparticles showed a single peak at 2θ scattered angle corresponding to the peak showed by the polymer and absence of the crystalline peaks of the drug indicates that the drug is molecularly dispersed in lyophilized SLN.

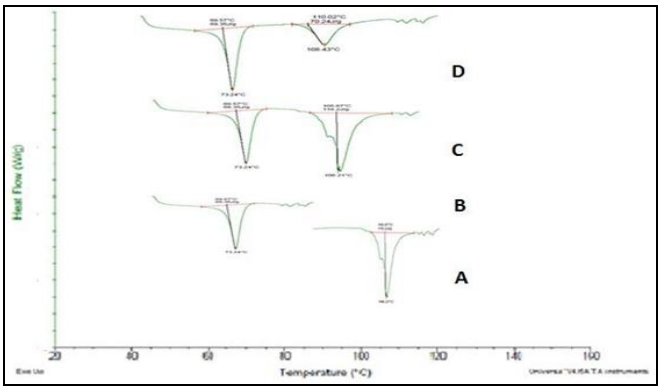

FIG. 4: DSC CURVE OF A) IMATINIB MESYLATE B) COMPRITOL 888 A TO C) PHYSICAL MIXTURE OF IMATINIB MESYLATE AND COMPRITOL 888 A TO D) FORMULATED SLN

***In-vitro* Release Studies:** In *in-vitro* release study (**Fig. 5**), the results shows that the drug release from the optimized formulation was found to be sustained and nearly 98% release was obtained by 24h. The release kinetics studies were performed and it shows a complex order drug release.

The correlation coefficient (r^2 value=0.956) indicates that the release mechanism is diffusion and the release exponent value, n of Peppas model (0.936) indicates that the mechanism of drug release follows supercase II transport.

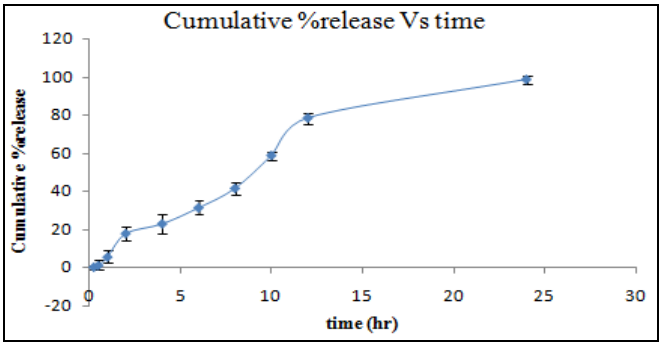

FIG. 5: *IN-VITRO* DRUG RELEASE OF SL

The average drug concentration obtained for samples of plasma collected during the time interval 0.5, 1.5, 3, 6, 9, 24h by HPLC analysis shown in the **Table 1**. The average drug concentration obtained in the rat blood plasma after the administration of formulated SLN and standard drug solution is shown in the **Fig. 7**. The result indicated the improved bioavailability of the imatinib mesylate from SLN compared with conventional dosage form. The sustained drug release from SLN also reduces the dosing frequency of the drug.

The drug concentration obtained for samples of lymph collected during the time interval 1, 2, 4, 6h by HPLC analysis shown in the **Table 1**. The rate of transport of imatinib mesylate from the formulated SLN and standard drug solution is shown in the **Fig. 6**. The significant increase in the transport of Imatinib mesylate from the SLN to the lymphatic system in turn will lead to an effective treatment of lymphoma in the body by inhibiting the uncontrolled proliferation of lymphocytes. The result indicated that the formulation of anticancer drug Imatinib mesylate as SLN has a remarkable advantage over conventional dosage form in the treatment of acute lymphoblastic leukemia/ lymphoma

TABLE 1: DRUG CONCENTRATION OBTAINED FOR SLN AND SOLUTION

Time	Drug Concentration in Lymph-SLN mcg/ml	Drug Concentration in Lymph-Solution mcg/ml	Average Drug Concentration from SLN in Blood Plasma	Average Drug Concentration from Solution in Blood Plasma
0.5	-	-	4.23	3.59
1	89.28	22.79	-	-
1.5	-	-	4.63	3.91
2	142.04	31.92	-	-
3	-	-	5.39	4.48
4	162.66	33.06	-	-
6	169.02	34.03	6.07	3.66
9	-	-	5.49	1.47

SLN, solid lipid nanoparticles, 6mg of Imatinib mesylaste

Pharmacokinetic Analysis and Evaluation of Lymphatic Targeting Efficiency: The result showed that the bioavailability of Imatinib mesylate from SLN is 1.9 times greater than from its standard solution, it indicates the improved AUC of SLN. The statistical analysis of the data (AUC0-24) was done by student's t test and analysis showed a significant difference between two formulations (P<0.001). The percentage dose of imatinib mesylate transported from SLN and standard solution *via* lymphatic system was found to be 0.28 % and 0.06% respectively. This indicates that the imatinib mesylate loaded SLN showed a 4.6 fold increase in the transport of imatinib mesylate to the lymphatic system compared to the standard solution.

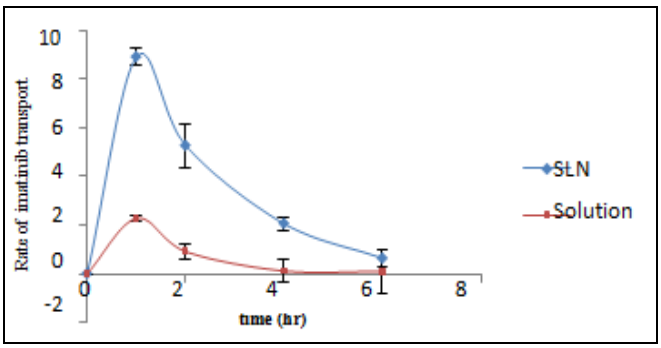

FIG. 6: THE RATE OF TRANSPORT OF IMATINIB MESYLATE IN INTESTINAL LYMPH FLUID AFTER THE ORAL ADMINISTRATION OF FORMULATED SLN AND STANDARD DRUG SOLUTION

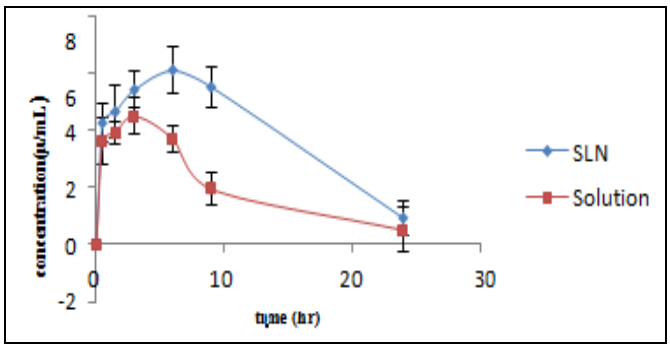

FIG. 7: AVERAGE DRUG CONCENTRATION OBTAINED FROM BLOOD PLASMA AFTER THE ORAL ADMINISTRATION OF FORMULATED SLN AND STANDARD DRUG SOLUTION

The statistical analysis of the data was done by student's t -test and the analysis showed a significant difference between two formulations ($P<0.001$).

Accelerated Stability Studies: On storage for 3 months the particle size of the lyophilized SLN was significantly increased from 190.7 to 197.1 nm. However the particles still retain the potential to be targeted to the lymphatic system as the particle size is below 250 nm which is the upper limit size of the particle for efficient lymphatic targeting. The drug content of the nanoparticles showed no significant reduction even after 3months storage.

CONCLUSION: The optimized formulation was prepared and the mean particle size of the SLN was 190 nm, the zeta potential was -30.1 mV, indicated the stability of SLN and the entrapment efficiency was determined as 62.5%. The FTIR spectrum, X-ray diffraction pattern and DSC analysis conformed that the drug was molecularly dispersed in the lipid matrix. The in vitro release studies were performed in 0.1N HCl and phosphate buffer (PB) pH 6.8, drug release obtained in 0.1N HCl indicated the acid stability of the polymer and in PB, a diffusion controlled supercase II drug release was noted. The *in-vivo* evaluation of the optimized formulation was done to establish the lymphatic targeting potential and bioavailability of imatinib mesylate loaded SLN. The results showed that compared to imatinib mesylate solution, SLN produced a 4.6 fold increase in lymphatic transport of imatinib mesylate and 1.9 fold increases in bioavailability of Imatinib mesylate from SLN.

Generally, most of the NP accumulates to the target lymph site due to their physicochemical characteristics such as particle size, surface coating with biodegradable polymers, and so on. As mentioned earlier, SLN can easily pass through the lymphatic system during systemic circulation, and this passive targeting enables the drug to be targeted to the lymphatic system. Based on this study we could conclude that the imatinib mesylate loaded SLN can be good candidates as a lymphatic delivery system of imatinib mesylate.

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CONFLICT OF INTEREST: There is no conflict of interest regarding this research work. All author/s (if present) agree that above content of the manuscript will not be copyrighted, submitted, or published elsewhere (either in print or electronic media), and is also not imitative from any language elsewhere, while acceptance by IJPSR is under consideration. I confirm that the data presented in the manuscript is authentic and in any circumstances, I/We will responsible to face any dispute, pointed out by anyone in future.

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