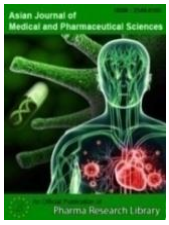

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Design, optimization of Nanostructured Lipid Carriers of Imatinib a QBD Approach

Rallabandi Swathi[1], Dr. K. Ramesh[2], Dr. Vijay Kumar Gampa*[3]
[1]Department of Pharmaceutics, KGR Institute of Technology and Management, Rampally, Keesara(m), Medchal-Malkajgiri District, Hyderabad -501302, Telangana, India.
[2]Professor and HOD, KGR Institute of Technology and Management, Rampally, Keesara(m), Medchal-Malkajgiri District, Hyderabad -501302, Telangana, India.
[3]Principal and Professor, KGR Institute of Technology and Management, Rampally, Keesara(m), Medchal-Malkajgiri District, Hyderabad -501302, Telangana, India.

A B S T R A C T
This study evaluates the pre-formulation of imatinib-loaded nanostructured lipid carriers (NLCs), focusing on drug characterization and excipient compatibility. Fourier Transform Infrared Spectroscopy (FTIR) identified key peaks for imatinib, including a C=C aromatic peak at 1469cm^{-1} and C-F bond peaks from 1635-1012cm^{-1}, confirming the compound's purity. Differential Scanning Calorimetry (DSC) showed a distinct endothermic peak, indicating thermal properties. Analytical method validation demonstrated linearity over 2 to 14µg/ml, with high regression coefficients for UV (0.999) and HPLC (0.9803). Precision studies yielded consistent results, while accuracy tests confirmed reliable recovery rates, with limits of detection and quantification at 0.086µg/ml and 0.261µg/ml, respectively. Process and product variable screening identified optimal excipients like Inwitor 900K and Cremophor EL, along with ideal processing conditions, including 10,000 rpm homogenization and 8 minutes of sonication. This analysis enhances the development of imatinib-loaded NLCs for improved drug delivery.

Keywords: Imatinib-loaded NLCs, Differential Scanning Calorimetry

A R T I C L E I N F O

***Corresponding Author:**
Dr. Vijay Kumar Gampa
Principal and Professor,
KGR Institute of Technology and Management,
Rampally, Keesara(m), Hyderabad -501302, Telangana, India.

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1. Introduction

Imatinib is a tyrosine kinase inhibitor widely used in the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST). Despite its efficacy, imatinib faces several challenges, including poor aqueous solubility, variable oral bioavailability, and dose-limiting toxicities. To address these issues, advanced drug delivery systems such as nanostructured lipid carriers (NLCs) have been explored. The development of NLCs for imatinib aims to enhance its solubility, stability, and therapeutic efficacy while minimizing side effects. Nanostructured lipid carriers are a promising class of drug delivery systems composed of a mixture of solid and liquid lipids, which form a stable matrix at room temperature. NLCs offer several advantages, including improved drug encapsulation efficiency, controlled release, and enhanced bioavailability. These carriers are particularly suitable for poorly soluble drugs like imatinib, as they can enhance drug solubility and protect the drug from degradation. The concept of Quality

by Design (QbD) has gained significant traction in pharmaceutical development, emphasizing a systematic approach to formulation design and optimization. QbD involves identifying critical quality attributes (CQAs) and critical process parameters (CPPs) that influence product quality, and using this knowledge to design robust and reproducible manufacturing processes. The application of QbD principles to the development of imatinib-loaded NLCs ensures a thorough understanding of the formulation and process variables, leading to a more reliable and effective drug delivery system.

The design of NLCs for imatinib involves several key steps, including the selection of lipids, surfactants, and solvents, as well as the optimization of formulation parameters such as lipid concentration, drug loading, and particle size. The choice of lipids is crucial, as it affects the stability, drug release profile, and biocompatibility of the NLCs. Solid lipids such as glycerylmonostearate and liquid lipids like medium-chain triglycerides are commonly used in NLC formulations. Surfactants like polysorbate 80 and soy lecithin are employed to stabilize the NLCs and prevent aggregation.

The preparation of NLCs typically involves methods such as high-pressure homogenization, solvent evaporation, and microemulsion techniques. High-pressure homogenization is a widely used method that applies mechanical shear forces to reduce particle size and ensure uniform distribution of the drug within the lipid matrix. Solvent evaporation involves dissolving the lipids and drug in a volatile organic solvent, which is then evaporated to form NLCs. The microemulsion technique utilizes a combination of lipids, surfactants, and co-surfactants to form a microemulsion, which is subsequently cooled to produce NLCs.

Optimization of the formulation and process parameters is critical to achieving the desired quality attributes of the NLCs. A systematic approach using design of experiments (DoE) can be employed to study the effects of various factors on the CQAs of the NLCs. Factors such as lipid concentration, surfactant concentration, homogenization pressure, and cooling rate can be varied and their impact on particle size, drug loading, encapsulation efficiency, and drug release profile can be evaluated. By analyzing the results, an optimal formulation can be identified that meets the desired quality attributes.

The evaluation of imatinib-loaded NLCs involves a series of characterization studies to assess their physicochemical properties, stability, and in vitro drug release. Particle size and zeta potential measurements are performed to determine the size distribution and surface charge of the NLCs. Drug loading and encapsulation efficiency are quantified to evaluate the amount of drug incorporated into the NLCs. In vitro release studies are conducted to investigate the drug release kinetics and mechanism from the NLCs. Stability studies are also performed to assess the physical and chemical stability of the NLCs over time. In conclusion, the design and optimization of nanostructured lipid carriers for imatinib using a QbD approach offer a promising strategy to enhance the therapeutic efficacy and safety of imatinib. By systematically studying the formulation and process variables and understanding their impact on the quality attributes of the NLCs, a robust and effective drug delivery system can be developed. This approach not only improves the bioavailability and stability of imatinib but also paves the way for the development of advanced drug delivery systems for other poorly soluble drugs.

2. Materials and Methods

List of Materials

The materials and reagents used in this study were sourced from various suppliers. Imatinib was obtained from CiplaPharma, India, and TherdosePharma, India. Compritrol 888 ATO was supplied by Gattefosse India, while Imwitor® 900 K was procured from IoIo Leo, Germany. Capmul MCM C8 was acquired from Abitech Corp, India, and Cremophor EL from Chemdyes Corporation, India. Lipoid PE was provided by Lipoid, Germany, and Lactose was sourced from MegglePharma, Germany. As for the reagents, Methanol (HPLC Grade) and Ethanol were purchased from Fischer Scientific, Mumbai. Purified water (Milli-Q) was obtained in-house, KH_2PO_4 from SUNLIFE, and NaOH from Fischer Scientific, Mumbai.

List of Equipments

The equipment used in this study includes a UV-Vis spectrophotometer from Labindia, a Differential Scanning Calorimeter (DSC Q2000) from TA Instruments, and an FTIR spectrometer (Alpha II) from Bruker. For stability testing, a stability chamber (TH 2000 S/G) from Thermolab was used. The weighing tasks were performed using an electronic weighing balance (AB204-S/FACT) from Mettler Toledo. In the preparation process, a Franz diffusion cell from Electrolab, a high-speed homogenizer from IKA, and a laboratory stirrer (Remi RQ-121) from Remi were employed. Additionally, an ultra sonicator from Lab sonic and a magnetic stirrer with a hot plate (Remi-2-MLH) from Remi were utilized. Particle size analysis was conducted using a Zeta sizer from Malvern.

Pre-formulation Study

FT-IR: To assess the drug's purity, infrared spectra were obtained using a Fourier Transform Infrared Spectrophotometer (Alpha II, Bruker). This procedure required dispersing the drug sample (either alone or combined with excipients) in potassium bromide (KBr) to prepare a 10% mixture. The sample was then finely ground in a mortar with KBr and compressed into pellets. Placed in the light path, the sample's spectra were recorded across a range from 4000 to 400cm^{-1}, with a resolution set at 2 cm^{-1}. For calibration, a KBr background spectrum served as a reference.

DSC: Thermal events during heating were tracked using a differential scanning calorimeter (Perkin Elmer, DSC-pyris-1, USA). Zinc's (419.5±0.30°C) and indium's (156.6± 0.2°C) melting points were used to calibrate the DSC. Two milligram samples were heated at a rate of 100 degrees

Celsius per minute from 55 to 2500 degrees Celsius in open aluminum pans. Nitrogen was used as the purge gas at a flow rate of 50 mL/min.

Validation of analytical method.

Linearity: Through the use of three independent measurements spanning concentrations from 2 to 14 µg/ml, the linear connection between drug concentration and absorbance was assessed. The concentration range was given in µg/ml. By mapping the absorbance against the drug concentration, calibration plots were created and analysed using ordinary least squares regression. The relationships between the peak area and drug concentration were tested linearly throughout a concentration range of 2-10 µg/ml using three independent measurements

Screening of Process/Product variables.

A) Screening of Solid Lipid.

Following the procedure outlined by M. Joshi et al., we screened solid lipids. At 55°C, place the solid lipid that has melted onto the magnetic stirrer. Once the lipid has melted to a super saturation point, add 0.5 mg of the medicine slowly until the mixture solidifies. Allow the solidified lipid to cool to room temperature. The quantity of medication administered to the lipid was recorded. [67]

(B) Surfactant Screening.

Studies of saturation solubility were used to screen surfactants. We tested Imatinib's solubility in several surfactants. In separate 5-milliliter (mL) surfactant tubes, an overabundance of the medicine was introduced. We centrifuged each sample after 24 hours, diluted the 0.5 millilitre upper layer appropriately, and then used the appropriate analytical procedure to analyse it.

(C) Liquid lipid screening procedure.

Saturation solubility experiments were used to screen the liquid lipid. We tested many liquid lipids to find out how well Imatinib dissolved. In separate tubes with screw caps, 5 millilitres of liquid lipids were added with an excess of the medication. After 24 hours, we centrifuged each sample and carefully diluted the 0.5 mL clear supernatant layer before running it via an appropriate analytical procedure.

D) Verifying that solid and liquid lipids mix well for NLCs as part of the compatibility test.

To conduct the compatibility tests, we followed the steps outlined in the paper by F. Tamjidi et al., which involved heating glass vials containing binary mixes Liquid and Solids ratios ranging from one to 9 and five to five ratio. After the combinations solidified at room temperature for 24 hours, they were visually inspected. Only those that managed to separate the oil droplets into a single phase were chosen. If the solid lipid does not pass the test, the screening study is used to pick the next solid lipid.

Screening of Process Variables.

A) The Rate of Homogenisation: The size of nanoparticles is significantly affected by the speed of homogenisation. Testing a range of homogenisation rates from 8,000 to 16,000 rpm allowed us to ascertain the impact.

(B) The Ratio of Compatibility:

The particle size, PDI, and entrapment efficiency were measured after homogenisation times ranging from 1 to 20 minutes.

C) Duration of Sonication:

Researchers looked at how changing the ultrasonication treatment time affected particle size. The duration of sonication ranged from one minute to twelve minutes. We found the particle size, the PDI, and the entrapment efficiency, in that order.

Making Nanocarriers ready

Putting together SLNs

We used the Hot Homogenisation and Ultra- Sonication method to make SLNs with imatinib and SLNs that were empty to sum up, of phase lipid, which consisted and Imatinib, was raised temperature in a heating vessel to 75 degrees Celsius. The surfactant-containing water phase, which consisted of 40 millilitres milliq water water, was brought to sixty degrees an independent water bath. After adding the liquid phase to the state of solid, they were mixed using a high-speed homogeniser set at 10,000 rpm for a duration of 10 minutes. This made a nanoemulsion, which was then ultrasonically sonicated for 8 minutes. In the same way, blank SLNs were made, but without the drug. After that, the mixtures were left to cool down at room temperature. Once the mixture is cool, it is freeze-dried with lactose acting as a cryoprotectant to make nanoparticles that can move around freely.

Evaluating the risk of on Critical Process parameters and Critical Quality Arbitrates:

Risk ratings help make goods safer, more useful, and last longer. Homogenisation speed, Homogenisation time, and Sonication time are the CPPs that were found during the risk assessment. They were found by reviewing the literature and using what was already known. Figure 12 shows an example of an Ishikawa layout. Figure 13 shows how CMAs, CPPs, and CQAs are connected to each other.

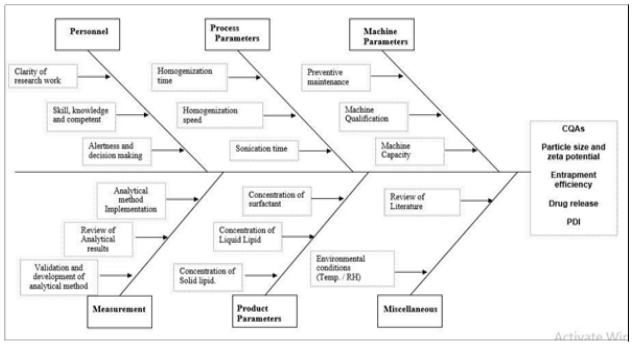


Figure 1: Fishbone analysis/Ishikawa diagram

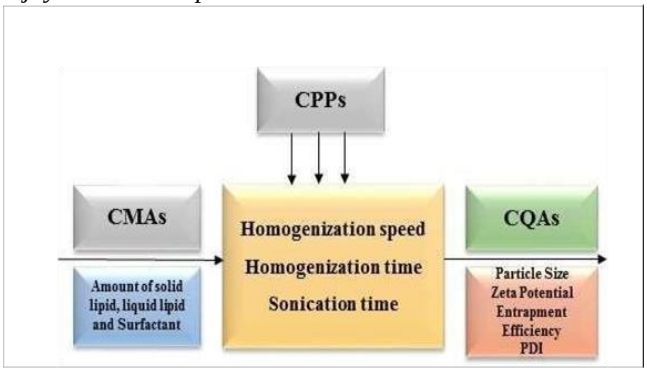


Figure 2: Effects of CMA s, CPPs and CQAs

Experimental Design for CPP Optimisation

Using a factorial design, we optimize the freeze-drying method and product factors for PEGylated NLCs. Contour plots were used to evaluate and record the responses of the independent variables, which were evaluated against the dependent variables. ANOVA was performed to determine the variance in the responses, and regression analysis was used to predict the best-fitting model. Table 18 lists the factorial design variables and levels. In order to validate the factorial design, we calculated the actual and anticipated responses, as well as the percentage error, and then prepared the formulation from the design space.

In-vitro Cell line evaluation

Cell line: A549Lungcarcinoma
Organism: Homosapiens, human Cell Type: epithelial cell
Tissue: Lung
Age: 58years
Gender : Male
Morphology: epithelial-like
Adherent Disease: Carcinoma.
96Welltitreplates
Lip of ectamine 2000 Phosphate buffer saline pH7.4

a. Plating out of cells:

After trypsinizing a sub confluent monolayer culture in a single T-25 flask, 5 mL of full growth media was injected. Trypsin was eliminated by removing the media, and then five milliliters of full growth medium including serum were added. A pipette was used to gently aspirate the cells. With the exception of column 1, which will serve as a control, cells were counted and diluted to 25 x103 cells/mL. The cell suspension was then transferred to 96-well plates using a multichannel pipette to achieve a cell concentration of 5 x 103 cells per well. Next, a multichannel pipette was used to add 200 µL of the whole medium to each well. The plate was covered with a lid. For every research period, three plates were made in the same way. The cells were kept in an incubator.

Solid state characterization

Bulk Density

An accurately wgd(25grams) quantity of powder was transferred to a 25mL measuring cylinder and the volume occupied by the powder in terms of ml was recorded.
Bulk Density=weight of powder/bulk volume
Tapped bulk Density
The loosely packed powder in the measuring cylinder was to tapponapla in hard wood ensurface and volume occupied in mL was noted.
Tapped Density= weight of powder/Tapped volume

Hausner's ratio

HausnerfoundthattheratioofTappeddensitytoBulkdensitywas relatedtointerparticlefrictionand assuch, could beused to predict powder flow properties.

Hausner ratio=Tapped density/Bulk density

Carr's Index

It was measured to determine the compressibility as well as flow properties of the powder. Carr's Index=Tapped density-Bulk density/Tappeddensityx100

Angle of Repose

It was calculated by fixed funnel method. Fix amount of powder was poured from funnel kept at fixed height and the height of pile formed on fix diameter base was measured.
θ=tan-1(/r),Where; h= Height of heapincm, r=Radius of heapincm.

%Losson Drying

% LOD was determined with the Halogen moisture analyzer, samples were placed in the moisture analyzer and were subjected to 105°C until constant weight is obtained. % LOD is recorded.

Stability study

One T-25 flask containing a sub confluent monolayer culture was In accordance with ICH norms, the stability investigation was conducted under accelerated stability circumstances. To evaluate the formulation's stability, the optimized freeze-dried powder was incubated in closed amber vials at 40 °C and 75% relative humidity. Periodically, PDI, particle size, and encapsulation effectiveness were assessed.

3. Results and Discussion

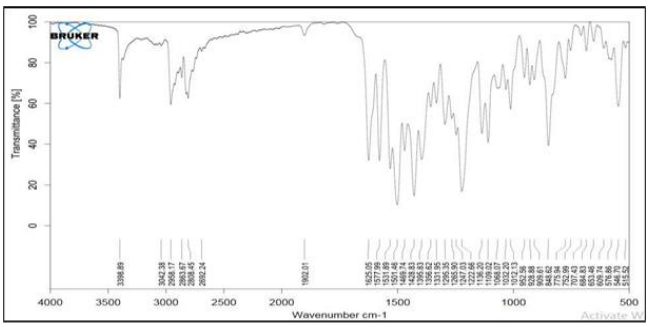


Figure 3: FT-IR spectra of Imatinib

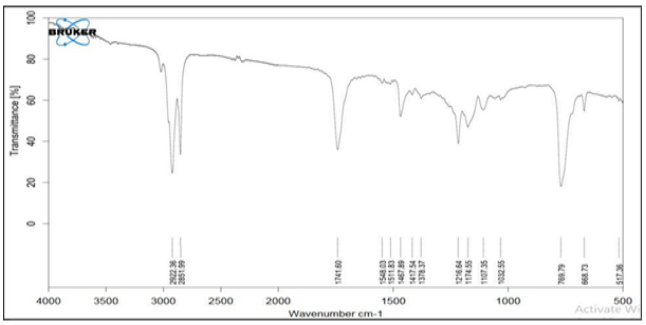


Figure 4: FT-IR spectra of Compritrol

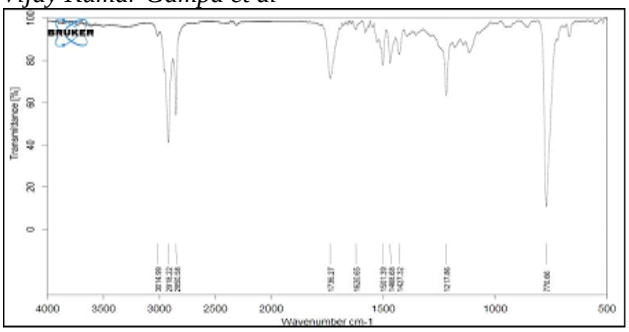


Figure 5: FT-IR spectra of Compritrol and Imatinib

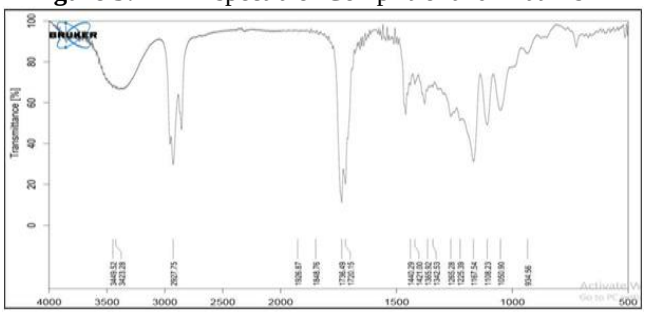


Figure 6: FTIR spectra of Capmul MCM

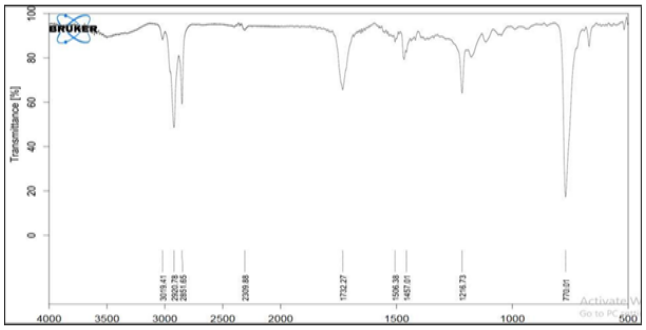


Figure 7: FTIR spectra of Capmul MCM+Imatinib

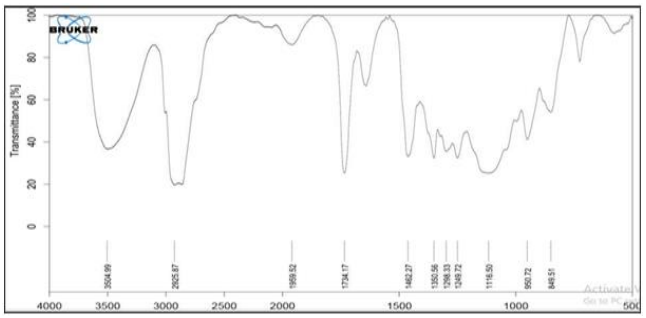


Figure 8: FTIR spectra of Cremophor EL

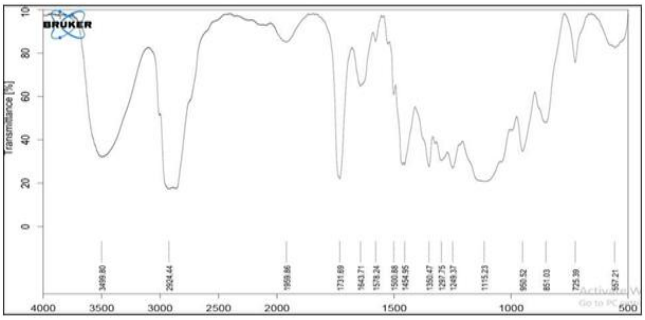


Figure 9: FT-IR spectra of Cremophor EL+Imatininb

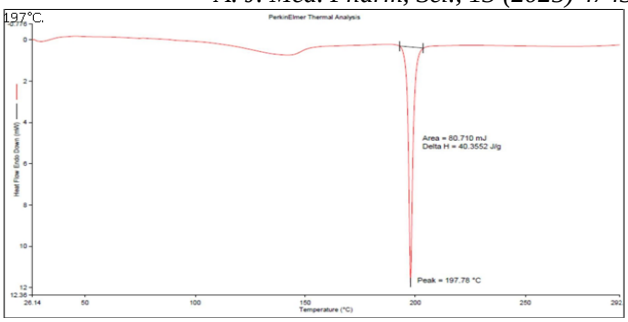


Figure 10: DSC spectra of Imatininb

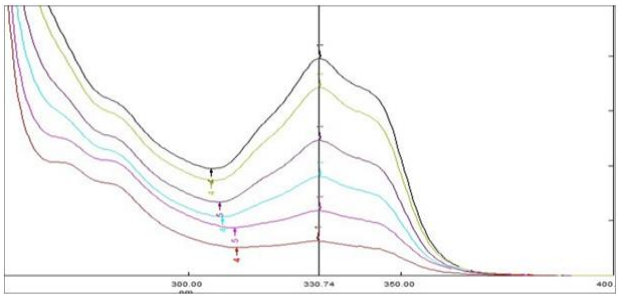


Figure 11: UV spectrum of Imatininb in Phosphate Buffer pH7.8 with 0.5%Tween 80at

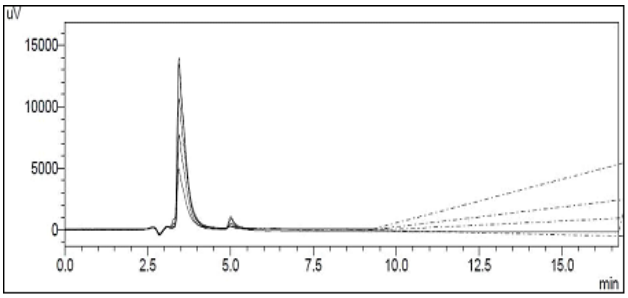
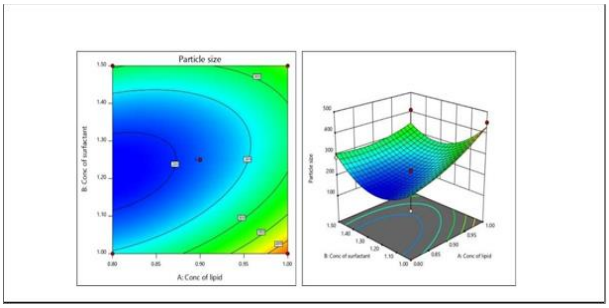


Figure 12: HPLC Chromatogram of Imatininb Phosphate Buffer pH7.8 with 0.5% Tween 80 at λmax of 310nm



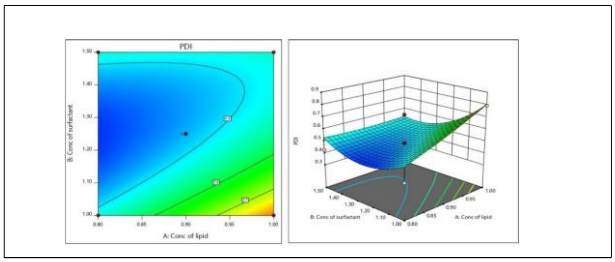


Figure 13: 3D and Opposing Strategies Checkpoint analysis for model validation.

Data Analysis for NLC formulation

An approach to response surfaces There are a lot of factors that can be tested at different levels with the CCD and BBD designs, which makes them the most hopeful. A mathematical relationship between factors and parameters was established through response surface regression analysis, which was conducted using Design-Expert® software. Figures 25, 26 show the analysed three-dimensional (3D) response surface graphs for the most statistically significant factors.

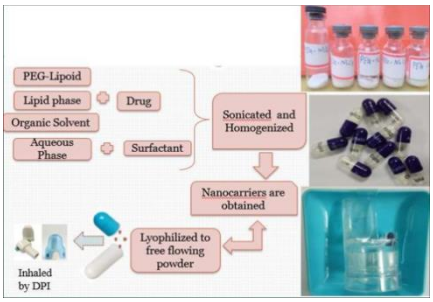


Figure 14: Process &Final Formulation of Nanocarriers.

Pre-formulation Study: FTIR analysis of Imatinib confirmed its purity, showing no significant changes with excipients like Capmul MCM, Cremophor EL, and Compritrol 888 ATO, indicating compatibility. DSC analysis displayed a characteristic endothermic peak, confirming Imatinib's thermal properties.

Validation of Analytical Method:

Imatinib demonstrated excellent linearity (2-14 µg/ml) with $r^2 = 0.999$ for UV and $r^2 = 0.9803$ for HPLC, along with high precision (%RSD 0.794% to 1.404%) and accuracy (recovery 101.58%-107.50%).

Screening of Process/Product Variables:

Inwitor 900K was chosen as the solid lipid and Cremophor EL as the surfactant due to superior solubility, while Capmul MCM C8 showed the best compatibility with Inwitor 900K.

Process Variables: Optimal conditions were found at 10,000 rpm homogenization speed for 10 minutes and 8 minutes of sonication, yielding the best particle size and entrapment efficiency.

Optimization:

Using a QbD approach with RSM, CCD, and BBD, lipid concentration significantly influenced particle size, optimizing the formulation with key excipients Inwitor 900K, Cremophor EL, and Capmul MCM C8.

Table 1: Linearity curve ranges of Imatinibin methanol.

Conc	Absobance -1	Absobance -2	Absobance -3	Avg	S.D	%R.S.D
0	0	0	0	0	0	0
2	0.127	0.126	0.129	0.127	0.002	1.200
4	0.237	0.239	0.237	0.238	0.001	0.486
8	0.41	0.415	0.414	0.413	0.003	0.641
10	0.53	0.499	0.51	0.513	0.016	3.064
12	0.678	0.679	0.65	0.669	0.016	2.461
14	0.784	0.788	0.787	0.786	0.002	0.265

Table 2: Linearity curve ranges of Imatininb in Phosphate buffer 7.8 with 0.5% Tween 80 by UV

Conc	Absobance -1	Absobance -2	Absobance -3	Avg	SD	%RSD
0	0	0	0	0	0	0
2	0.128	0.127	0.129	0.128	0.001	0.781
4	0.237	0.238	0.239	0.238	0.001	0.420
8	0.431	0.435	0.432	0.433	0.002	0.481
10	0.456	0.487	0.457	0.467	0.018	3.775
12	0.668	0.671	0.67	0.670	0.002	0.228
14	0.784	0.8	0.787	0.790	0.009	1.076

Table 3: Linearity curve ranges of Imatininbin Phosphate buffer 7.8 with 0.5% Tween 80 by HPLC

Conc	Peakarea -1	Peakarea -2	Peakarea -3	Avg	S.D	%R.S.D	Retension time
0	0	0	0	0	0	0	0
2	10141.2	10139.5	10141.8	10140.83	1.193	0.012	3.438
4	15883.7	15882.8	15881.3	15882.60	1.212	0.008	3.438
8	20236.5	20239.5	20238.7	20238.23	1.553	0.008	3.447
10	25970.9	25969.8	25971.2	25970.63	0.737	0.003	3.45

Table 4: Intra-day and Inter-day studies

Amt of drug	Intraday amt of drug found				Sd % RSD		Inter day amt of drug found				Sd %Rsd	
	1	2	3	Avg			1	2	3	Avg		
2	0.128	0.13	0.131	0.130	0.002	1.178	0.125	0.126	0.127	0.126	0.001	0.794
10	0.515	0.519	0.522	0.519	0.004	0.677	0.512	0.516	0.518	0.515	0.003	0.593
14	0.797	0.788	0.805	0.797	0.009	1.068	0.79	0.126	0.807	0.794	0.011	1.404

Table 5: 30 ANOVA analysis of effect of Particle size on SLN formulation

Source	Sum of squares	Df	Mean square	F – value	P - value
Model	91072.58	5	18214.52	6.33	0.0156
X1-Conc of lipid	22830.72	1	22830.72	7.94	0.0259
X2-conc of surfactant	782.36	1	782.36	0.2720	0.6181
X1X2	4767.90	1	4767.90	1.66	0.2389
$X1^2$	4984.34	1	4984.34	1.73	0.2295
$X2^2$	61196.75	1	61196.75	21.28	0.0024
Residual	20134.59	7	2876.37		
LackofFit	19650.83	3	6550.28	54.16	0.0011
Pure Error	483.75	4	120.94		
Cor Total	1.112E+05	12			

Table 6: 31 ANOVA analysis of effect of PD Ion SLN formulation

Source	Sum of squares	Df	Mean square	F – value	P - value	
Model	0.1739	5	0.0348	4.56	0.0361	significant
X1-Conc of lipid	0.0402	1	0.0402	5.27	0.0554	insignificant
X2-conc of surfactant	0.0338	1	0.0338	4.43	0.0733	insignificant
X1X2	0.0199	1	0.0199	2.61	0.1505	insignificant
$X1^2$	0.0010	1	0.0010	0.1316	0.7275	insignificant
$X2^2$	0.0800	1	0.0800	10.49	0.0143	significant
Residual	0.0534	7	0.0076			
Lack of Fit	0.0525	3	0.0175	81.34	0.0005	not significant
Pure Error	0.0009	4	0.0002			
Cor Total	0.2273	12				

4. Conclusion

The pre-formulation and process screening identified optimal conditions for Imatinib's solid lipid nanoparticle (SLN) formulation, with validated analytical methods confirming the accuracy and precision of the process, leading to an optimized formulation with favorable particle size and entrapment efficiency.

5. References

[1] ScioliMontoto S, Muraca G, Ruiz ME. Solid lipid nanoparticles for drug delivery: pharmacological and biopharmaceutical aspects. Front MolBiosci. 2020;7:587997.

[2] Souto EB, Wissing SA, Barbosa CM, Müller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm. 2004, 278(1): 71–7.

[3] Sakellari GI, Zafeiri I, Batchelor H, Spyropoulos F. Formulation design, production and characterisation of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for the encapsulation of a model hydrophobic active. Food Hydrocoll Health. 2021;1:1.

[4] Souto EB, Müller RH. Investigation of the factors influencing the incorporation of clotrimazole in SLN and NLC prepared by hot high-pressure homogenization. J Microencapsul. 2006, 23(4): 377–88.

[5] Nguyen TT, Nguyen TTD, Tran NM, Van Vo G. Lipid-based nanocarriers via nose-to-brain pathway for central nervous system disorders. Neurochem Res. 2022;47(3):552–73.

[6] Jores K, Mehnert W, Mäder K. Physicochemical investigations on solid lipid nanoparticles and on oil-loaded solid lipid nanoparticles: a nuclear magnetic resonance and electron spin resonance study. Pharm Res. 2003;20(8):1274–83.

[7] Jores K, Haberland A, Wartewig S, Mäder K, Mehnert W. Solid lipid nanoparticles (SLN) and oil-loaded SLN studied by spectrofluorometry and

Raman spectroscopy. Pharm Res. 2005;22(11):1887–97.

[8] Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Adv Pharm Bull. 2015;5(3):305–13.

[9] Musielak E, Feliczak-Guzik A, Nowak I. Synthesis and potential applications of lipid nanoparticles in medicine. Materials (Basel). 2022;15(2):682.

[10] Liu J, Hu W, Chen H, Ni Q, Xu H, Yang X. Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. Int J Pharm. 2007, 328(2): 191–5.

[11] Al Haj NA, Abdullah R, Ibrahim S, Bustamam A. Tamoxifen drug loading solid lipid nanoparticles prepared by hot high pressure homogenization techniques. Am J Pharmacol Toxicol. 2008; 3(3): 219–24.

[12] Lee D, Minko T. Nanotherapeutics for nose-to-brain drug delivery: an approach to bypass the blood brain barrier. Pharmaceutics. 2021; 13(12): 2049.

[13] Arabi MH, Chabok H, Mirzapour A, Ardestani MS, Saffari M. Preparation of nanoliposomes containing Rosmarinusofficinalis L essential oil: a comparative study. Biosc Biotech Res Comm. 2017;10(1):103–8.

[14] Cunha S, Costa CP, Moreira JN, Sousa Lobo JM, Silva AC. Using the quality by design (QbD) approach to optimize formulations of lipid nanoparticles and nanoemulsions: a review. Nanomedicine. 2020; 28: 102206.

[15] Khosa A, Reddi S, Saha RN. Nanostructured lipid carriers for site-specific drug delivery. Biomed Pharmacother. 2018, 103: 598–613.

[16] Iqbal MA, Md S, Sahni JK, Baboota S, Dang S, Ali J. Nanostructured lipid carriers system: recent advances in drug delivery. J Drug Target. 2012;20(10):813–30.

[17] Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS Pharm Sci Tech. 2011, 12(1): 62–76.

[18] Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. Nanostructured lipid carriers (NLC): a potential delivery system for bioactive food molecules. Innov Food SciEmerg Technol. 2013, 19: 29–43.

[19] Psimadas D, Georgoulias P, Valotassiou V, Loudos G. Molecular nanomedicine towards cancer: In-labeled nanoparticles. J Pharm Sci. 2012; 101(7): 2271–80.

[20] Anton N, Benoit JP, Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates-a review. J Control Release. 2008, 128(3): 185–99.