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Original Article

Development and Evaluation of Dasatinib-Loaded Nanostructured Lipid Carriers for Enhanced Oral Bioavailability, Sustained Drug Release, and Cytotoxic Anticancer Activity Against HL-60 Leukaemia Cells

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ABSTRACT

Background/Aim: Dasatinib monohydrate is a second-generation Tyrosine Kinase Inhibitor (TKI) that is effective in treating Chronic Myeloid Leukaemia (CML) and Philadelphia chromosome-positive Acute Lymphoblastic Leukaemia (Ph+ ALL). The limited aqueous solubility, pH-dependent precipitation, high first-pass metabolism, and low oral bioavailability, however, restrict the usefulness of this compound for therapeutic purposes. In order to get around these restrictions and enhance medication administration, this study set out to create and assess Nanostructured Lipid Carriers (NLCs) loaded with dasatinib. **Materials and Methods:** The preparation of Dasatinib Monohydrate loaded NLCs was done by hot homogenisation and ultrasonication method. Surfactants used were Tween 80 and Span 60 and solid and liquid lipids used were stearic acid and oleic acid, respectively. Entrapment efficiency, particle size, Polydispersity Index (PDI), zeta potential, optical microscopy and Transmission Electron Microscopy (TEM) morphology, *in vitro* drug release and cytotoxicity against HL-60 leukaemia cells were characterised. **Results:** The optimised NLC exhibited an entrapment efficiency of 77.7%, particle size of 258.8 nm, PDI of 0.27 and zeta potential of 0.8 mV. TEM analysis confirmed nanoparticles were spherical and uniformly distributed with minimal aggregation. The formulation achieved a 96.19% cumulative drug release over 12 h, compared to 36.17% for pure Dasatinib Monohydrate. Moreover, it demonstrated concentration-dependent cytotoxicity (IC_{50} 64.02 µg/mL) against HL-60 cells. **Conclusion:** Dasatinib Monohydrate loaded NLCs showed potential in achieving better release of the drug and demonstrated promising anticancer activity, which can be used to increase oral bioavailability and therapeutic efficacy of Dasatinib Monohydrate beyond the biopharmaceutical limitations of conventional Dasatinib Monohydrate formulation.

Keywords: Cytotoxicity, Dasatinib Monohydrate, Leukemia, Lipid-Based Drug Delivery, Nanostructured Lipid Carriers, Oral bioavailability, Sustained Drug Release.

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INTRODUCTION

Dasatinib Monohydrate is a highly effective, oral TKI of the second generation. Its pharmacological effect is mediated by inhibition of BCR-ABL kinase and of the Src family kinases, which form an essential part of oncogenic signalling pathways that mediate unchecked proliferation and survival of cells. Although dasatinib Monohydrate offers superior kinase inhibition profile to first-generation inhibitors, it suffers from formulation-related intrinsic challenges affecting its absorption and systemic availability, which affect its clinical performance after oral administration.[1,2] Such restrictions emphasise the need to develop more sophisticated delivery systems that can achieve the maximum therapeutic benefits. Dasatinib Monohydrate belongs to Biopharmaceutical Classification System (BCS) Class II. In case of these compounds, the rate of dissolution is the rate-limiting step for oral absorption and not the rate of membrane permeation. Dasatinib Monohydrate has desirable permeability characteristics, but the drug is also poorly soluble, limiting its supply of dissolved drug in the gastrointestinal tract for bioavailability absorption. Thus, random

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dissolution characteristics directly affect the pharmacokinetics and consequently the therapeutic response. One of the primary difficulties with Dasatinib Monohydrate is its extremely low aqueous solubility that is further compounded by its appreciable pH-dependent solubility profile.[3,4] The drug has relatively high solubility in gastric conditions but when moving into an intestine with a more alkaline environment, the solubility significantly drops, which results in a very fast precipitation. This effect greatly decreases the percentage of the drug that is available for absorption at the primary absorption site in the gastrointestinal tract. Additionally, dasatinib Monohydrate is highly metabolised by the liver to produce metabolites, so diminishing the amount of drug available in the blood. Another factor that can contribute to decreased absorption is the presence of efflux transporters like P-glycoprotein in the intestinal epithelium, which pump the drug back into the intestine. All of these factors contribute to low and highly variable oral bioavailability in humans, which compromises therapeutic efficacy of dasatinib.[5–8] Poor solubility and variable absorption cause fluctuations in plasma drug levels, potentially resulting in inadequate exposure to and risk of toxicity. Low levels of dasatinib Monohydrate may reduce its ability to fight cancer, which can cause the cancer to grow or become resistant to dasatinib Monohydrate. On the other hand, when it is necessary to improve the bioavailability by giving a higher dose, this can make it more likely that adverse effects will occur, which can decrease patient adherence. These constraints are significant to disease management in cancer therapy, where stable and optimum drug levels are essential.[9,10] Dasatinib Monohydrate intrinsic solubility and bioavailability problems can't be solved with conventional oral dosage forms such as pills and capsules. These formulations are based on passive dissolution processes that do not work for poorly soluble drugs, especially those with pH dependent solubility. Moreover, they have no ability to protect against first-pass metabolism, enzymatic degradation and efflux mechanisms. The need for advanced drug delivery systems which can enhance solubility, maintain the dispersion of the drug in the gastrointestinal tract and facilitate effective absorption is ever increasing. Improving the pharmacokinetic profile and therapeutic efficacy of dasatinib requires the development of such systems.[11,12]lipid-based systems enhance drug solubilisation by forming fine emulsions or colloidal dispersions upon contact with gastrointestinal fluids. Lipids also stimulate the secretion of bile salts and phospholipids, which facilitate the formation of mixed micelles capable of solubilising hydrophobic drugs. In addition to improving solubility, lipid-based systems can enhance drug permeability across the intestinal membrane and reduce the impact of efflux transporters, thereby promoting greater absorption.[13,14]These properties make lipid-based carriers particularly suitable for drugs like Dasatinib Monohydrate, whose absorption is limited by solubility. Among various lipid-based systems, NLC have emerged as promising and advanced drug delivery platform. NLC are made up of combination of solid and liquid lipids, resulting in less ordered crystalline structure with numerous imperfections. This structural characteristic provides additional space for drug incorporation, drug loading capacity and minimising risk of drug expulsion during storage. NLCs possess better physical stability, encapsulation efficiency and better control of release rate as compared to conventional solid lipid nanoparticles. The multiple interconnected mechanisms can explain the enhancement of drug solubility and bioavailability by NLCs. Surfactants enhance wettability and homogenous dispersion of drug particles in gastrointestinal fluids,[15,16] and the lipidic nature of NLCs also ensures better absorption through lymphatic routes in intestine, thus some bypass of hepatic first pass metabolism. In addition, some lipid excipients and surfactants are known to be efflux transporters inhibitors, which would promote drug retention and enhance drug absorption. All these mechanisms help to enhance the oral bioavailability substantially. The use of NLCs is especially beneficial for Dasatinib Monohydrate, because of its lipophilic properties and its pH dependent solubility. The drug can be encapsulated in a lipid matrix, which can keep the drug in the solubilised state even in alkaline intestinal conditions, avoiding drug precipitation and improving absorption. Furthermore, the lipid carrier allows better interaction with biological membranes, resulting in increased permeability and effective transport of drugs across the intestinal barrier. Several formulation strategies for dasatinib have been investigated to enhance the solubility of Dasatinib Monohydrate such as solid dispersions, cyclodextrin inclusion complexes and nanoemulsions, but these formulations have limitations in terms of stability, scalability, and successful achievement of bioavailability improvement. Moreover, many of the current research efforts have been directed towards increasing either the solubility or bioavailability of a drug, but not both. Although, the potential of nanostructured lipid carriers to overcome pH-dependent precipitation and enhance dasatinib Monohydrate lymphatic transport is fairly under-explored,[17,18] it is evident that an extensive research-oriented approach to Dasatinib Monohydrate formulation is required that can successfully resolve several issues related to dasatinib Monohydrate delivery. In the present study, a novel formulation strategy for overcoming multiple biopharmaceutical barriers in a single formulation by development of dasatinib Monohydrate loaded nanostructured lipid carrier is introduced. The composition of solid lipid and liquid lipids is optimised in the presence of suitable surfactants, formulation objectives include to achieve the appropriate drug loading, control drug release and improve the drug solubility. This integrated approach is thought to lead to better dissolution properties, to inhibit precipitation in the gastrointestinal tract and to increase the systemic exposure of poorly soluble anticancer drugs through mechanisms like lymphatic uptake and efflux inhibition.[19,20] This is a major step forward in the formulation

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of poorly soluble anticancer drugs. The aim of the present work is to design and test the nanostructured lipid carriers containing dasatinib Monohydrate, in order to increase its solubility and oral bioavailability. The developed system is expected to enhance dissolution properties, to ensure drug solubilisation in different pH environment, to increase intestinal absorption and to increase systemic drug exposure. Overall, the goal is to increase the therapeutic effectiveness, minimise drug response variability, and create a more effective and reliable oral drug delivery system for dasatinib Monohydrate.[21]

MATERIALS AND METHODS

Materials

Dasatinib monohydrate (Hetero lab hyderabad), Stearic acid, Span 60 Tween 80, Methanol, Ethanol, Oleic acid (Research-Lab Fine Chem Industries, Mumbai), Dialysis membrane (Dolphin Pharmacy Instrument Pvt. Ltd.,).

Methods

NLCs were selected as the delivery system for Dasatinib Monohydrate owing to their ability to overcome the major biopharmaceutical challenges associated with the drug, including poor aqueous solubility, pH-dependent precipitation, and low oral bioavailability. NLCs are composed of blend of solid liquid lipids that create an imperfect lipid matrix, providing higher drug loading capacity and preventing drug expulsion during storage. The nanoscale particle size enhances the surface area available for dissolution, while the lipidic nature of the carrier promotes intestinal absorption and lymphatic transport, thereby reducing the impact of first-pass metabolism. Additionally, NLCs offer improved physical stability, controlled drug release, enhanced drug protection, and better therapeutic performance compared to conventional dosage forms and other lipid-based systems.[22,23] Therefore, NLCs were considered a suitable and promising delivery platform for improving the oral delivery and anticancer efficacy of Dasatinib Monohydrate.

Ethical Considerations

Laboratory-based formulation development and *in vitro* evaluation was carried out with a human cell line. There were no human participants or experimental animals involved; hence, there was no need for ethical approval, but subject to institutional guidelines. Experiments were carried out in controlled laboratory conditions, according to standard procedures.

Selection of excipients

Solid lipid

An excess amount of dasatinib was added to accurately weighed quantities of selected solid lipids which are GMS, stearic acid and Compritol 888 ATO. The lipids were melted at a temperature approximately 5-10°C above their respective melting points and drug was dispersed in the molten lipid under continuous stirring to facilitate solubilisation. The mixture was maintained under constant stirring for 30-60 min to allow the system to reach equilibrium solubility.[24] Since solid lipids tend to solidify upon cooling to room temperature-making the separation of undissolved drug difficult-methanol was added to the mixture to dissolve both the lipid and the drug, resulting in a uniform solution. This step improved handling and enabled efficient separation of any undissolved drug particles. The resulting solution was then centrifuged at an appropriate speed to separate insoluble drug particles. The clear supernatant was collected, suitably diluted if necessary, and analysed for drug content using UV-visible spectrophotometry. Dasatinib showed a greater solubility in stearic acid than glyceryl monostearate and Compritol 888 ATO.[25]

Liquid lipid

A fixed volume (2-5 mL) of selected liquid lipids like oleic acid, Capryol 90 and isopropyl myristate was mixed with an excess amount of dasatinib in a glass beaker. Drug solubilisation was carried out by continuous stirring with a glass rod at ambient temperature or slightly higher temperature (if necessary) after vortexing the mixtures. Equilibrium solubility was achieved by maintaining the samples under constant agitation for 24-48 hr. The mixes were centrifuged quickly after equilibration in order to extract the medication that had not dissolved. Carefully, the clear supernatant was gathered. To make it possible for quantitative estimation, the supernatant was mixed with methanol and then the drug and lipid were completely dissolved to obtain a transparent solution for analysis. This solution was then suitably diluted and their dasatinib content was analyzed using UV-visible spectrophotometry. The solubility of dasatinib in oleic acid as observed from this procedure was higher than Capryol 90 and isopropyl myristate.[26,27]

Surfactant (Solubility study)

Tween 80 was chosen as the surfactant for the formulation of Nanostructured Lipid Carriers (NLC) although it was found to have the lowest drug solubility in the solubility study. The less soluble the drug is in the surfactant, the better it is in NLC systems because the partitioning of the drug into the aqueous phase is decreased, and the drug remains in the lipid matrix and improves the entrapment efficiency. Additionally, Tween 80, due to its high Hydrophilic-Lipophilic Balance (HLB) value, effectively reduces interfacial tension and stabilises the oil-in-water dispersion,

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Table 1: Formulation table for Dasatinib Monohydrate loaded NLC.

Formulation No	Total Lipid Ratio (1%W/V)	Surfactant (1%V/V)	%EE	Water (mL)	After 24 h
F1	70:30	Span˚20	70.49	100	Unstable
F2	80:20	Span˚20	63.65	100	UnStable
F3	90:10	Span˚20	65.5	100	Phase separation
F4	70:30	Tween˚80	77.7	100	Stable
F5	80:20	Tween˚80	73.3	100	Stable
F6	90:10	Tween˚80	55.6	100	Unstable
F7	70:30	S_{mix}	61.3	100	UnStable
F8	80:20	S_{mix}	82.3	100	Phase separation
F9	90:10	S_{mix}	69.1	100	Stable

(EE: Entrapment efficiency, S_{mix}: surfactant and co-surfactant mixture).

leading to the formation of nanosized particles with improved physical stability. Compared to lipophilic surfactants such as Span 60 and Span 20, Tween 80 provides superior emulsification efficiency and prevents aggregation of nanoparticles. Therefore, it was selected as the optimal surfactant by balancing adequate stabilisation with favourable drug retention in the lipid core.[28]

Formulation of NLC

The Nanostructured Lipid Carriers (NLCs) were prepared by the hot-melt high-speed homogenisation technique. In brief, the lipid phase (the solid lipid stearic acid) was first warmed using a magnetic stirrer to a temperature 10°C higher than its melting point, followed by the addition of the liquid lipid (oleic acid). A measured amount of dasatinib was then added and completely dissolved in the compounded lipid mixture. The composition of the formulation is presented in Table 1. The aqueous phase (100 mL of double-distilled water containing 100 mM Tween 80) was prepared at the same temperature. The hot lipid phase was subsequently dispersed in the aqueous phase with continuous magnetic stirring at 800 rpm to obtain a coarse pre-emulsion. A hot nanoemulsion was then prepared by homogenising the pre-emulsion using a high-speed homogeniser at 10,000 rpm for 5 min. The nanoemulsion was then subjected to probe sonication. Finally, the dispersion was cooled to 4°C, resulting in the formation of NLCs.[29]

Evaluation of Dasatinib Monohydrate-Loaded Nanostructured Lipid Carriers (NLC)

Optical microscopy

Optical microscopy of Nanostructured Lipid Carriers (NLCs) is used for preliminary morphological assessment to evaluate dispersion uniformity and detect aggregation, phase separation, or drug crystallisation. Although individual nanoparticles cannot be resolved due to size limitations, it provides useful information about formulation homogeneity and the presence of larger particles or instability, serving as a rapid initial quality assessment tool before advanced characterisation.[30,31]

Thermodynamic Stability Studies

The stability of generated NLC formulations was assessed by looking at their physical appearance during centrifugation, freeze-thaw cycles, and heat-cool cycles. The formulations were subjected to six cycles of heat-cool test with 48 h exposure to each temperature. The formulations that showed any phase separation, creaming or cracking were subjected to the centrifugation at 3500 rpm for 30 min period. The ones which remained stable were further examined after experiencing freeze-thaw cycles, in which they were alternately stored at -21°C and 25°C for 48 h at each temperature (three cycles).[32,33]

The determination of Droplet Size Analysis and Polydispersity Index (PDI)

The droplet size is very vital part and affects the rate and extent of drug release and absorption in the self-emulsification process. All NLC samples were diluted 10-fold in distilled water prior to analysis. The particle size and Polydispersity Index (PDI) of nanosuspension obtained were then determined by the Dynamic Light Scattering (DLS) technique using a photon correlation spectrometer, which assesses the Brownian motion of the particles. The measurements were made at 25°C at a scattering angle of 90°.[34–36]

Zeta Potential Determination

The zeta potential of diluted NLC formulae was measured with help of Zetasizer (Malvern Instruments). Samples were collected in clear cuvette and results were obtained. Charge on suspension and their zeta potential values were obtained.[37,38]

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Transmission Electron Microscopy (TEM)

Surface morphology and globule size of the prepared NLC formulae were observed by Transmission electron microscopy. Prior to analysis, the NLC samples were diluted 10 times with distilled water. A thin liquid film was formed by a drop from the resultant nanosuspension on the film-coated copper grid. The films were then negatively stained with 2% (w/v) phosphotungstic acid solution. The air-dried stained films were then taken for TEM photography.[39,40]

Drug Entrapment efficiency

Dasatinib Monohydrate-loaded Nanostructured Lipid Carriers (NLCs) will be entrapped by centrifugation method, and the entrapment efficiency will be calculated. The formulation will then be placed in a 2 mL centrifuge tube and spun at 10,000 rpm for 20 min to separate the unentrapped (free) drug from the lipid-bound drug. The clear supernatant will then be carefully collected following centrifugation and filtered through a 0.45 µm membrane filter to remove any particulate matter and 1 mL of the filtered supernatant will be pipetted and suitably diluted in an appropriate solvent (e.g., methanol) to achieve complete solubilisation of the drug. UV-visible spectrophotometry will be used to measure the concentration of free dasatinib at 324 nm.[41–42]

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount of drug in formulation}}{\text{Amount of drug added}} \times 100$$

Fourier Transformed Infrared Spectroscopy (FTIR)

FTIR Spectra of prepared optimised NLC formulae were obtained using Fourier transformed infrared spectrophotometer (Shimadzu).[43,44]

In vitro Drug release study

The Liquid Nanostructured Lipid Carrier (L-NLC) dispersion was used to determine the drug release profile *in vitro* and to compare it with 3 mg of Dasatinib Monohydrate. Prior to the study, dialysis membrane tubing (MWCO 12,000-14,000 Da) was soaked In Phosphate-Buffered Saline (PBS, pH 6.8) for 24 h at room temperature. A 5 mL accurately measured dispersion of L-NLC (5 mL/equivalent to 3 mg of Dasatinib Monohydrate) was transferred separately into dialysis bags and the ends were tightly closed. The dialysis bags were placed in separate 200 mL of PBS (pH 6.8) and shaken in a water bath at 100 rpm and 37±0.5°C for 24 h. The release medium was changed every hour at a time point with 1 mL withdrawn and replaced with fresh PBS (pH 6.8) to ensure sink conditions. Withdrawn samples were analysed by a UV-visible spectrophotometer at 319 nm and cumulative percentage drug release was calculated and compared with that of Dasatinib Monohydrate.[45–47]

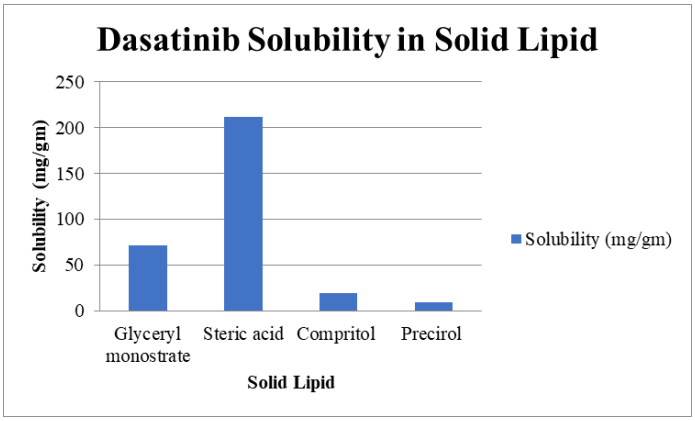


Figure 1: Solubility study of Dasatinib Monohydrate in Solid Lipid.

Cytotoxicity Study of NLC Using Cell MTT Assay

The cytotoxicity study was performed by using Human Leukemia cells (HL-60) to assess the anticancer activity of Dasatinib Monohydrate-loaded Nanostructured Lipid Carriers (NLCs) by the MTT assay. This assay is used to assess cell viability and to evaluate the activity of the formulation in inhibiting the growth of cancer cells. In the study, the developed NLC system is found to be effective in the therapeutic application and it can be used as a lipid-based carrier for targeted treatment of leukaemia.[23,47-48]

RESULT AND DISCUSSION

Screening of solid lipid

A screening of solid liquid is performed solid liquid screening is done. It was found that Dasatinib is soluble in the different solid lipids assessed for a potential lipid matrix for formulation development as illustrated in Figure 1. The solid lipids that were tested, including stearic acid, Glyceryl Monostearate (GMS), Compritol® and Precirol®, showed varying solubility properties when tested with Dasatinib. It had the best solubility in stearic acid (211.7mg/g) than the other lipids that were tested which showed good compatibility with stearic acid. It was determined that the order of solubility was: stearic acid > glyceryl monostearate >Compritol® >Precirol®. The relatively higher solubility of Dasatinib in stearic acid might be explained by its long-chain saturated fatty acid structure, which may favor drug-lipid interactions and offer more space for the accommodation of the drug within the lipid matrix. Based on this result, the stearic acid which has the highest drug solubilisation capacity and favorable biocompatibility was used for further formulation study.

Screening of liquid lipid

Dasatinib Monohydrate solubility in different liquid lipids was explored and used to choose an appropriate liquid lipid for the formulation. The liquid lipids tested were oleic acid, oleic acid Capryol® 90, castor oil and Isopropyl Myristate (IPM). Of these,

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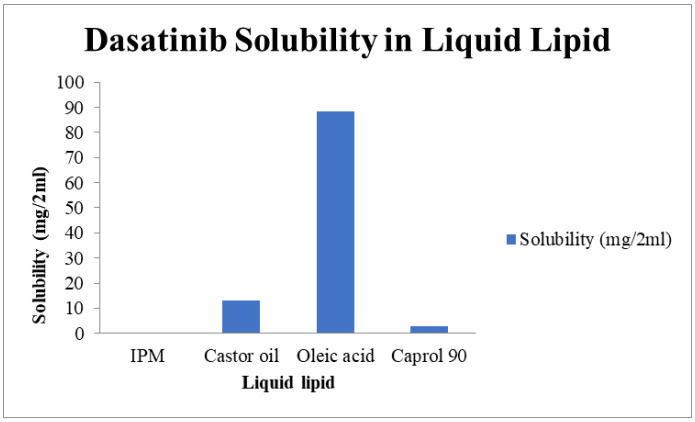


Figure 2: Solubility study of Dasatinib Monohydrate in Liquid lipid.

Dasatinib Monohydrate was the most soluble in oleic acid, 88.3 mg/2 mL, which is more solubilising than the other tested lipids as seen in Figure 2. The following order of solubility was found: oleic acid >Capryol® 90 > Isopropyl Myristate (IPM) > castor oil. The improvement in solubility in oleic acid can be explained as a result of having unsaturated fatty acid structure which helps in improving the drug-lipid interaction and drug partitioning. Considering the result from the solubility data, oleic acid was chosen for further study since it has the highest solubilisation potential, which will help in drug loading and encapsulation efficiency in combination with the selected solid lipid.

Screening of surfactant

Solubility screening studies were used to select surfactants for forming Dasatinib Monohydrate loaded Nanostructured Lipid Carriers (NLCs). We tested different surfactants for their capacity to solubilise Dasatinib Monohydrate because this parameter is of critical importance to obtain an effective incorporation and stability of Dasatinib in the formulation. Interestingly, the more poorly soluble the surfactant for Dasatinib Monohydrate, the more suitable it was for this purpose, as it would result in less drug partitioning into the aqueous phase and more drug encapsulated within the lipid matrix, leading to an increase in encapsulation efficiency. Based on this criterion Tween 80 and Tween 20 were chosen to formulate NLCs for Dasatinib as it exhibited comparatively less solubility in these surfactants. Besides this, both surfactants are non-ionic and are extensively utilised owing to their remarkable biocompatibility, low toxicity, and excellent steric stabilisation, which helps to stabilise and form uniform nanosystem.

Miscibility study / screening of lipid ratio

The miscibility study of solid and liquid lipids was carried out to assess the compatibility and stability of various lipid ratios for the development of Nanostructured Lipid Carriers (NLCs). Solid and liquid lipids in various proportions (6:4, 7:3, 8:2 and 9:1) were mixed and observed visually for any evidence of phase separation, crystallisation or formation of oil droplets. The ratio of 7:3 was found to be most miscible, showing little lipid separation and no oil droplets, among the ratios that were tested. Furthermore, in filter paper tests the formulation yielded a uniform smear, which suggests a stable and homogeneous lipid blend, and good integration of both lipid components. This behaviour indicates that a suitable concentration of liquid lipid will destroy the crystalline structure of the solid lipid and thus will lower the possibility of expulsion of the drug and improve drug compatibility inside of the lipid matrix. Other ratios, on the other hand, showed signs of instability, including phase separation or non-uniformity. Thus, considering its good miscibility, stability and uniformity, the lipid ratio 7:3 was chosen for the preparation of Dasatinib loaded NLCs.

Preparation and Optimisation of Dasatinib-Loaded NLCs

Conventional Solid Lipid Nanoparticles (SLNs) were distinguished by using a hybrid lipid matrix of solid stearic acid and liquid oleic acid for preparing Dasatinib Monohydrate loaded Nanostructured Lipid Carriers (NLCs). The non-ionic surfactant, Tween 80 and 20 were used because of their low toxicity and good stabilising properties. Dasatinib Monohydrate (100 mg) was included in the lipid phase and the lipid phase and surfactant concentration were maintained at 1% (w/v) and 1% (v/v), respectively. The NLCs were prepared by hot homogenisation technique and then the probe sonication. First, the lipid phase (stearic acid and oleic acid) was melted at a slightly higher temperature than the melting temperature of stearic acid and Dasatinib Monohydrate was dissolved in the melted lipid phase. At the same time, the aqueous phase (tween 80 and tween 20) was heated to the same temperature. The molten lipid phase was then slowly fed to the hot aqueous phase with continuous stirring and the resulting coarse oil-in-water emulsion was obtained. This coarse emulsion was further processed by high speed homogenisation to decrease particle size, and probe sonication to achieve a finer and more uniform nano-dispersion. Finally, the formulation was quickly cooled down at 4°C by means of ice bath, resulting in solidification of the lipid matrix and the formation of stable Dasatinib loaded NLCs.

Evaluation of Dasatinib Monohydrate-Loaded Nanostructured Lipid Carriers (NLC)

Optical microscopy

The initial morphology and dispersion of the prepared Dasatinib Monohydrate loaded Nanostructured Lipid Carriers (NLCs) were assessed by optical microscopy. A small volume of the NLC dispersion was transferred to a clean glass slide and a cover glass was placed on it, and viewed under an optical microscope at the appropriate magnification. This analysis can be used to detect phase separation, large particles or aggregates in the

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Table 2: Results of Thermodynamic Stability of Dasatinib Monohydrate -Loaded Nanostructured Lipid Carriers (NLC).

Batch	Result
F4	Stable
F5	Unstable
F9	Unstable

formulation, the NLCs were seen to be dispersed without any noticeable aggregation or crystal growth, which suggested good homogenisation and incorporation of the drug in the lipid matrix.

Results of thermo dynamic Stability Studies

Thermodynamic stability study was conducted to assess the physical stability of prepared NLC. From Table 2, it can be seen that none of the tested batches (F4, F5, F9) showed any aggregation, phase separation, or instability over the period of the study. But batches F5 and F9 were determined to be unstable. Hence, F4 was considered as the optimised formulation for further characterisation and evaluation studies, which showed good thermodynamic stability.

Entrapment Efficiency (%EE)

NLCs containing Dasatinib Monohydrate were prepared by the hot homogenisation and probe sonication method with different solid to liquid ratios of the lipids, i.e., stearic acid (solid) and oleic acid (liquid). The optimised batch exhibited good physical stability in the prepared batches, as indicated by its satisfactory entrapment efficiency as shown in Figure 3. The %EE of the optimised Dasatinib loaded NLCs was determined to be 77.7% indicating the effective loading of the drug in the lipid matrix. The relatively high entrapment could be explained by the fact that the NLC system is a combination of solid and liquid lipids creating an imperfect crystal structure which allows enough space for the drug to be accommodated. This outcome validates the chosen lipid formulation, demonstrating its efficacy in improving drug loading and formulation stability.

Particle Size (PS) , Polydispersity Index (PDI) , Zeta Potential (ZP)

The formulated Dasatinib Monohydrate loaded Nanostructured Lipid Carriers (NLCs) showed acceptable physicochemical properties suggesting the formation of nanoparticles. The optimised formulation had a particle size of 258.8 nm, validating its nanometric range that is favourable for improving drug dissolution and bioavailability as evident in the Figure 4. The relative uniform and narrow particle size distribution profile, with minimal aggregation, was indicated by the Polydispersity Index (PDI) value of less than 0.3 (ideal value). Homogeneity which results will make the surface area and wettability of the drug better which will enhance its dissolution rate in the gastrointestinal tract according to the Noyes-Whitney equation and favoring better absorption. The surface charge of the formulation was determined to be -0.8 mV, although the surface charge is low, the nanosystem can be physically stabilised primarily by steric stabilisation that is achieved through the layer of surfactant (non-ionic surfactant such as Tween 80). These surfactant molecules coat the surface of the nanoparticles, providing them with a protective layer of hydrophilic groups which will repel other nanoparticles through the generation of steric hindrance between the particles. This mechanism is particularly useful for maintaining the stability of dispersion without the need for a large electrostatic repulsive force, which helps to ensure the stability of the formulation as a whole.

Transmission Electron Microscopy (TEM)

The Dasatinib Monohydrate loaded Nanostructured Lipid Carrier (NLCs) had a uniform dispersion and spherical shape as observed in TEM micrograph and showing a well formed nanosystem where the aggregation is minimal. The particle size observed by TEM was found to be in the range of 240-255 nm, which is slightly smaller than the size obtained by Dynamic Light Scattering (DLS). This difference can be attributed to the fact that DLS measures the hydrodynamic diameter of particles in a hydrated state, including the surrounding solvent layer, whereas TEM provides the actual size of dried particles. The results confirm the successful formation of nanosized, monodispersed lipid carriers with suitable morphology for drug delivery applications as described.

Compatibility study of NLC using FTIR Spectroscopy

FTIR was used to assess the compatibility and possible interactions between dasatinib monohydrate, the chosen lipids and the surfactant used to prepare the NLC dispersion. The characteristic peaks of dasatinib monohydrate, lipids and surfactant were preserved in the NLC dispersion without the significant peak shift or disappearance or appearance of new peaks. The results showed that there were no significant chemical interactions or incompatibility between the drug, lipids and surfactant. Thus, it can be concluded from the FTIR results that the formulation components used were compatible and the prepared NLC dispersion was stable.

In vitro Drug Release Study

The *in vitro* drug release study was carried out to compare the release behaviour of pure Dasatinib Monohydrate and Dasatinib Monohydrate-loaded Nanostructured Lipid Carriers (NLCs). The results demonstrated a significant difference in the release profiles of both formulations. The pure drug exhibited a comparatively slow and limited drug release, showing only 36.17% cumulative drug release at the end of 12 h. In contrast, the Dasatinib-loaded NLC formulation showed a markedly enhanced and

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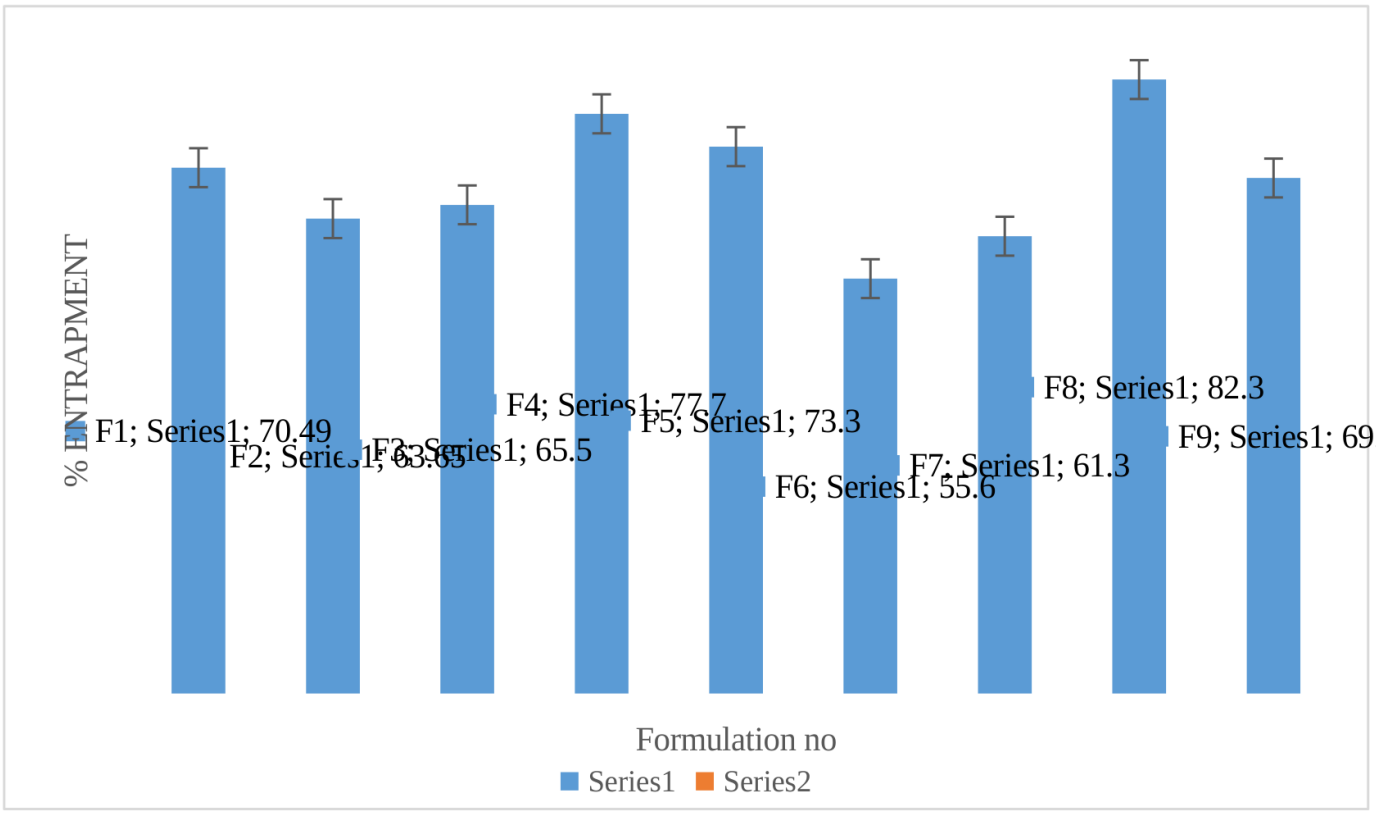


Figure 3: Drug Entrapmentof Dasatinib Monohydrate -Loaded Nanostructured Lipid Carriers (NLC).

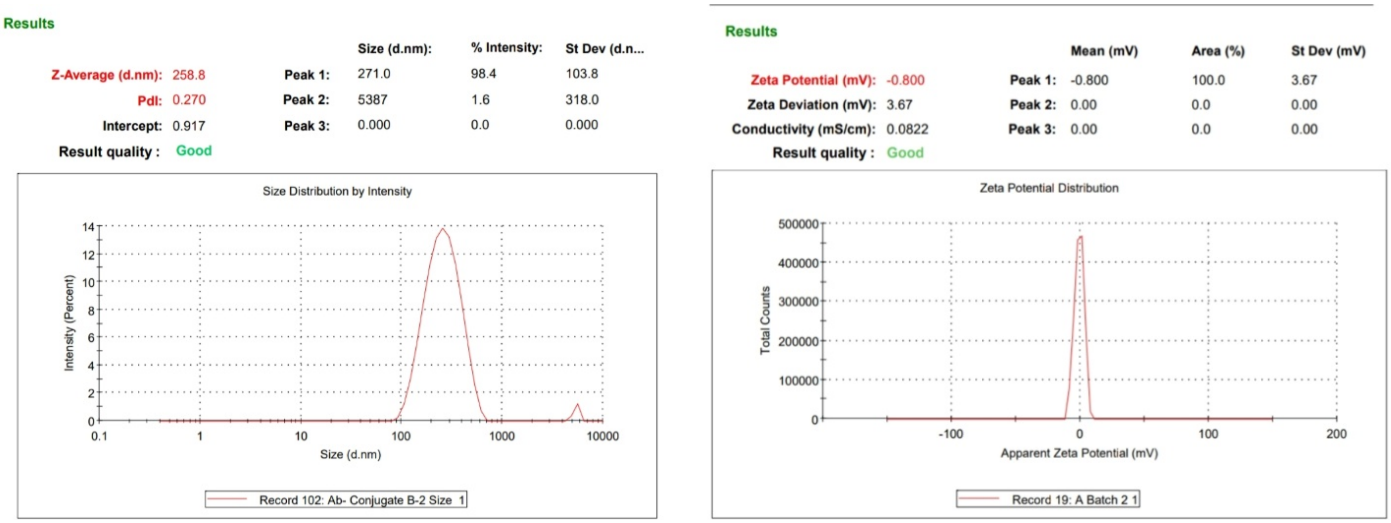


Figure 4: Particle Size (PS), Polydispersity Index (PDI) and Zeta Potential (ZP) of Dasatinib Monohydrate -Loaded Nanostructured Lipid Carriers (NLC).

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sustained drug release pattern, with 96.19% cumulative drug release observed within 12 h. The optimised NLC formulation exhibited an initial burst release during the early hours, followed by a prolonged and controlled release phase. The initial burst effect can be explained by the interaction of drug with the surface of the nanoparticles, and the sustained release effect can be explained by the interaction of Dasatinib Monohydrate with the solid lipid matrix of NLC system. The dissolution and diffusion of the drug was also favored due to the nanosized particles and larger surface area of NLCs. The results show that the NLC formulation has a beneficial effect on the release profiles of Dasatinib Monohydrate compared to the plain drug, suggesting that its formulation could enhance its oral bioavailability and therapeutic activity. In previous studies, similar sustained release profiles of lipid nanocarriers have been described, in which the lipid matrix was responsible for the diffusion of the encapsulated drug over a long period of time.

Cytotoxicity study of NLC

The human leukaemia cell line, HL-60 was used to assess the cytotoxicity of Dasatinib Monohydrate-Nanostructured Lipid Carriers (Dasatinib Monohydrate NLCs) by MTT assay. The findings reveal cell viability reduction in a concentration-dependent manner proving the anticancer effect of the formulated product as depicted (Table 3). The viability of Dasatinib MonohydrateNLC progressively decreased from 6.25µg/mL to 100µg/mL, suggesting that leukaemia cells were increasingly inhibited with greater concentration of Dasatinib Monohydrate NLC. The optimal formulation had an IC_{50} value of 64.02 µg/mL, which indicated that the optimal formulation had moderate to significant cytotoxicity against the HL-60 cells. The decrease in absorbance with increasing concentrations confirmed further reduction in metabolic activity, as well as decrease in cells survival. The results showed that the formulated Dasatinib NLC have a promising anticancer activity and can be used as an effective lipid-based drug delivery system in leukaemia treatment which can enhance the cellular uptake and efficacy of Dasatinib.

Accelerated Stability Study Of NLC

The optimised NLC formulation was subjected to an accelerated stability study for 3 months under accelerated storage conditions to evaluate its physical and formulation stability. As presented in Table 4, the formulation remained white and homogeneous with no visible phase separation throughout the study, indicating good physical stability. The entrapment efficiency showed only a slight decrease from 77.77% initially to 77.3%, 76.9%, and 76.5% after 1, 2, and 3 months, respectively, suggesting minimal drug leakage from the lipid matrix. The PDI increased marginally from 0.27 to 0.30, indicating only a minor change in particle-size distribution, while the zeta potential showed slight variations from +0.80 mV to +0.78, +0.74, and +0.76 mV during the study period. Overall, the NLC demonstrated good stability under accelerated storage conditions, with no marked deterioration in its critical quality attributes over the 3-month.

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Table 3: Cytotoxicity study of Dasatinib Monohydrate -Loaded Nanostructured Lipid Carriers (NLC).

Sl. No.	Concentration (µg/mL)	Absorbance (OD)				Cell Viability (%)	IC_{50} value (µg/mL)
		1	2	3	Mean±SD		
1.	Control	2.136	2.139	2.137	2.137±0.00152		
2.	**Standard - 5FU**						
	6.25	1.324	1.325	1.326	1.325±0.001	62.00	15.75 µg/mL
	12.5	1.233	1.235	1.236	1.234±0.0015	57.77	
	25	0.721	0.725	0.726	0.724±0.0026	33.87	
	50	0.615	0.614	0.612	0.613±0.0015	28.71	
	100	0.512	0.516	0.515	0.513±0.0015	24.03	
3.	**Sample - NLC**						
	6.25	1.52	1.524	1.526	1.523±0.0030	71.28	64.02 µg/mL
	12.5	1.401	1.402	1.403	1.402±0.001	65.60	
	25	1.311	1.315	1.316	1.314±0.0026	61.48	
	50	1.235	1.236	1.239	1.236±0.0020	57.86	
	100	0.784	0.785	0.789	0.786±0.0026	36.78	

(NLC: Nanostructured Lipid Carrier; OD: Optical Density; SD: Standard Deviation; IC_{50}: Half-Maximal Inhibitory Concentration; 5-FU: 5-Fluorouracil).

Table 4: Accelerated Stability Study of Dasatinib Monohydrate -Loaded Nanostructured Lipid Carriers (NLC).

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	White, homogeneous dispersion; no phase separation	White, homogeneous dispersion; no phase separation	White, homogeneous dispersion; no phase separation	White, homogeneous dispersion; no phase separation
Entrapment Efficiency (EE) (%)	77.77%	77.3%	76.9%	76.5%
PDI	0.27	0.28	0.28	0.30
Zeta potential	+0.80	+0.78	+0.74	+0.76

(NLC: Nanostructured Lipid Carrier; EE: Entrapment Efficiency; PDI: Polydispersity Index).

CONCLUSION

Dasatinib Monohydrate loaded Nanostructured Lipid Carriers (NLCs) were successfully formulated and evaluated to enhance the solubility and oral bioavailability of Dasatinib Monohydrate. Optimised NLCs had nanosized particles, low PDI, good zeta potential, high entrapment efficiency and satisfactory stability. *In vitro* drug release studies showed sustained and enhanced release of the drug in comparison to the pure drug. Further improvements in storage stability and handling properties were obtained by solidification of NLCs. In conclusion, the developed NLC formulation is a promising oral delivery system for poorly water-soluble anticancer drugs with the potential to increase therapeutic efficacy, decrease in dosing frequency and increase in patient compliance.

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ABBREVIATIONS

NLC: Nanostructured Lipid Carrier; **CML:** Chronic myeloid leukaemia; **OD:** Optical Density; **SD:** Standard Deviation; **IC_{50}:** Half-Maximal Inhibitory Concentration; **5-FU:** 5-Fluorouracil; **EE:** Entrapment Efficiency; **S_{mix}:** Surfactant and co-surfactant mixture; **PDI:** Polydispersity Index.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTION

Aniket A. Askat: Conceptualization, formulation development, experimental work, data collection, data analysis, and manuscript preparation. **Kedar Bavaskar:** Supervision, formulation guidance, topic selection, study design, and critical revision of the manuscript. **Ashish Jain:** Provision of laboratory facilities, technical support, and guidance during the experimental work. **Shrikant V. Joshi:** Guidance in study methodology, data interpretation, and critical review of the manuscript. **Vilas Surana:** Technical guidance, support in characterisation studies, and critical review of the manuscript. **Rajesh Dodiya:** Scientific guidance, data interpretation, and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data include the formulation, characterisation, *in vitro* drug release, cytotoxicity, and stability data generated during the study.

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