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Development, Optimization and Pharmacokinetic Studies of Dasatinib loaded Solid Lipid Nanoparticle and its Therapeutic Efficacy

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ABSTRACT

This research study emphasises the synthesis and evaluation of Dasatinib-loaded solid lipid nanoparticles (SLNs) to enhance the drug's solubility, bioavailability, and therapeutic efficacy. Dasatinib, a tyrosine kinase inhibitor for Chronic Myeloid Leukaemia (CML), exhibits poor water solubility and restricted oral bioavailability, necessitating the advancement of an enhanced drug delivery method. Solid lipid nanoparticles (SLNs) were chosen as a nanocarrier to enhance medication encapsulation, stability, and controlled release, while minimising systemic adverse effects. The findings of this research suggest that Dasatinib-loaded solid lipid nanoparticles (SLNs) are a viable approach to enhance drug solubility, stability, bioavailability, and therapeutic efficacy in the treatment of chronic myeloid leukaemia (CML).

Keywords: *SLNPs, Dasatinib, Optmization, Therapeutic efficacy, Evaluation*

1. INTRODUCTION

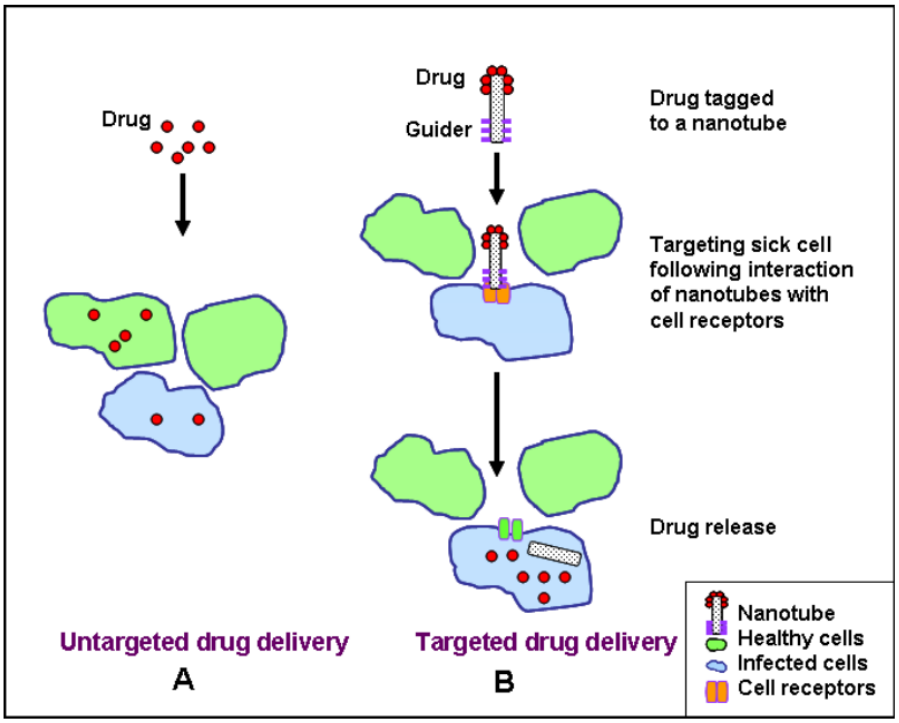
The oral route of drug administration remains the most prevalent and favoured way of drug delivery. Despite the ubiquity and versatility of the oral route, significant issues remain. Not all drug molecules exhibit the requisite physical, chemical, or biological characteristics for effective oral therapy. Issues like as inadequate solubility, chemical instability inside the gastrointestinal tract, insufficient permeability across biological membranes, and susceptibility to metabolic processes are widely recognised as reasons for the dismissal of putative medications as viable products. Lipid-based drug delivery systems have been presented as effective means to circumvent certain resistive chemical or physical barriers associated with poorly absorbed medicines. These prospective drug delivery systems include traditional dosage forms like emulsions and microemulsions, as well as contemporary options such as liposomes, microspheres, and lipid nanoparticles. Lipid nanoparticles are categorised into two types: solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Consequently, many drug delivery systems have been developed to enhance the oral bioavailability of poorly soluble pharmaceuticals. The drug delivery systems encompass enhancing drug solubility through solid dispersions, complexation with cyclodextrins, and floating systems, which improve stability and prolong residence time. Multiple floating systems enhance mucoadhesive properties, while buccal drug delivery systems circumvent first-pass metabolism. Additionally, various colloidal carriers, including transferosomes, nano-emulsions, and semisolid dispersions, are utilised, alongside particle size reduction via micronization using nanosuspensions. Colloidal carrier systems will safeguard delicate pharmaceuticals against deterioration in bodily fluids. This safeguards against stomach discomfort and is also appropriate for extended medication activity through a sustained release effect. Colloidal particles serve as a good candidate for medication targeting as drug carriers. The most accurate targeting may be achieved with these colloids combined with a 'homing device' that would direct the particle precisely to the required bodily structure.

Nanotechnology-Based Drug Delivery Systems

Nanomedicine and nano delivery systems are an emerging and swiftly advancing field that utilises nanoscale materials as diagnostic tools or for the targeted and controlled delivery of medicinal drugs. Nanotechnology has numerous advantages in the treatment of chronic human diseases by site-specific and targeted delivery of precise medications. Recently, numerous exceptional uses of nanomedicine, including chemotherapeutic medicines, biological agents, and immunotherapeutic agents, have emerged in the treatment of diverse diseases.

Design of nanotechnology – based drug delivery Systems:

Nanoparticles facilitate targeted drug delivery to illness sites, enhancing the absorption of poorly soluble medications, directing pharmaceuticals to specific locations, and improving drug bioavailability. Figure 1.3 presents a schematic comparison of untargeted and targeted drug delivery systems. Numerous anti-cancer agents, such as paclitaxel, doxorubicin, 5-fluorouracil, and dexamethasone, have been effectively manufactured utilising nanomaterials. Nanoparticles based on polylactic/glycolic acid (PLGA) and polylactic acid (PLA) have been developed to encapsulate dexamethasone, a glucocorticoid that acts intracellularly. Dexamethasone is a chemotherapeutic agent with anti-proliferative and anti-inflammatory properties.



The main objectives of the research study are stated as follows:

- To develop Dasatinib-loaded solid lipid nanoparticles (SLNs) with various lipid matrices.
- To determine process and formulation parameters for efficient and stable SLN production.
- To determine the characterization of SLNs for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, and morphology.
- To determine the in-vitro drug release profile and release kinetics of SLNs.
- To determine the in-vitro cytotoxicity of SLNs against leukemia cell lines.

Research Methodology

Drug Profile – Dasatinib

Classification: Tyrosine kinase inhibitor (TKI) for the therapy of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL).

Molecular Formula: C22H26ClN7O2S

Molecular Weight: 488.01 g/mol

Solubility: Limited solubility in water, greater solubility in acid and buffer systems (pH-dependent).

Mechanism of Action: Binds to BCR-ABL kinase, inhibiting cancer cell growth.

Difficulty: Poor aqueous solubility, poor oral bioavailability, and rapid metabolism.

Excipients Profile:

Excipient	Function	Examples Used
Lipids	Carrier for drug encapsulation, stabilizes nanoparticles	Dynasan-114, Dynasan-116, Dynasan-118
Surfactants & Stabilizers	Prevents particle aggregation, enhances solubility	Soy lecithin, Poloxamer-188
Solvents	Dissolves drug and lipid for nano-formulation	Methanol, Chloroform
Cryoprotectant	Protects nanoparticles during lyophilization	Mannitol (10% w/v)
Buffering Agents	Maintains pH stability in drug release studies	0.1N HCl, pH 6.8 phosphate buffer

The choice of surfactants, lipids, and stabilizers was quite critical in regulating the size, stability, as well as drug release characteristics of the prepared Dasatinib-loaded solid lipid nanoparticles (SLNs).

Disease Profile – Chronic Myeloid Leukemia (CML):

Chronic Myeloid Leukemia (CML) is a malignancy of blood cancer in the bone marrow that results in excessive production of white blood cells (WBCs). CML is also characterized by the Philadelphia (Ph) chromosome, resulting in the creation of the abnormal BCR-ABL1 fusion gene, resulting in uncontrolled cell growth.

Causes and Risk Factors:

- Genetic Mutation: t(9;22) translocation results in the creation of Abnormal BCR-ABL fusion gene resulting in uncontrolled tyrosine kinase activity.
- Radiation exposure: Long-term radiation exposure has been shown to elevate CML risk.
- Gender and Age: Adults and elderly adults with greater male predominance, respectively.

Symptoms:

- Immunocompromised and weakness
- Weight loss conscious or unconscious
- Night sweats and fever
- Abdominal discomfort secondary to splenomegaly
- Bleeding and bruising easily with low platelets

Phases of CML:

- Chronic Phase: Either asymptomatic or mildly symptomatic only; the majority of cases are in this phase.
- Accelerated Phase: Rising WBC, anemia, drug resistance.
- Blast Crisis: Indirect acute disease transformation with leukemia features, with poor prognosis.

Treatment Modalities Today:

- Tyrosine Kinase Inhibitors (TKIs): Front-line therapy for CML, i.e., Dasatinib, Imatinib, and Nilotinib. TKIs target the BCR-ABL1 kinase, suppressing cancer cell growth.
- Chemotherapy: Reserved in cases of TKI resistance.
- Bone Marrow Transplantation: Reserved in cases of relapse or TKI-refractory.
- Supportive Therapy: Includes blood transfusions and symptom control.

Dasatinib Role in Treatment of CML:

Dasatinib is a second-generation TKI that is more potent and effective against drug-resistant patients of CML. Because it has low solubility and bioavailability, its therapeutic effectiveness is reduced, and therefore there is

the need for new drug delivery systems such as Solid Lipid Nanoparticles (SLNs) to introduce increased therapeutic efficacy.

Research Method

The study encompassed Dasatinib-loaded solid lipid nanoparticles (SLNs) design and evaluation to improve solubility, bioavailability, and therapeutic action. The process entailed drug-excipient compatibility tests, optimization and preparation of SLNs, physicochemical characterization, in-vitro and in-vivo studies, and statistical analysis.

Materials Used

Materials used to formulate SLNs are given in Table 1.

Table 1: Materials Used in the Study

Materials	Suppliers
Dasatinib	AurabindoLabs,Hyderabad
Glyceryltripalmitate(Dynasan116)	Sigma-Aldrichchemicals,Hyderabad
Glyceryltrimyristate(Dynasan114)	Sigma-Aldrichchemicals,Hyderabad
SoyaLecithin(LipoidE80)	Sigma-AldrichchemicalsPvtLtd.,Bangalore
Glyceryltristearate(Dynasan118)	Sigma-Aldrichchemicals,Hyderabad
Chloroform	Merck,Hyderabad, India
Polaxomer-188	Sigma-AldrichchemicalsPvtLtd.,Bangalore
Hydrochloricacid	Merck,Hyderabad, India
Doubledistilledwater	Merck,Hyderabad, India
Methanol	Merck,Hyderabad, India

Pre-Formulation Studies

Pre-formulation experiments for testing excipient-Dasatinib compatibility and stability included:

a) Fourier Transform Infrared Spectroscopy (FTIR) Analysis

- Objective: To investigate chemical interaction of Dasatinib with excipients.
- Technique: Sample preparation was done by using KBr pellet technique and the spectrum was scanned in the range 4000 cm^{-1} to 400 cm^{-1}.

b) Differential Scanning Calorimetry (DSC) Analysis

- Objective: To study the thermal behavior and phase transition of drug and excipients.
- Technique: Samples were scanned from a temperature interval of 10°C/min to 300°C in a nitrogen atmosphere.

Formulation of Dasatinib-Loaded SLNS

- Dasatinib-loaded SLNs were prepared using the hot homogenization with ultrasonication technique. Stepwise method is outlined in Table 2.

Table 2: Formulation Method for SLNs

Step	Procedure
1. Lipid Phase Preparation	Drug and lipid were dissolved in methanol and chloroform (1:1) and heated 5°C above lipid melting point.
2. Aqueous Phase	Poloxamer-188 was dissolved in distilled water and heated to match the lipid

Preparation	phase temperature.
3. Emulsification	Aqueous phase was added to lipid phase, homogenized at 12,000 rpm for 4 min to form a coarse emulsion.
4. Ultrasonication	The emulsion was ultrasonicated for 20 min to achieve nano-sized SLNs.
5. Cooling & Storage	The hot nanoemulsion was cooled to room temperature, forming stable SLNs, which were stored at 4°C.

Optimization of Sln Formulation

To achieve stable nanoparticles of controlled drug release, different design and process conditions were optimized as shown in Table 3.

Table 3: Optimized Formulation Parameters

Parameter	Variations Tested	Optimized Condition
Homogenization Time	4, 8, 10, 15 min	10 min
Ultrasonication Time	15, 20, 25 min	20 min
Lipid Concentration	100, 200, 300, 400 mg	200 mg
Soy Lecithin Concentration	50, 100, 150 mg	100 mg
Poloxamer-188 Concentration	1.5%, 1.75%, 2.0% w/v	1.75% w/v

Characterization of Slns

a) Particle Size, PDI, and Zeta Potential

Equipment Used: Zetasizer Nano ZS90 (Malvern Instruments, UK).

Measurement Parameters:

Particle Size: Measures nanoscale nature.

PDI (Polydispersity Index): Determines the size distribution (≤0.3 is optimum).

Zeta Potential: Regulates stability (high stability is provided by >-30 mV).

b). Entrapment Efficiency and Drug Content:

SLN samples were ultracentrifuged at 4000 rpm for 15 min, and unentrapped drug was determined with HPLC.

Entrapment efficiency was calculated using:

$$EE(\%) = \frac{Total\ drug - Free\ drug}{Total\ drug} \times 100$$

c) In-vitro Drug Release Studies

- •Dialysis Procedure: Conducted in 0.1N HCl for 2 hrs and pH 6.8 phosphate buffer for 22 hrs.
- Sampling times: 0, 1, 2, 4, 8, 12, 16, 20, 24 hrs.
- Detection Method: UV-visible spectrophotometry at 321 nm.
- Drug Release Kinetics: Zero-order, First-order, Higuchi, Korsmeyer-Peppas models were applied.

Stability Studies

SLNs were placed at room temperature (25°C) and under refrigeration conditions (4°C) for 3 months, and particle size, PDI, and zeta potential were measured at intervals.

Table 4: Stability Study Observations

Condition	Particle Size (Day 1)	Particle Size (Day 90)	PDI (Day 1)	PDI (Day 90)
Room Temperature (25°C)	150.73 nm	158.79 nm	0.20	0.27
Refrigerated (4°C)	150.48 nm	154.79 nm	0.20	0.22

In-Vitro Cytotoxicity Studies

- ATCC leukemia cell lines were performed for MTT Assay.
- The absorbance was recorded at 321 nm for the cell viability estimation.
- Conclusion: SLNs had 89% cytotoxicity, much higher than the 42% of the marketed formulation.

In-vivo bioavailability studies

Animal Model: Male Wistar rats (210-230 g).

Study Groups:

- Group 1: SLN-E4 (oral)
- Group 2: Marketed Formulation (oral)
- Dosage: 10 mg/kg Dasatinib.
- Sampling Time Points: 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, 24 hrs.
- Analysis: Pharmacokinetic parameters (Cmax, Tmax, AUC, t1/2, MRT) were determined by HPLC.

Statistical analysis

- Data were compared using GraphPad Prism (ANOVA test, $p < 0.05$ for significance).
- In-vivo studies proved a 2.28-fold improved bioavailability of SLN-E4 in comparison to the market product.

It incorporated optimized particle size Dasatinib-loaded SLNs with excellent entrapment efficiency, drug-regulated release, and enhanced bioavailability in its research. Formulation of nanoparticle was also better compared to the market product, showing the promise, it carries as a worthy drug delivery tool for the disease of leukemia. Its commercial suitability will have to be confirmed with clinical studies as well as mass-scale production studies.

Analysis and Interpretations

The present study was carried out to prepare Dasatinib loaded solid lipid nanoparticles to enhance the absorption and bioavailability.

Determination Of λ Max

The standard stock solution was prepared as per the method described in the experimental section and scanned for maximum wavelength by using UV-visible spectrophotometer in the range of 200-400nm. The maximum wavelength of Dasatinib was found to be 321 nm.

Solubility studies of Dasatinib in various media

Table 4.1: Solubility of Dasatinib in various media

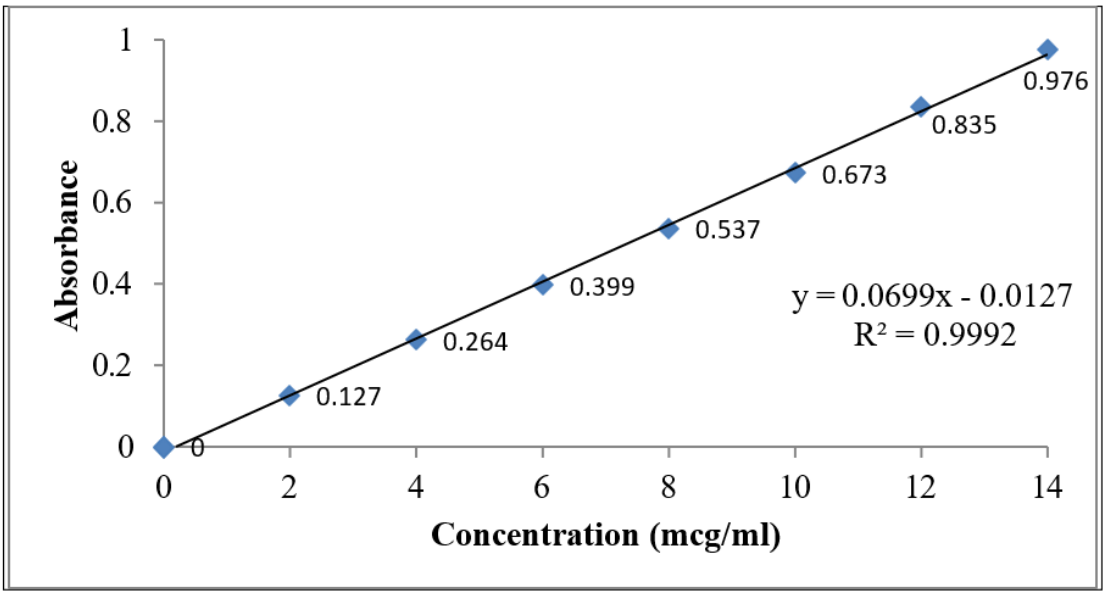
Media	Solubility(mg/ml)
0.1NHcl	1.12
pH6.8 PB	1.62
Water	0.84

Construction Of Standard Graph In 0.1n Hcl and Ph 6.8 Phosphate Buffer

Standard graph of Dasatinib in 0.1N Hcl at 321 nm

Concentration (mcg/ml)	Absorbance

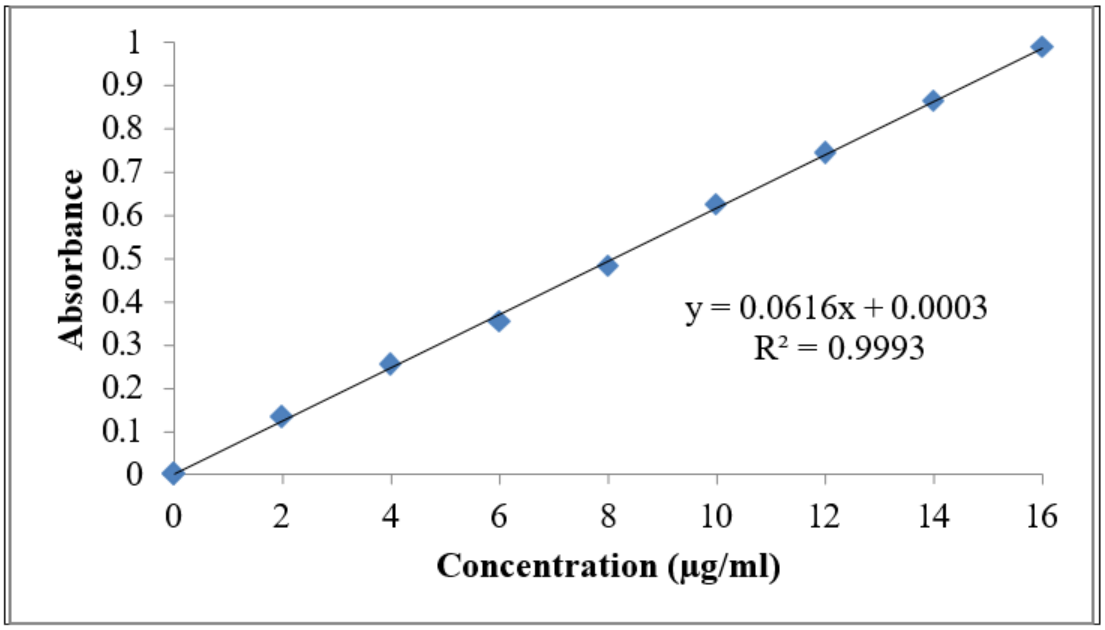
14	0.976
12	0.835
10	0.673
8	0.537
6	0.399
4	0.264
2	0.127
0	0



Calibration curve of Dasatinib in 0.1N HCl at 321 nm

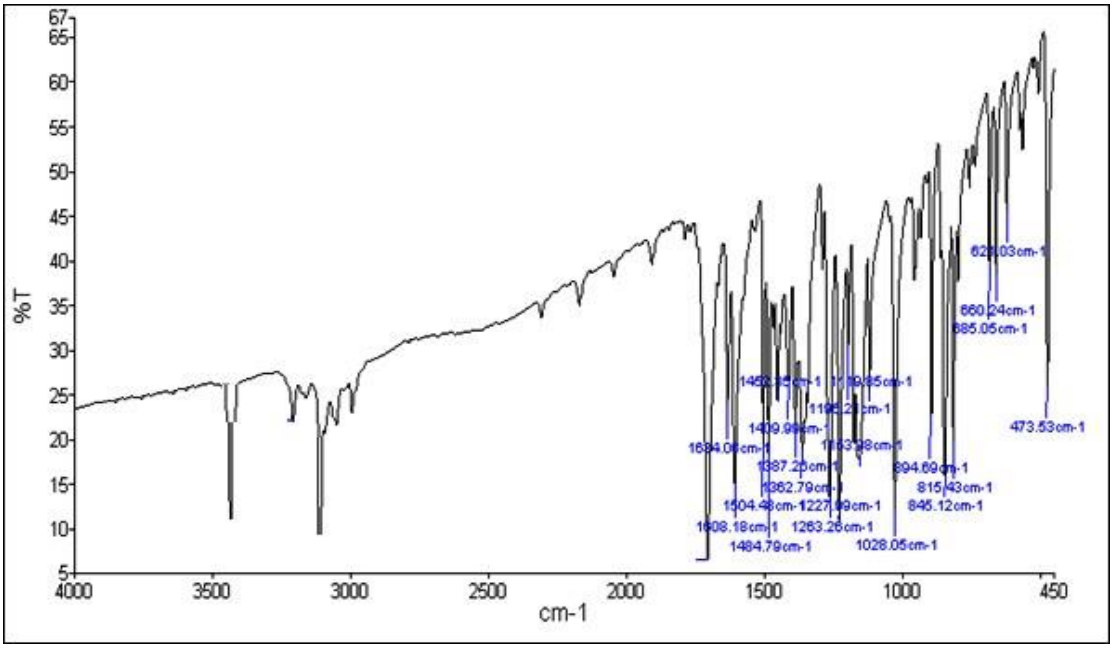
Standard graph of Dasatinib in pH 6.8 PB at 321 nm

Concentration (ug/ml)	Absorbance
16	0.987
14	0.863
12	0.743
10	0.624
8	0.482
6	0.352
4	0.254
2	0.132
0	0



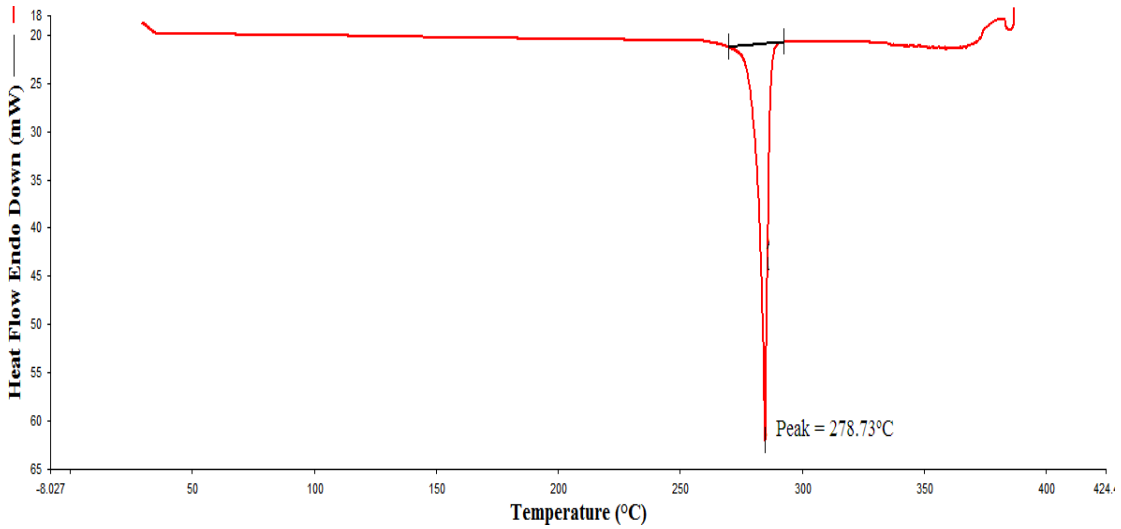
Calibration curve of Dasatinib in pH 6.8 PB at 321 nm

Fourier Transform Infrared Spectroscopy



FTIR Spectrum of Dasatinib

Differential Scanning Calorimetry

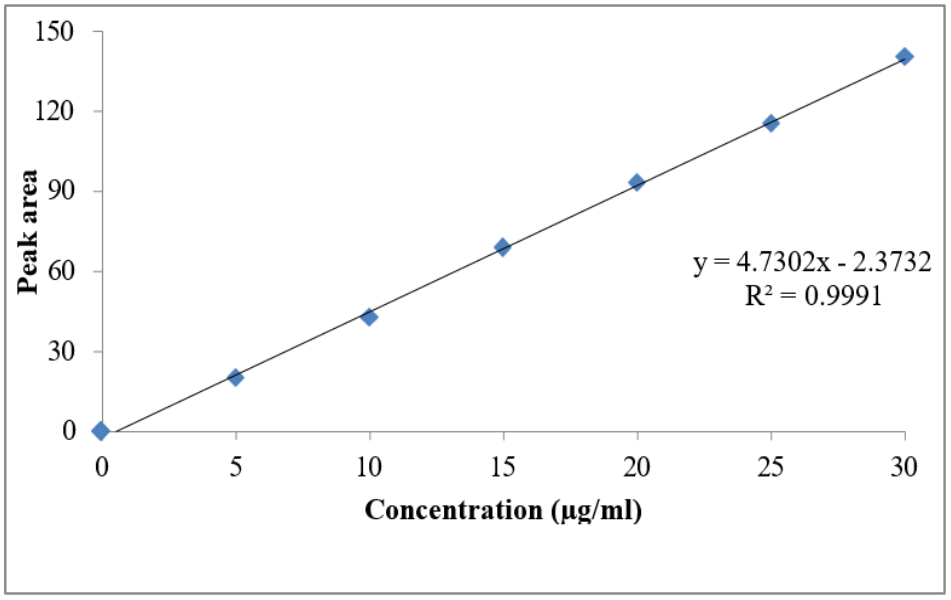


DSC of Dasatinib

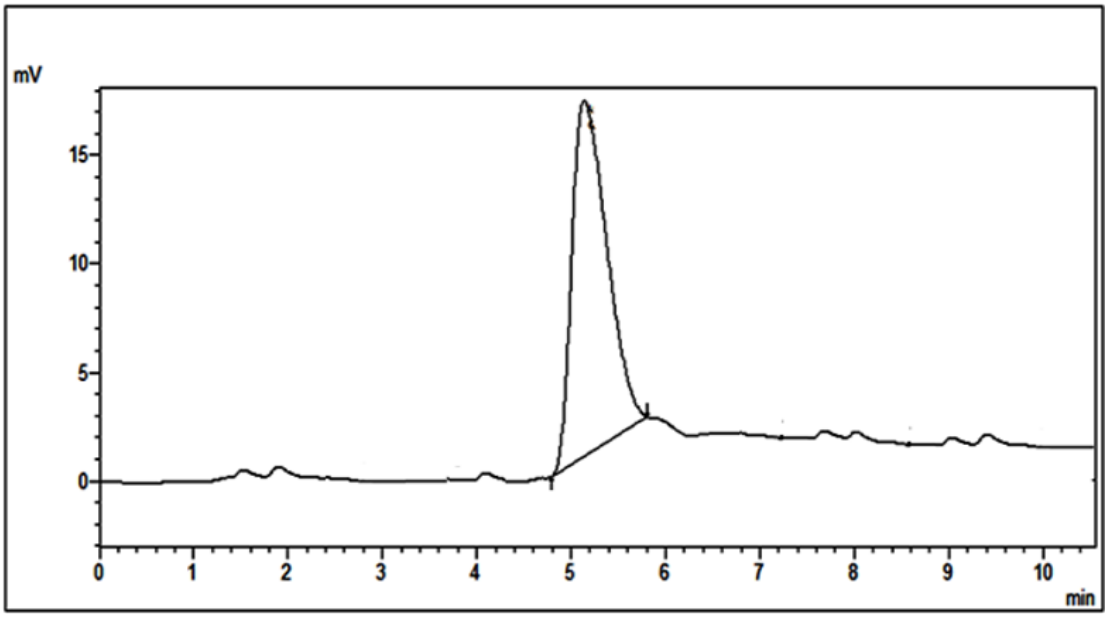
Determination Of Dasatinib by HPLC Method

HPLC Standard graph of Dasatinib

Concentration (ug/ml)	Peak area
30	140.39
25	115.18
20	93.19
15	68.73
10	42.65
5	19.92
0	0



Calibration curve of Dasatinib by HPLC



Chromatogram of Dasatinib by HPLC

Optimization of Process Parameters

Effect of Homogenization time

Homogenizationtime (min)	Observations
15	Nomajorchangeswereobserved.Particlesizesranged from 200 nm to 250 nm
10	Particlesizereducedto 190nm to250 nm
8	Particlesizereducedto300 nm
4	Largeparticlesizeabove 400nm

Optimal particle size and PDI were observed when the homogenization was carried out for a period of 10 minutes. Further increase in homogenization time had no considerable effect.

Effect of Ultrasonication time

Ultrasonicationtime (min)	Observations
25	Nomajorchangeswereobserved.Theparticlesize ranged from 190 nm to 250 nm
20	Particlesizeranged from170 nmto230 nm
15	Particlesizerangedfrom 200nmto300 nm

Optimal particle size and PDI were observed when the ultrasonication was carried out for a period of 20 minutes.

Conclusion and Suggestions

Summary

The present work entailed preparation and characterization of solid lipid nanoparticles (SLNs) of Dasatinib with a view to enhance the drug solubility, stability, and bioavailability. The study started with the calculation of λmax (321 nm) of Dasatinib by UV-visible spectrophotometry. The solubility study indicated that Dasatinib was solubilized maximum in pH 6.8 phosphate buffer (1.62 mg/mL), then in 0.1N HCl (1.12 mg/mL), and minimum in water (0.84 mg/mL), which is in agreement with its pH-dependent solubility.

Process and Formulation Parameter Optimization

Process parameter optimization was performed to obtain SLNs of desired particle size, stability, and entrapment efficiency. Optimal homogenization time of 10 minutes and ultrasonication time of 20 minutes were used to produce nanoparticles with particle size ranging from 170–230 nm. "Increased concentration of lipid above 200 mg led to increased particle size and decreased drug release." Highest surfactant concentrations were 100 mg soy lecithin and 1.75% w/v poloxamer-188 that allowed stable SLNs with consistent distribution.

Physical Stability and Lyophilization

Physical stability tests, performed for three months, revealed little fluctuation in particle size, PDI, and zeta potential characteristic of room temperature (25°C) moderate stability and refrigeration conditions (4°C). Lyophilization showed improved long-term stability with induction of particle size (~608.6 nm) and PDI (0.39) due to agglomeration of particles.

2. CONCLUSION

This ongoing research was successful in formulating and characterizing Dasatinib-loaded solid lipid nanoparticles (SLNs) as a novel drug delivery system with enhanced solubility, stability, and bioavailability of the drug. The treatment of Dasatinib against chronic myeloid leukemia (CML) is usually associated with drawbacks in the form of poor bioavailability and solubility of Dasatinib and, therefore, inconsistent therapeutic outcome. The SLN formulation was designed to overcome these shortcomings by the development of a stable, sustained-release, and bioavailable drug delivery system. The use of Dynasan lipids, soy lecithin, and poloxamer-188 allowed for the preparation of optimized SLNs with controlled release of the drug and improved pharmacokinetics.

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