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Original Article

DEVELOPMENT AND ASSESSMENT OF A SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM FOR ENHANCED SOLUBILITY OF DASATINIB

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ABSTRACT

Objective: The objective of this study was to increase the water solubility of Dasatinib (DAS) by incorporating it into a Self-Nano Emulsifying Drug Delivery System (SNEDDS). Dasatinib, a Biopharmaceutics classification system (BCS) class II drug, has poor solubility in aqueous media, affecting its oral bioavailability. Various oils, surfactants, and co-surfactants were chosen based on solubility tests, with the highest solubility selected.

Methods: Various compositions of oils, surfactants and co-surfactants with Smix concentrations as 1:1, 1:2 and 2:1 and there were 9 formulations under each of these groups with Oil: Smix concentrations of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. Capmul MCM, Cremophor EL, and Tween 20 were selected as oil phase, surfactant, and co-surfactant, respectively. A pseudo-ternary phase diagram using the water titration technique optimized the nano-emulsification ratio. The optimized formulation was characterized and evaluated for thermodynamic stability, cloud point measurement, zeta potential, Poly dispersity Index (PDI), globule size, percent transmittance, robustness to dilution, and dissolution studies.

Results: Transmittance of 95% was demonstrated by the formulation, indicating transparency and stability. The zeta potential was over 30 mV, indicating strong electrical stability, and the average globule size was measured to be 85 nm. The formulation was shown to be stable at body temperature, as evidenced by the cloud point being reported above 95 °C. The formulation maintained its stability when diluted in water, 0.1N acid, and phosphate buffer. The formulation contained 85% of the dasatinib, according to the drug content study. The optimized SNEDDS formulation significantly increased drug release in *in vitro* drug release experiments as compared to the pure medication. The oral bioavailability of dasatinib in the SNEDDS formulation was shown to be 3.24 times higher than that of the pure medication, according to *in vivo* pharmacokinetic tests.

Conclusion: Consequently, the findings indicated that the formulation of dasatinib SNEDDS functions as a means of achieving increased drug loading, better dissolving profiles, and increased bioavailability for the BCS Class II drug dasatinib.

Keywords: Self-nano emulsifying drug delivery system (SNEDDs), Dasatinib, Nano-emulsification, Oral bioavailability

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INTRODUCTION

Chronic Myeloid leukemia (CML) is a relatively uncommon form of blood cancer that arises from an abnormal rearrangement between chromosomes 9 and 22. This translocation results in the fusion of the breakpoint cluster region protein(BCR) and Abelson murine leukemia viral oncogene (ABL) genes, leading to the formation of the BCR-ABL gene on chromosome 22, commonly known as the Philadelphia chromosome [1]. This genetic alteration gives rise to tyrosine kinases, pivotal enzymes responsible for initiating the uncontrolled proliferation of myeloid stem cells in the bone marrow [2, 3]. The landscape of CML treatment has witnessed notable advancements, with several drugs proving effective in managing the disease. Among these, Dasatinib (DAS) stands out as a common therapeutic agent [2]. Functioning as a tyrosine kinase inhibitor (TKI), Dasatinib works by blocking the activity of the BCR-ABL gene, thereby stopping the aberrant cell proliferation. Other drugs employed in CML therapy, such as Nilotinib, Bosutinib, Imatinib, and Ponatinib, share a similar mechanism of action to Dasatinib [3, 4].

Despite the efficacy of these drugs, their preferred mode of administration is through the oral route. However, challenges arise in the oral delivery of TKIs, particularly Dasatinib. Classified as a class II compound in the Biopharmaceutical Classification System (BCS), Dasatinib exhibits poor solubility and high permeability [5]. While the drug is soluble in acidic mediums, its solubility sharply declines at pH levels above 4. This limitation in aqueous solubility translates to decreased oral bioavailability, impacting the effectiveness of the drug in various dosage forms [6, 7] Additionally, Dasatinib undergoes a high first-pass metabolism, a process in which the drug is metabolized in the liver before reaching systemic circulation. This metabolism significantly decreases the bioavailability of Dasatinib, limiting its therapeutic potential [8].

One promising avenue of exploration is the use of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS). SNEDDS are composed of a mixture of oil, surfactant, co-surfactant, and the drug itself. When exposed to an aqueous medium and subjected to moderate agitation, these components form a nanoemulsion with droplet sizes ranging from 20-200 nm [9-11]. This unique formulation provides a solution to the solubility challenges faced by Dasatinib. In a SNEDDS formulation, Dasatinib exists in its solubilized state within the oil phase, preventing precipitation during pH changes in the surrounding environment. This feature is particularly advantageous considering the fluctuating pH levels encountered in the gastrointestinal tract [12–14]. Moreover, being dissolved in a lipidic phase, Dasatinib can be absorbed through the lymphatic system present in the intestine [15]. The lymphatic absorption route is crucial as it allows Dasatinib to bypass the first-pass metabolism, a significant contributor to its decreased bioavailability. By evading the initial metabolism in the liver, Dasatinib can enter systemic circulation more efficiently, potentially leading to higher concentrations of the drug at the target site [16–21].

In conclusion, this study focusing on SNEDDS formulations for Dasatinib represents a significant leap forward in addressing the challenges associated with oral administration of this crucial drug for CML treatment. By leveraging the unique properties of SNEDDS to enhance solubility and absorption, researchers aim to unlock the full therapeutic potential of Dasatinib. As this research unfolds, it not only holds promise for CML patients but also contributes to the broader landscape of drug delivery systems, offering potential solutions for

other medications struggling with solubility limitations. In the pursuit of elevating bioavailability, this study marks a crucial step towards advancing cancer treatment and improving patient outcomes.

MATERIALS AND METHODS

Materials

Dasatinib, Methanol, Capryol 90, Capmul MCM, Laurglycol FCC, Labrafil M1944cs, Castor oil, Tween 80, Triton X 100, Triacetin, Tween 20, Poly EthyleneGlycol (PEG) 400, Cremophor EL, Acconon MC8, Cinnamon Oil.

Analytical method

Analytical method development using UV-spectroscopy

Dasatinib was added to Methanol and scanned for Lambda max (λmax) using a UV-Vis Spectrophotometer and it was found to be 322 nm. A primary stock solution of 1000mcg/ml of Dasatinib in methanol was made and concentrations ranging from 2 mcg/ml–12mcg/ml were prepared. These samples were used to construct a calibration curve for Dasatinib in Methanol [22].

Analytical method development using high performance liquid chromatography (HPLC)

A Kromasil C18 reverse-phase column was used for the chromatographic separation. The mobile phase consisted of acetonitrile (ACN) and phosphate buffer pH 6.8 in a 45:55 v/v ratio, with a 10 mmol concentration at a flow rate of 1.2 ml/min. The analysis was conducted for ten minutes at 321 nm. To prepare the solution, 10 mg of dasatinib was carefully weighed and added to 10 ml of the drug in a volumetric flask. The concentration of the primary stock solution was increased to 1000 parts per million (ppm) by adding methanol to adjust the volume. Subsequently, working stock solutions (10 ppm) and secondary stock solutions (100 ppm) were prepared using proper dilutions with methanol as the diluent. Stock solutions were prepared in different quantities using methanol as a diluent. HPLC analysis determined the peak area at λmax (321 nm). The calibration curve was created by averaging three values [23, 24].

Solubility studies

The solubility of Dasatinib in each excipient was examined. An excess amount of the drug was added to 1 ml of each surfactant, co-surfactant, and oil. The mixture was then vortexed to achieve uniform dissolution and kept in a tube rotator for 72 hour at room temperature. After equilibration, the samples were centrifuged at 10,000 RPM (rotation per minute) for 10 min. The supernatants were suitably diluted in methanol and analyzed using an in-house developed UV-Vis method [25].

Formulation of dasatinib loaded SNEDDS

Screening of surfactant and co-surfactant for emulsification ability

Various compositions of oils, surfactants and co-surfactants were decided upon based on the solubility studies. These mixtures were prepared in 3 groups with Smix concentrations as 1:1, 1:2 and 2:1 and there were 9 formulations under each of these groups with Oil: Smix concentrations of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. They were diluted several times with water to check for any visible signs of turbidity. Any turbidity would indicate that a nanoemulsion is not formed [25]. The oils and surfactants that showed the highest solubility concerning Dasatinib were selected.

Construction of pseudo ternary phase diagram

Ternary phase diagrams consist of triangles in which each corner represents the concentration of oil, surfactants, and co-surfactants. The oils and surfactants that showed the highest nanoemulsification power were selected for further studies. These oils and surfactants were combined in ratios ranging from 10% oil and 90% surfactant mixture to 10% surfactant mixture and 90% oil. Water was added to these compositions until a clear solution was obtained. The total volume of each composition was then added up to 100% and the amount of water, surfactant mixture and oil was calculated. These percentages were then fed into the CHEMIX software to generate a pseudo-ternary phase diagram [26, 27].

Optimization of the formula

Based on the pseudo-ternary phase diagram that was produced, a range of ratios showed a nanoemulsification region. The globule size and PDI of these ratios were determined using the Dynamic Light Scattering (DLS) technique using a Zeta sizer and the optimum ratios were narrowed down. Each sample was diluted 100x with water and subjected to size analysis. The formulations that showed less globule size were selected for drug loading [28–30].

Preparation of SNEDDS

The SNEDDS formulation was made by adding 20 mg of Dasatinib to the selected oil phase and vortexing until the drug was solubilized. The chosen surfactant and co-surfactant were then added to the oil phase containing the drug and subjected to vortexing until a homogenous mixture was obtained [29, 31, 32].

In vitro characterization of dasatinib loaded SNEDDS

Zeta potential and size

Zeta Potential and globule size were tested for the formulation having the lowest globule size in the blank formulations. Each formulation was diluted 100x with water and scanned by a zeta sizer to obtain the results for zeta potential and globule size [27, 33].

Cloud point determination

The dasatinib loaded SNEDDS formulations were diluted 100 times with water and stored in Eppendorf. These eppendorfs were kept in a water bath whose temperature was gradually raised until the formulation became visibly cloudy. The temperature at which cloudiness appeared was recorded. It indicates the stability of the optimized formulation at body temperature [34, 35].

Percentage transmittance

The formulations were diluted 1000 times using deionized water, and the percentage transmittance was recorded. Percentage transmittance is an important criterion in establishing the dilution and transparency of the formulation. This is significant because ultimately the formulation ends up in the gut lumen and drug precipitation must not occur in order to form a stable nanoemulsion [36, 37].

Robustness to dilution

The formulations were diluted several times with varying solvents, namely water, 0.1N HCl and phosphate buffer. These dilutions were subjected to stirring at 100 RPM for 24 h and observed for any physical signs of phase separation. If the drug is not solubilized properly in the lipidic phase, there is a high chance of precipitation. The solvent capacity of the oil phase decreases upon dilution. Therefore, to determine the stability of the system, dilution tests in various solvents are crucial [36, 38, 39].

Thermodynamic stability

The formulations were stored at-20 °C for 2 days in a freezer followed by 50 °C for 2 days in a hot air oven (Freeze-thaw cycles) and this cycle was repeated three times. At the end of the cycles, the formulations were physically examined for any signs of physical degradation [39–41].

Drug content determination

The percentage drug content should be uniform. One part of the formulation was diluted with 9 parts of methanol. This mixture was then centrifuged at RPM of 10,000 for a total of half an hour. The supernatant was diluted accordingly. The drug content was determined using a UV-vis Spectrophotometer [36, 42–44].

Dissolution studies

The drug loaded SNEDDS formulation and powdered form of Dasatinib, both equivalent to 10 mg of the drug were added into hard gelatin capsules (HGC) of size "00". These HGC were dropped in

900 ml of dissolution medium of pH 1.2 and 6.8 at 37±0.5 °C in USP type II (paddle) apparatus with 50 RPM. Aliquots of 1 ml were collected at predetermined time points, and fresh buffer media (1 ml) was incorporated after each sampling. Membrane filters were used for filtration of each sample. Drug release of Dasatinib SNEDDs was measured using UV spectrophotometrically at λmax 322 nm, after appropriate dilution with media against an equal amount of blank [36, 45, 46].

Bioanalytical method development for the quantification of dasatinib in wistar rat plasma and tissue homogenate

Using the protein precipitation method, dasatinib was extracted from the plasma or tissue homogenate of Wistar rats. In short, 5 µl of the corresponding standard calibration solution was added to 95 µl of blank plasma or tissue homogenate in a labeled tube. After vortexing each tube, 20 µl of the internal standard (Ketoconazole, 200 µg/ml) was added and mixed. Next, each sample was centrifuged for 10 min at 4 °C at 20,000 rpm. Following centrifugation, the supernatant was injected into autosampler vials and monitored at 321 nm for chromatographic analysis [47].

***In vivo* pharmacokinetics study**

In our study on the pharmacokinetics of dasatinib and dasatinib SNEDDS, we utilized wistar rats weighing 250±50g maintained at a temperature of 25±1 °C with access to water prior to the experiment. All institutional and national guidelines for the care and use of experimental animals were strictly followed. Prior to the commencement of the study, approval was obtained from the Institutional Animal Ethics Committee (IAEC/KMC/23/2022) of manipal academy of higher education. The handling and care of the animals were in accordance with institutional and national regulations. The study involved administering Dasatinib suspension and dasatinib SNEDDS to two groups of Wistar rats. The rats were given 10 mg/kg of dasatinib orally via gavage using the appropriate formulations. Blood samples (0.2 ml) were collected from the retro-orbital venous plexus at pre-determined time intervals following oral administration. The plasma was separated by centrifuging the blood samples for 10 min at 20,000×g RPM in a centrifuge set at 4 °C. Rat plasma concentrations were monitored concurrently using HPLC-UV technology [48, 49].

Statistics

A one-way ANOVA was used for the statistical analysis (GraphPad Prism 6.0). Tukey's post-hoc test revealed significant differences between the treatment groups; $p<0.05$ indicated statistical significance.

RESULTS AND DISCUSSION

Analytical method development for dasatinib

The method developed using UV-spectroscopy and HPLC showed high accuracy and precision. The developed methods were successfully applied to the analysis of dasatinib in SNEDDs formulations, yielding consistent and reliable results.

Solubility studies

The phase solubility studies were carried out by dissolving excess amounts of the drug in different oils, surfactants, and co-surfactants (table 1). The excipients that displayed a high amount of solubilization were selected for further studies which aligned with the study done previously [50, 51].

Table 1: Solubility of dasatinib in different excipients

S. No.	Name of excipient	Solubility of dasatinib (mg/ml) (mean±SD)*
1	Capryol 90	3.54±0.16
2	Capmul MCM	9.48±0.51
3	Lauroglycol FCC	0.566±0.08
4	Labrafil M1944cs	0.409±0.02
5	Castor oil	0.61±0.05
6	Tween 80	4.12±0.19
7	Triton X 100	8.87±0.32
8	triacetin	0.35±0.06
9	Tween 20	15.79±0.24
10	PEG 400	15.1±0.72
11	Cremophor EL	12.21±0.36
12	Acconon	11.167±0.55
13	Cinnamon Oil	5.89±0.31

*Each value is represented as mean±SD; n = 3.

Formulation of dasatinib loaded SNEDDS

Screening of surfactant and co-surfactant for emulsification ability

The excipients were selected based on the highest solubility of Dasatinib in them. Various combinations of oils and surfactant/co-surfactant (Smix) were selected at random from the ones showing high solubility to determine the best composition. 27 different ratios were made for each composition and subjected to water dilution to determine emulsification ability as shown in table 2.

The oil that was able to achieve nanoemulsification with the help of surfactant was Capmul MCM. Capmul MCM exhibited transparency upon dilution with two Smix combinations, Tween 80 and Acconon MC8 and with Tween 20 and Cremophor EL; Composition 4 and Composition 5 respectively. These were the compositions that were chosen for further studies and for plotting pseudo-ternary phase diagrams. The SNEDDS formulation was created with the oil Capmul MCM, the co-surfactant Tween 80 or Tween 20, and the surfactant Acconon MC8 or Cremophor EL in conjunction with earlier research [52, 53].

Table 2: Screening of various compositions (27 different ratio) for nanoemulsification ability

Composition number	Formulation	Composition	Nano emulsion
1	F1 to F27	Cinnamon oil, Tween 80, PEG 400	No
2	F28 to F54	Cinnamon oil, Capmul MCM, PEG400	No
3	F55 to F81	Capmul MCM, Tween 80, PEG 400	No
4	F82 to F108	Capmul MCM, Tween 80, Acconon MC8	Yes
5	F109 to F135	Capmul MCM, Cremophor EL, Tween 20	Yes
6	F136 to F162	Capmul MCM, Cremophor EL, Labrafil 1944CS	No
7	F163 to F189	Capmul MCM, Cremophor EL, Tween 80	No
8	F190 to F216	Cinnamon Oil, Capmul MCM, Tween 80	No

Plotting of pseudo ternary phase diagram

Pseudo ternary phase diagram was plotted shown in fig. 1 and 2 to determine a range of Capmul MCM, Cremophor El, Tween 20 and Capmul MCM, Acconon MC8 and Tween 80 required for the formation of nanoemulsion when loaded with Dasatinib respectively. The boundary ratios for the formation of nanoemulsion can be narrowed by using this diagram. In composition 4 (table 3), Acconon MC8 and Tween 80 were mixed in the ratios 1:1, 1:2 and 2:1 to prepare the Smix. Similarly, in Composition 5 (table 4), Tween 20 and Cremophor EL were taken in 1:1, 1:2, and 2:1 ratio to prepare Smix.

Numerous formulations were prepared with compositions 4 and 5 in which Capmul MCM was added ranging from 10% to 90%. These formulations were then subjected to a water titration method on which distilled water was added to each formulation in 5µl* amounts until a transparent solution was obtained. The percentage of water, Smix and oil was then calculated. These values for percentage were fed into the CHEMIX software to construct the pseudo-ternary phase diagram [54, 55].

The coloured areas in the diagrams indicate nanoemulsification region. The Smix ratio diagram showing largest Nanoemulsification area, or the coloured region was selected. In the case of composition 4, Smix ratio 1:2 was selected and in the case of Composition 5, Smix ratio 2:1 was selected.

Globule size and PDI determination

The ratios that fell between the nanoemulsification region in the pseudo ternary phase diagram were prepared for Composition 4 and Composition 5 without the drug depicted in table 5. They were diluted 100 times with distilled water and their size and PDI were checked to further narrow down the optimized ratio. The research has noted that droplet sizes in SNEDD devices range from 20 to 200 nm. The PDI value for self-nanoemulsifying systems should be less than 0.4 [52, 56].

Table 3: Water titration recordings for composition 4 (Oil-Capmul MCM, Smix-acconon MC8 and tween 80)

Smix ratio	%Oil	%Smix	% Water
1:1	26.19	56.93	16.88
	35.92	50.19	13.89
	45.01	41.93	13.06
	53.68	33.34	12.98
	61.71	24.64	13.64
	68.37	15.92	15.7
	75.85	7.85	16.3
1:2	27.23	59.6	13.17
	35.19	49.5	15.31
	46.92	44.01	9.07
	55.98	35	9.02
	63.23	25.42	11.36
	69.45	16.28	14.27
	77.71	8.1	14.19
2:1	36.04	50.02	13.94
	44.37	41.04	14.59
	54.28	33.47	12.25
	63.45	25.16	11.39
	69.6	16.1	14.3
	78.45	8.06	13.49

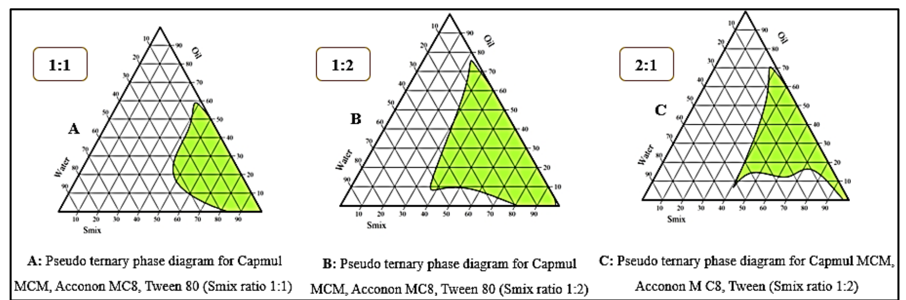

Fig. 1: Pseudo ternary phase diagram of composition (Capmul MCM, Cremophor El, Tween 20)

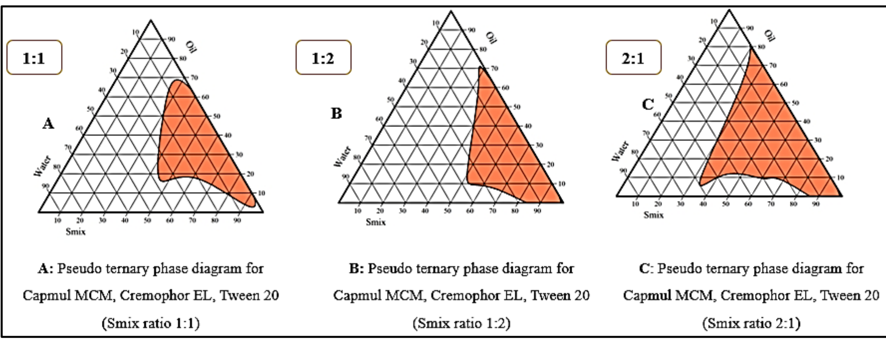

Fig. 2: Pseudo ternary phase diagram of composition (Capmul MCM, Acconon MC8 and tween 80)

Table 4: Water titration recording for composition 5 (Oil-capmul MCM, Surfactant-cremophor EL, Co surfactant-tween 20)

Smix ratio	% Oil	% Smix	% Water
1:1	37.58	44.25	18.17
	44.46	34.9	20.64
	54.18	28.35	17.47
	63.09	21.22	15.69
	71.34	14	14.66
	80.8	7.05	12.15
1:2	38.3	46.89	14.81
	49.76	40.62	9.62
	59.77	32.52	7.71
	67.21	23.51	9.28
	75.48	15.4	9.12
	83.46	7.57	8.97
2:1	32.46	57.07	10.46
	42.16	47.65	10.19
	51.88	39.09	9.03
	60.7	30.49	8.81
	71.13	22.97	5.9
	75	14.13	10.88
	82.46	6.9	10.63

Table 5: Globule size and PDI of various ratios of composition 4 (Capmul MCM, Acconon MC8, Tween 80) and composition 5 (Capmul MCM, cremophor EL, Tween 20)

Composition 4 (Smixratio 1:2)	Oil: Smix ratio	Globule size (nm)*	PDI*
F91	1:9	450.12±0.36	0.326±0.04
F92	2:8	480.09±0.96	0.219±0.07
F93	3:7	500.00±0.24	0.428±0.09
F94	4:6	520.3±0.86	0.684±0.05
F95	5:5	525.00±0.55	0.344±0.04
F96	6:4	622.00±0.76	0.612±0.01
Composition 5 (Smix ratio 2:1)	Oil: Smix ratio	Globule Size (nm)	PDI
F127	1:9	35.00±0.68	0.284±0.11
F128	2:8	57.88±0.51	0.541±0.32
F129	3:7	74.07±0.63	0.311±0.03
F130	4:6	74.56±0.48	0.344±0.13
F131	5:5	145.5±0.37	0.315±0.04
F132	6:4	259.7±0.14	0.412±0.09

*Each experiment is performed in Triplicates; values are expressed as mean±SD.

Based on the globule size and PDI analysis, it was clear that Composition 4 showed a higher size of globules and was an unsuitable choice for further studies. Composition 5 showed globule sizes mostly within 200 nm and hence was selected. It can also be seen from the above-stated test results that the 5:5 Oil: Smix ratio is the last ratio to be less than 200 nm. As regulatory authorities do not permit more than 60% usage of surfactants in oral formulations, the two ratios that were selected for drug loading were 4:6 (F130) and 5:5 (F131) of Composition 5 i. e., Capmul MCM, Tween 20 and Cremophor EL.

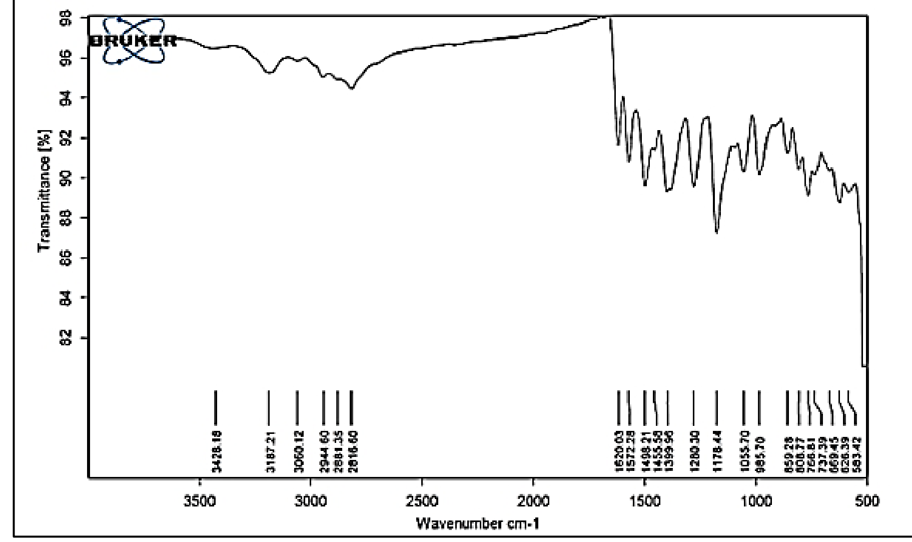

Fig. 3: IR spectrum of dasatinib

Drug excipient compatibility tests

ATR FTIR was performed on the Dasatinib (fig. 3), Dasatinib-loaded samples of Oil: Smix ratio of 4:6 (F130) and 5:5 (F131) and placebo samples (fig. 4). The IR spectrum showed that there were significant changes and shifts in the peaks observed in the pure drug spectrum and the drug-loaded SNEDDS spectrum of F130 and F131. This can be attributed to the fact that the drug, Dasatinib, has been completely solubilized in the lipid phase and will not precipitate out when diluted with water. It was also noted that there was no interaction between drug and excipient as the peaks of placebo SNEDDS and drug-loaded SNEDDS do not show a significant change or shifts in both formulations. Certain functional groups that are characteristic of the drug were seen in the IR spectrum of both F130 and F131 formulations as described in table 6, and not in the blank formulations, further confirming the presence of Dasatinib [19, 57].

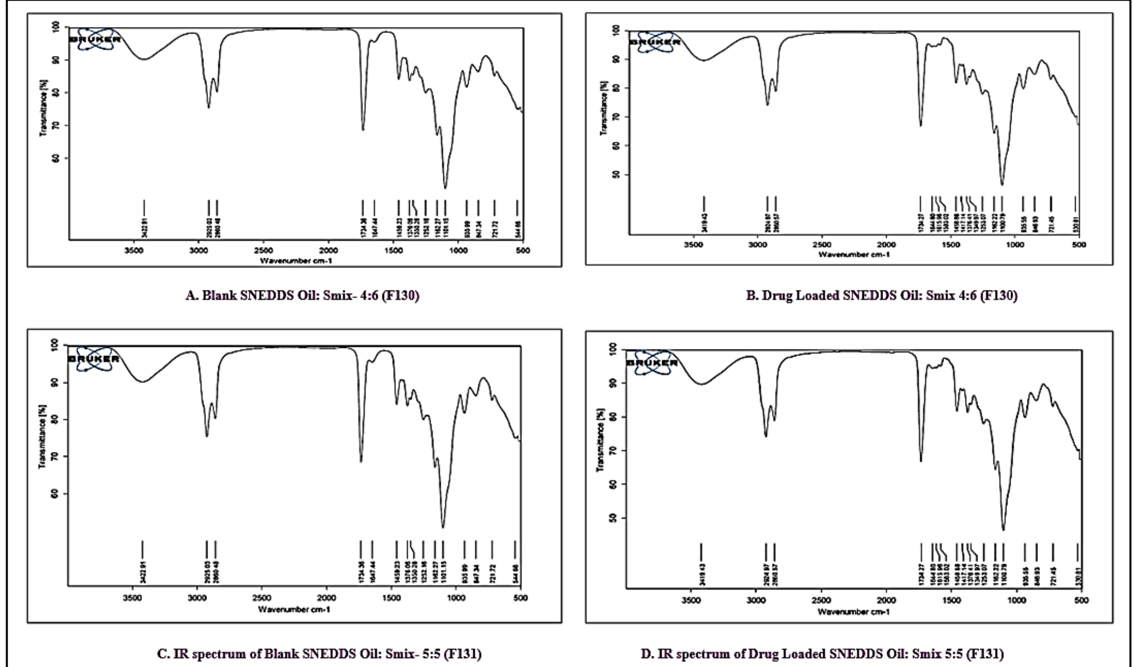

Fig. 4: IR spectrum of A. Blank SNEDDS Oil: Smix-4:6 (F130); B. Drug loaded SNEDDS Oil: Smix 4:6 (F130); C: IR spectrum of blank SNEDDS Oil: Smix-5:5 (F131); D. Drug loaded SNEDDS oil: Smix 5:5 (F131)

Table 6: FTIR characteristics peaks in dasatinib and SNEDDS

Functional groups	IR frequencies of pure drug (cm^{-1})	IR frequencies of drug loaded SNEDDS (cm^{-1})
C=O	1620	1615.96
CH=CH	1582	1583
C-H, CH=CH	1456	1417

Globule size and zeta potential

The optimized SNEDDS formulation F130 had a globule size of 83.52 nm and a zeta potential of 31.6mV. The formulation F131 had a globule size of 201.5 nm and a zeta potential of 36.5mV. Both formulations F130 and F131 have a zeta potential above 30mV which is essential for maintaining the stability of nanoemulsion. The electrostatic repulsion experienced by the particles in the formulation is well within the required range to achieve a stable system. However, the globule size of F131 was significantly higher than F130 [56].

Cloud point measurement

Cloud Point gives an idea about the effect of temperature on the formulation and its phase behaviour. The impact of temperature is one of the more critical parameters to be evaluated when developing nanoemulsions. It is the temperature above which the formulation does not remain transparent. An ideal formulation is supposed to retain the single-phase clarity at storage temperature and at the temperature it is to be used in. Phase separation is a common phenomenon at high temperatures due to reduction in solubilization capacity of surfactant. In case of SNEDDS, the cloud point should be greater than 37 °C as that is the body temperature and the formulation must remain stable in a single phase in the body [58]. The formulations F130 and F131 did not turn cloudy upon heating up to 95 °C hence it was concluded that both the formulations would remain stable at body temperature.

Percentage transmittance

The percentage of F130 and F131 was measured at 325 nm with UV spectrophotometer using purified water as blank. The results indicated that the percentage transmittance of F130 was 95% and of F131 was 90%. These results indicate that the nanoemulsion formed had high clarity which is a significant criterion for nanoemulsion. This transparency can be attributed to the smaller globule size as bigger globules decrease the transparency and thereby the value of percentage transmittance [59]. These results indicated that the formulation contained nano globules in the SNEDDS solution.

Robustness to dilution

After diluting both SNEDDS formulations (F130 and F131) up to 1000 times in different dissolution media and storing for 24 h, the systems remained stable as represented in table 7. There was no physical evidence of phase separation or drug precipitation even after 24 h. This was a strong indicator that the formulations were stable. This demonstrated that both formulations could tolerate different dilution scenarios [60].

Table 6: Robustness to dilution test of F 130 and F 131

Buffer	Formulation 130				Formulation 131			
	50x	100x	250x	1000x	50x	100x	250x	1000x
Water	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable
0.1N HCl	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable
Phosphate Buffer	Stable	Stable	Stable	Stable	Stable	Stable	Stable	Stable

Thermodynamic stability

Both F130 and F131 were subjected to 3 consecutive freeze thaw cycles and were subsequently observed for phase separation or drug precipitation. No sign of phase separation or precipitation was observed hence it was clear that the formulation is resistant to deterioration under environmental stress.

Drug content determination

The drug content in F 130 and F 131 was determined using UV Spectrophotometer and was found to be 87.9% in F130 and 63.2% in F131. This confirmed that F130 had higher accuracy in dose formulation. Based on the results of globule size measurement, percentage transmittance, and drug content determination, it was noted that F130 was the more robust and optimized formulation and was selected for further studies [60].

Dissolution studies

In vitro release studies of F130 were carried out in 900 ml dissolution buffer using USP type II apparatus. The dissolution medium were pH 1.2 hydrochloric acid buffer and pH 6.8 phosphate buffer. The paddle speed was 50 RPM and temperature was 37°C throughout the study. The final formulation would be administered orally and hence the dissolution profile of the drug and optimized formulation was compared in two dissolution media. 0.1N HCl was used to mimic the condition in the stomach at pH1.2. Similarly, phosphate buffer was used to mimic the conditions in the intestine at pH 6.8. The comparative dissolution profile of pure drug and optimized SNEDDS formulation was calculated and presented in fig. 5 and 6 below. The in vitro release studies showed a higher amount of drug release from SNEDDS as compared to the pure drug in all dissolution media. The plausible explanation for this enhanced drug release could be the increased solubilization of drug in lipid phase [58]. The drug already exists in its solubilized state, thus bypassing the rate limiting step of dissolution.

In vivo pharmacokinetics study

An important factor that influences a drug's therapeutic effectiveness is its increased oral bioavailability. In a study using Wistar rats, the pharmacokinetic properties of Dasatinib suspension and SNEDDs formulation were investigated. After administering these samples orally, the plasma concentration of Dasatinib was measured over time to create concentration curves and determine related pharmacokinetic characteristics. The drug-time curve shown in fig. 7 and table 8 indicated that 2.5h after oral administration of Dasatinib suspension, the plasma exhibited a maximum concentration of 452.98±14.26ng/ml. However, in the Dasatinib SNEDDS formulation, the highest plasma concentration of Dasatinib at 10h was significantly greater (1089.92±42.71 ng/ml). When comparing the Dasatinib SNEDDS AUC (0–48h) to the Dasatinib suspension group, it was found to be 3.24 times higher. This finding showed that the Dasatinib SNEDDS significantly increased the rate of drug absorption. First, when the SNEDDS enter the human body, they can emulsify spontaneously into a tiny nanoemulsion in the GI tract during peristaltic movement. This significantly improves both GI and lymphatic drug absorption. Second, by inhibiting P-gp and increasing intestinal barrier permeability, the surfactant enhances medication absorption [52, 57].

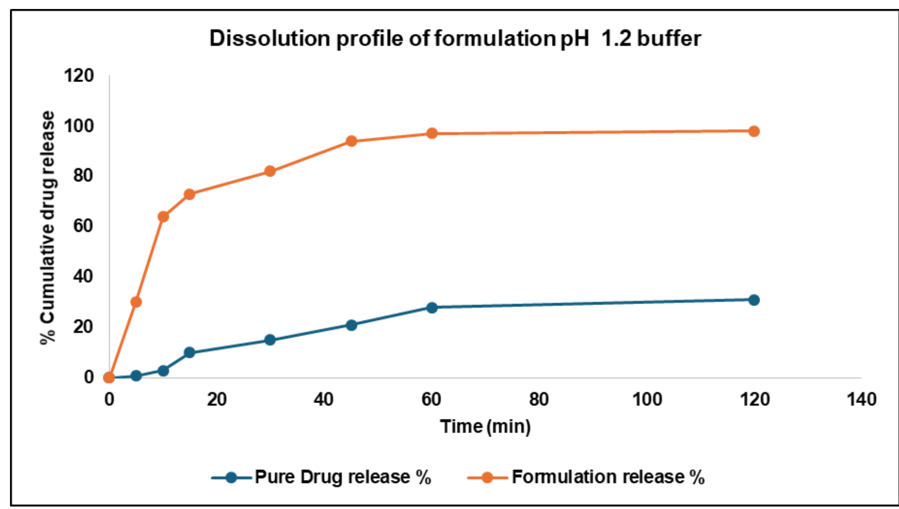

Fig. 5: Dissolution profile of F130 and pure drug in pH 1.2 acid buffer. Results are expressed as mean of triplicates

Table 7: Pharmacokinetic profile of dasatinib and dasatinib SNEDDs

PK parameters	Pure dasatinib	Dasatinib SNEDDs
C_{max} (ng/ml)	452.98±14.26	1089.92±42.71
T_{max} (h)	2.5±0.00	10±0.00
$AUMC_{0-48}$ (h)	2376.5±5.16	10430±140.72
AUC_{0-48} (h)	3698.535±62.1	12008.3±157.8
MRT (h)	6.428±1.83	11.64±0.84
K_{el} (ng/h)	0.202±0.00	0.143±0.0015
t½ (h)	3.414±1.28	4.838±0.05

*Each experiment is performed in triplicates; value sareexpressed as mean±SD; AUC=area under the curve; t1/2=elimination half-life; K_{el}=elimination rate constant, MRT=mean residential time

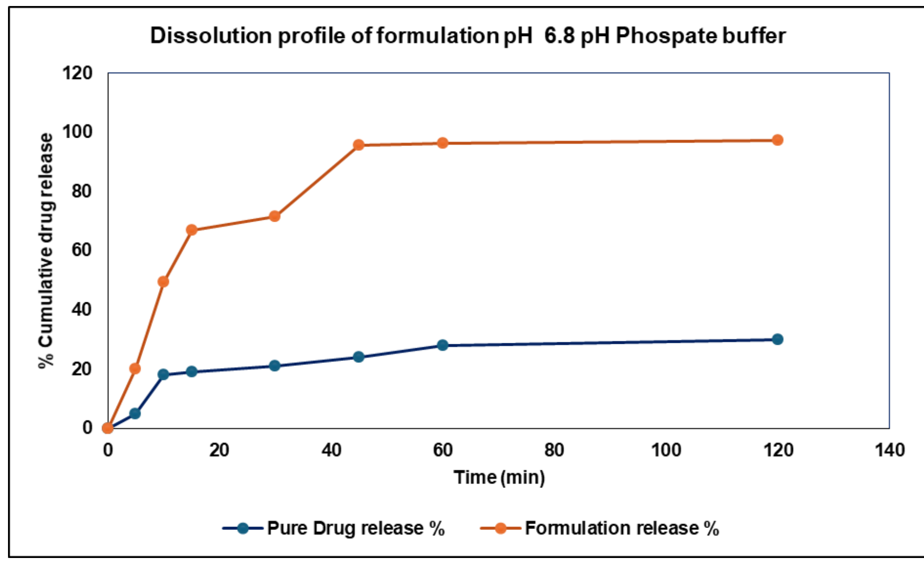

Fig. 6: Dissolution profile of F 130 and pure drug in pH 6.8 phosphate buffer. Results are expressed as mean of triplicates

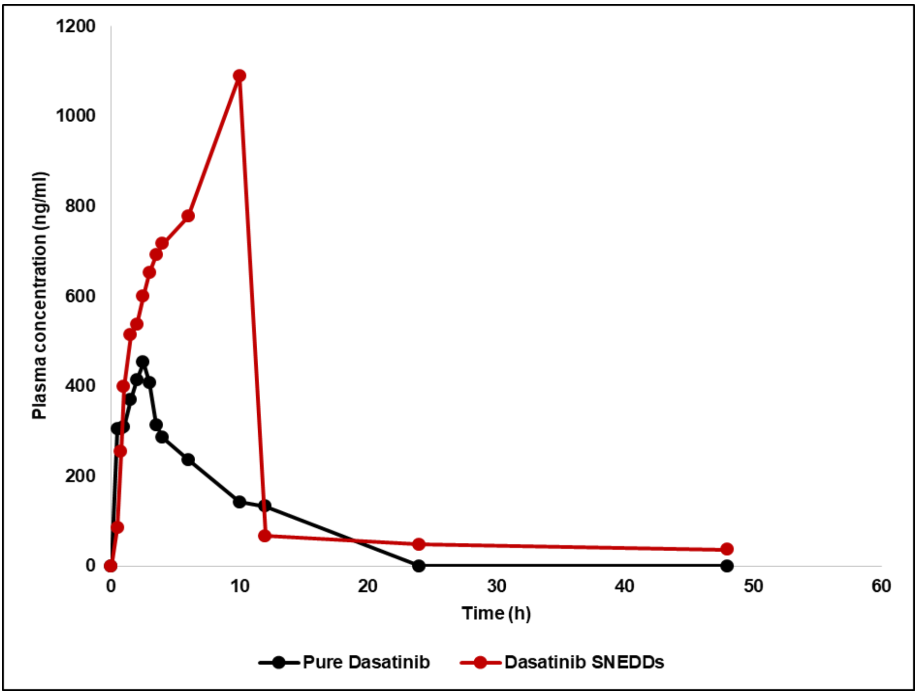

Fig. 7: *In vivo* pharmacokinetic plasma concentration vs. time profile of Dasatinib vs. Dasatinib SNEEDs, results are expressed as mean of triplicates

CONCLUSION

The SNEDDS formulation exhibited a much higher solubility and dissolution profile of Dasatinib when the formulation was diluted up to 99% and was able to keep the drug solubilized in *in vitro* conditions. There was a 3.24-fold increase in the oral bioavailability of the drug when incorporated in the SNEDDS formulation as compared to the pure drug. It could be concluded from the results that Capmul MCM, Cremophor EL and Acconon MC8 can be further explored as potential vehicles so as to achieve higher drug loading, improvised dissolution profiles and enhanced bioavailability for the BCS Class II drug Dasatinib.

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AUTHORS CONTRIBUTIONS

Authors involved in Conceptualization-Dr. Mahalaxmi Rathnanand, Ms. Eesha Shukla, Ms. Pragathi Devanand Bangera; and Methodology-Mahalaxmi Rathnanand, Eesha Shukla, Pragathi Devanand Bangera, Divya Dhatri Kara, Mahesha Keerikkadu, Vamshi Krishna Tippavajhala; along with Validation-Mahalaxmi Rathnanand, Eesha Shukla, Pragathi Devanand Bangera; Resources-Mahalaxmi Rathnanand; The Writing —original draft preparation was

attributed to Eesha Shukla, Pragathi Devanand Bangera; after which Writing-review and editing was done by Mahalaxmi Rathnanand, Eesha Shukla, Pragathi Devanand Bangera, Rajeshwari roychowdhury; The was conducted under the Supervision of Dr. Mahalaxmi Rathnanand.

CONFLICT OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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