Nat. Volatiles & Essent. Oils, 2021; 8(6): 4978-4992

NVEO
Natural Volatiles &
Essential Oils

Solid Supersaturable-Snedds Of Ibrutinib: Development And Evaluation

K.Navaneetha[1*] , V.V.Basava Rao[2]

[1]Department of Pharmaceutics, Malla Reddy Pharmacy College, Maisammaguda, Secunderabad, Telangana, India

[2]University College of Technology, Osmania University, Hyderabad, Telangana, India

ABSTRACT

The aim of this study was to develop a solid supersaturable self-nanoemulsifying drug delivery system (S-SNEDDS) of ibrutinib for enhancement of its solubility and dissolution rate**.** Crossential O94– Croduret 40SS – Carbitolare chosen based on the maximum solubility of ibrutinib and were used to construct ternary phase diagrams and 15 Formulations with Smix in 3:1 ratio and 70mg drug loading were prepared and evaluated for various tests.Out of all formulation F15 exhibited good results with highest drug release of 98.25% in 60min. LSS9 with 3% HPMC E4M as best PPI exhibited smallest droplet size of 65.4nm, a zeta potential of -17.7mV, and a PDI of 0.453. SSS1 with magnesium trisilicate as an adsorbent showed best flow characteristics and highest drug content of 99.72%. The DSC, FT-IR and stability studies confirmed the complexation of ibrutinib and amorphous state of the drug and formulation to be stable for 3months.Thus, this study indicated that the solid SNEDDS could be used as a potential drug carrier for ibrutinib with improved solubility and dissolution rate.

Keywords: Ibrutinib, Solubility, L-SNEDDS, Precipitation inhibitor, Magnesium trisilicate.

INTRODUCTION

Self-nano emulsifying drug delivery system (SNEDDS) is one of the techniques which is gaining more attention for improving the solubility of the lipophilic drug. SNEDDS is an isotropic mixture of oil, surfactant, and co-surfactant which forms oil in water (o/w) nanoemulsion with slight agitation. Oil is selected based on their solubility capacity and both surfactant and co-surfactant is selected based on their emulsifying ability. To prevent the precipitation of the drug and to reduce the dosing frequency, suitable precipitation inhibitors can be used (maintains supersaturation state and blocks the formation and growth of the crystals). By introducing precipitation inhibitors into the formulation, the surfactant concentration can be minimized (reduce GI side effects). Hence, Supersaturable SNEDDS (S-SNEDDS) is an effective method for the oral delivery of poorly water-soluble drug, in order to improve its bioavailability (Reddy et al., 2021).

Ibrutinib is a selective and covalent inhibitor of the enzyme Bruton's tyrosine kinase (BTK), it is used for treatment of B-cell malignancies. It has been reported to exhibit pH-dependent solubility as it is

slightly soluble at pH 1.2 while practically insoluble at pH 3 to 8, which lead to low bioavailability and impede its in vivo antitumor effect after oral administration (Amin et a., 2014).
The present work described an innovative approach by designing a supersaturated solid-self-emulsifying formulation (S-SNEDDS) to improve the solubility and dissolution of a poorly soluble drug, ibrutinib.

METHODS

Determination of melting point

The open capillary tube method was used to determine the drug's melting point. (Vilegave Kailash. et al, 2013).

Solubility analysis

Apparent solubilities of ibrutinib were determined in different oils, surfactants and co-surfactants and ibrutinib was quantified by using UV spectrophotometry at 259 nm (Shantanu et al., 2012)

Ternary phase diagram

The chosen vehicles from the solubility studies were blended in different ratios ranging from 1:9 to 9:1. Each apex of the triangle was represented by a ternary phase diagram containing surfactant, co-surfactant, and oil. CHEMIX software is used to create a pseudo ternary phase diagram. (Jyothi et al., 2011)

Effect of Ibrutinib loading

The effect of Ibrutinib loading on transmittance, phase behaviour, and area of nanoemulsion formation on Crossential O94– Croduret 40SS – carbitol compositions with Smix in a 3:1 ratio was investigated.The transmittance of the resultant dispersions was measured using a UV spectrophotometer set to 610 (Date and Nagarsenker et al., 2007). By creating pseudo-ternary phase diagrams, the area of nanoemulsification region was found, as mentioned above. (Shiva Kumar Mantri et al., 2012).

Preparation and Evaluation of Ibrutinib liquid-SNEDDS (L-SNEDDS)

From a 70 mg loaded Ibrutinib system (which generated more nanoemulsification region based on drug loading), a series of SNEDDS (F1-F15, the composition was presented in Table 1)

Characterization of liquid SNEDDS

The prepared liquid SNEDDS were characterised for thermodynamic stability studies(Ujilestari T et al 2018), dispersibility test (Priyani et al., 2020), turbiditymeasurement, robustness to Dilution (Ping Z et al., 2008), percentage drug content (Grove et al., 2004), entrapment efficiency (Zhang et al., 2008), measurement of droplet size analysis and zeta potential and polydispersity index(Balakrishnan et al., 2009).

In Vitro Dissolution Study

The dialysis membrane was used to conduct in vitro release tests on produced ibrutinib SNEDDS. The release tests were performed in a USP XXIV dissolution device with 900 mL of 3.0% w/v Polysorbate 20 in 50 mM Phosphate Buffer, pH 6.8 as the dissolution medium. The speed of the equipment is

adjusted to 75 rpm, and the temperature is kept at 37 ±0.5°C. The amount of ibrutinib in each dissolution sample was measured spectrophotometrically at 259 nm, as stated in the literature. (Patel et al., 2020)

Preparation of liquid Supersaturable-SNEDDS (S-SNEDDS).

The liquid SNEDDS was anisotropic mixture of drug ibrutinib and SNEDDS preconcentrate [Crossential O94+ Croduret 40SS+ Carbitol](Dash et al 2015)(Table2). The formulations are designated as LSS1-LSS9 (LSS-Liquid supersaturable SNEDDS)

Screening for a precipitationinhibitor

To stabilize the supersaturated Ibrutinib solution, polymers such as HPMC 50-60, HPMC E4M, and PVP K25 were used in varied quantities (1, 3 and 5% w/w). A 100 mL sample of simulated gastric fluid (SGF) was kept at 37 °C with a 100-rpm stirring speed. In the medium, one gram of improved Ibrutinib SNEDDS formulation with different polymers was added. At 5, 15, 30, 45, 60, 90, 120, 180, and 240 minutes, one milliliter samples of the solution were obtained without volume replenishment, and the aliquots were centrifuged at 3000rpm for 3 minutes. The concentration of Ibrutinib was determined from supernatant using UV analysis at 259 nm. (Zhang, N, et al., 2016).

Characterization of liquid S-SNEDDS

Measurement of droplet size and zeta potential

In volumetric flasks, either S-SNEDDS (0.1 g) or liquid SNEDDS (0.1 g) were diluted to 50 ml with water (HPLC) and gently mixed by inverting the flask. Using a Zeta potential/Particle sizer, measurements were taken at 25°C.

Preparation of solid S-SNEDDS

Adsorption experiments were conducted to create solid S-SNEDDS using a commonly used porous adsorbent such as magnesium trisilicate, microcrystalline cellulose (MCC), Syloid 244FP and Florite RE. In a nutshell, 10 g of each optimised liquid S-SNEDDS was poured onto 15 g of adsorbents in a mortar and stirred for 5 minutes to form a homogeneous mass. A lubricant, talc (2 g), was added to the aforesaid material, gently mixed, and passed through a mesh (250-mm). Solid SNEDDS was created by adsorbing liquid SNEDDS onto the previously described excipients. S-SNEDDS powder (equal to 70 mg ibrutinib) was packed with size "1" firm gelatin capsules (Capsugel, Mumbai, India) and stored in glass bottles at 25°C until utilised in following tests (Subramanian et al., 2019).

Characterization of solid S-SNEDDS

Angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were used to analyse the micromeritic characteristics of solid S-SNEDDS **(**Durgacharan Arun Bhagwat et al., 2012)

In Vitro Dissolution Study

Dissolution tests were performed with a USP Type I Dissolution Apparatus (basket type) in 900 ml of 3.0% w/v Polysorbate 20 in 50 mM Phosphate Buffer, pH 6.8 at 37±0.5°C and 100 rpm paddle rotation. The dissolving medium was encapsulated with a formulation containing 70 mg of ibrutinib (equal to a single dose). To maintain a consistent volume, 5 ml of material was taken and replaced

with fresh dissolving medium (SGF) at specified time intervals. To determine the amount of medication released at each sampling point, the samples were spectrophotometrically examined at 259 nm. (Reddy et al., 2016)

CHARACTERIZATION OF FINAL OPTIMISED SOLID SUPERSATURABLE SNEDDS FORMULATION

FTIR studies

Identification of pure drug Ibrutinib and also, to verify the possibility of interaction of chemical bonds between drug and polymer was carried out using Infrared absorption spectroscopy.

Differential Scanning Calorimetry (DSC):

Pure ibrutinib drug and solid S- SNEDDS powder thermograms were acquired using DSC Q200 TA, Universal V 24.4 software, Bangalore, India, as described by Kaur et al., 2016.

Accelerated Stability Studies

Optimised formulation was packed in HDPE screw-capped bottles and stored for 3 months in humidity chambers maintained at 40 ± 2°C/ 75 ± 5% RH as per ICH recommendations for Zone III (Reddy et al., 2016).

RESULTS AND DISCUSSIONS

Melting point

Melting point of Ibrutinib was found to be in a range of 149-158°C complies with the standard reported value. The reported value is 155 °C.

Determination of Ibrutinib solubility in various excipients

Crossential O94oil was chosen as the oil phase due to its higher Ibrutinib solubilization (12.64±0.34 mg/ml) than other oils(Figure 1).

Croduret 40SS as surfactant and co-surfactant carbitol was chosen for future research because of its increased solubilizing capacity. (Taha et al., 2004) (figure 2 and 3).

Construction of Ternary Phase Diagrams

When compared to 1:1 and 2:1 Smix ratios (Fig. 4A and 4B), the Crossential O94– Croduret 40SS – Carbitol of 3:1 Smix system had a bigger nanoemulsification zone (Fig. 4C).

Effect of Ibrutinib loading

The use of Ibrutinib (70 mg, 140 mg, and 210 mg) resulted in a significant reduction in transmittance values (Figure 5A, 5B and 5C). Because the area of nano emulsification was significantly reduced as Ibrutinib loading was increased in the Crossential O94– Croduret 40SS – carbitol system with a 3:1 Smix ratio, a system containing 70 mg of Ibrutinib was chosen for the formulation of Ibrutinib SNEDDS and subsequent experiments.

Preparation and Evaluation of Ibrutinib SNEDDS

According to the above findings, a 3:1 oil: Smix ratio with 70mg loaded Ibrutinib drug produced SNEDDS with a transmittance greater than 90 and good stability.

Thermodynamic stability studies

L-SNEDDS was tested for centrifugation, heating-cooling cycle and freeze thaw cycles and passed the tests with no phase separation, creaming, or cracking.

Dispersibility and turbidity measurement

Almost all formulations swiftly created nanoemulsion (Grade A and B), and the turbidity of the diluted liquid SNEDDS ranged from 15.03-21.16 NTU, with F15 exhibiting the least.

Robustness to Dilution

Nano emulsions showed to be resistant to all dilutions and had no separation or drug precipitation after 24 hours of observation.

Percentage drug content and Entrapment efficiency

The drug content of all formulations ranged from 95.15±2.16 to 98.31±1.39%, with F15 having the highest value. The entrapment efficiency of all formulations ranges from 94.7±1.19 to 97.8±0.92%, with F15 having the highest value.

Droplet size, zetapotential and polydispersity index

The particle size of the SNEDDS was found to be between 74.5 ± 3.17 and 159.35 ± 1.47nm, and the polydispersity index was found to be between 0.578 ± 0.05and 0.756 ± 0.01.
The SNEDDS' Zeta Potential was determined to be between 20.0 ± 4.15 to -22.85 ± 4.61.

In Vitro Dissolution Tests

From figure 6, Ibrutinib SNEDDS was found to have a faster release rate than the pure drug. Ibrutinib SNEDDS F1-F15 released more than 60% of the drug in 30 minutes, compared to 31.92 percent in 60 minutes for pure drug. In 60 minutes, Formulation F15 had the greatest drug release rate of 98.25 percent. The drug release from the SNEDDS formulation increased proportionally with the increase in surfactant concentration, resulting in substantial drug release in F15.
Due to reduced turbidity values and faster drug release values among the other SNEDDS, ibrutinib SNEDDS formulation F15 was chosen as the optimal formulation

Preparation of liquid Supersaturable-SNEDDS (S-SNEDDS)

For the creation of supersaturable SNEDDS, F15 was used.

Screening of precipitation inhibitor (PPI)

The concentration of Ibrutinib in the blank L-SNEDDS formulation fell to about 255.5 µg/mL at t = 20 minutes, and then rapidly to about 185.59 µg/mL after 60 minutes due to precipitation. In comparison to the SNEDDS formulation, the supersaturable L-SNEDDS formulation had a consistently higher apparent Ibrutinib concentration-time profile. It is observed that the formulation LSS9 with L-SNEDDS+ HPMC E4M (2%) exhibited better release of 405.11 µg/ml in 60min while blank L=SNEDDS showed 185.59µg/ml at the end of 60min. (Fig 7, 8, and 9).

Droplet size, zeta potential and PDI

With the smallest droplet size of 65.4nm, a zeta potential of -17.7mV, and a PDI of 0.453, LSS9 outperformed the other nine supersaturable L-SNEDDS formulations.

Preparation of solid S-SNEDDS

LSS9 was found to have good release and the smallest particle size and zeta potential in concentration time profiles tests of supersaturable L-SNEDDS, and was considered to be used for future development of LSS9 to solid S-SNEDDS as indicated in table 3 below.

Evaluation of solid S-SNEDDS

Drug content and micromeritic properties solid S-SNEDDS

SSS1 with magnesium trisilicate as an adsorbent had the best flow characteristics and the highest drug content of 99.72 percent among the four formulations evaluated. (Table 4)

In-vitro dissolution of solid S-SNEDDS

The dissolution profile demonstrates that solid S-SNEDDS released the drug faster than pure drug, with a maximum drug release of 31.92 percent in 60 minutes. The S-SNEDDS (SSS1 = 99.67 ± 0.82 percent) performed better in terms of dissolution, with a greater mean dissolution rate, indicating rapid drug release from the solid S-SNEDDS(Craig et al., 1995)(fig 10)

CHARACTERIZATION OF OPTIMISED IBRUTINIB SOLID S-SNEDDS FORMULATION

FTIR

The FTIR spectrum of (figure 11) the pure drug ibrutinib had characteristic peaks at 835.21, 1120, 943.22 cm^{-1}, and the spectrum contained stretching vibrations of Ibrutinib C=O stretching vibration (1244.13 cm^{-1}), hydrocarbon stretching vibration of long fatty chain (2926.11 and 2858.60 cm^{-1}), and P–O stretching vibration (1112.96 cm^{-1}) one stretching vibration at 3396.76 cm^{-1} (Chen Z et al 2016). The compatibility study carried out by comparing FTIR spectra of pure drug, physical mixture and optimised formulation (Figure 11). The optimised formulation shows all principal peaks present in the FTIR of pure drug indicating the compatibility

Differential Scanning Calorimetry (DSC)

DSC thermogram of pure ibrutinib showed a prominent endothermic peak at 154 ^{o}C, whichindicates the presence of crystalline ibrutinib. The drug's endothermic peak was seen in the physical mixture of ibrutinib and magnesium trisilicate, but it was weaker. Over the whole temperature range investigated, no notable peaks for magnesium trisilicate were found. For solid S-SNEDDS, however, there was no typical peak of ibrutinib, indicating that the self-emulsifying components are capable of keeping the drug dissolved and/or limiting recrystallization. (Figure 12)

Stability studies

After 3 months of storage at accelerated settings of 40±2° C/75±5 percent RH, no major differences were noticed. (Table 5)

CONCLUSION

In summary, a novel supersaturable solid-SNEDDS formulation of ibrutinib was successfully designed by incorporation of HPMC E4M polymer as a precipitation inhibitor (LSS9). An optimized Solid supersaturable SEDDS containing ibrutinib was developed by using magnesium trisilicate as the insert reservoir (SSS1). The in vitro dissolution test under supersaturation condition clearly

demonstrated that HPMC E4M effectively suppressed the drug precipitation and maintained a metastable supersaturated state. Further, the FT-IR and DSC study of the final optimised formulation (SSS1) showed no interaction of porous carriers used with developed self-emulsifying system.In a nutshell, the supersaturable solid-SNEDDS formulation provides an effective approach to improve the solubility and dissolution of poorly water-soluble drug ibrutinib**.**

REFERENCES

1. Amin A and Ranjana HA: Bruton's tyrosine kinase inhibitors and their clinical potential in the treatment of B-cell malignancies: focus on ibrutinib. The rAdvHematol 2014; 5(4): 121–133.
2. Balakrishnan, P., Lee, B.J., Oh, D.H., Kim, J.O., Hong, M.J., Jee, J.P., Kim, J.A., Yoo, B.K., Woo, J.S., Yong, C.S., Choi, H.G. Enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS). Eur J Pharm Biopharm 2009: 72, 539-545
3. Chen Z, Zhai J, Liu X, Mao S, Zhang L, Rohani S, et al. Solubility measurement and correlation of the form an of ibrutinib in organic solvents from 278.15 to 323.15 K. J ChemThermodyn. 2016; 103:342–8.
4. Craig, D. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. International Journal of Pharmaceutics, 1995; 114(1), 103–110.
5. Dash, R. N., Mohammed, H., Humaira, T., & Reddy, A. V. Solid supersaturatable self-nanoemulsifying drug delivery systems for improved dissolution, absorption and pharmacodynamic effects of glipizide. Journal of Drug Delivery Science and Technology, 2015; 28, 28–36.
6. Date, A.A., Nagarsenker, M.S. Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int J Pharm 2007; 329, 166-172.
7. Durgacharan Arun Bhagwat. John Intru D' Souza. Formulation and evaluation of solid self-micro emulsifying drug delivery system using Aerosil 200 as solid carrier. International current pharmaceutical journal, 2012; 1(12): 414 – 419.
8. Grove, Müllertz A, Nielsen JL, Pedersen GP. Bioavailability of seocalcitol II: Development and characterisation of self-microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides. Eur J Pharm Sci 2004; 28:233-42.
9. Jyothi B Jeevana; K Sreelakshmi. Design and evaluation of self-nanoemulsifying drug delivery system of Flutamide. Journal of young pharmacists, 2011; Vol.3 (1): 4 -8.
10. Kaur, P., Garg, V., Gulati, M., Singh, S.K. Oral delivery of antidiabetic polypeptide-k: Journey so far and the road ahead. Curr. Drug Deliv. 2016; 13, 236-244
11. Patel PR, Patel KD and Mahajan A: Formulation and evaluation of novel self-nanoemulsifying drug delivery system of sumatriptan succinate. Int J Pharm Sci & Res 2020; 11(6): 2739-51.
12. Ping Z, Ying L, Nianping F, Jie X. Preparation and evaluation of self-microemulsifying drug delivery system of oridonin. Int J Pharm 2008; 355:269–76
13. Priani, S. E., Maulidina, S. S., Darusman, F., Purwanti, L., &Mulyanti, D. Development of self-nanoemulsifying drug delivery system for black seed oil (Nigella sativa L.). Journal of Physics: Conference Series, 2020; 1469, 012022.
14. Reddy BS, Harish G, Md. Ul-Haq F: Formulation and in-vitro Characterisation of Solid - Self Nanoemulsifying Drug Delivery System (S-SNEDDS) of Rilpivirine. Int J Pharm Sci Res 2016; 7(7): 3117-29.

15. Reddy, M. R., Mishra, K., & Suresh, R. Development and Validation of a Liquid Chromatographic Method for the Determination of Selected Anti-Cancer Drugs in Bulk and Pharmaceutical Formulations. International Journal of Pharma Research and Health Sciences, 2018; 6(1), 2303–2307.
16. Reddy, Muthadi& Gubbiyappa, Kumar. A comprehensive review on supersaturable self-nanoemulsifying drug delivery system. Asian Journal of Pharmaceutical and Clinical Research. 2021; 40-44. 10.
17. Shantanu Bandyopadhyay; O.P. Katare; Bhupinder Singh. Optimized self-nanoemulsifying systems of Ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides. Colloids and Surfaces B, Biointerfaces 100, 2012: 50-61.
18. Shiva Kumar Mantri, ShailajaPashikanti and K. V. Ramana Murthy, "Development and Characterization of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) of Atorvastatin Calcium", Current Drug Delivery 2012; 9: 182.
19. Singh, H., Nathani, S., Singh, N., Roy, P., Paul, S., Sohal, H. S., & Jain, S. K. Development and characterization of Solid-SNEDDS formulation of DHA using hydrophilic carrier with improved shelf life, oxidative stability and therapeutic activity. Journal of Drug Delivery Science and Technology, 2019; 10132
20. Subramanian, Poonguzhali& Rajnikanth, P. & Kumar, Manish &Kumarappan, Chidambaram. In-Vitro and In-Vivo Evaluation of Supersaturable Self-Nanoemulsifying Drug Delivery System (SNEDDS) of Dutasteride. Current Drug Delivery. 2019; 16. 10.2174
21. Taha, E. I., Al-Saidan, S., Samy, A. M., & Khan, M. A. Preparation and in vitro characterization of self-nanoemulsified drug delivery system (SNEDDS) of all-trans-retinol acetate. International Journal of Pharmaceutics, 2004; 285(1-2), 109–119.
22. Ujilestari T, Martien R, Ariyadi B, Dono ND, Zuprizal. Self-nanoemulsifying drug delivery system (SNEDDS) of Amomum compactum essential oil: Design, formulation, and characterization. J App Pharm Sci, 2018; 8(06): 014-021.
23. Vilegave, Kailash & Vidyasagar, Gali & Chandankar, Pratibha. Preformulation Studies of Pharmaceutical New Drug Molecule & Products: An Overview. 2013; 1.
24. Zhang P, Liu Y, Feng N, Xu J. Preparation and evaluation of self microemulsifying drug delivery system of oridonin. Int J Pharm 2008; 355:269-76.
25. Zhang, N, Xiao, Y., Liu, Y., Yang, S., Zhang, B., Wang, T., Jiang, D. Sorafenib and gadolinium co-loaded liposomes for drug delivery and MRI-guided HCC treatment. Colloids and Surfaces B: Biointerfaces, 2016; 141, 83–92.

TABLES

Table 1: Composition of Ibrutinib liquid-SNEDDS

S. No	Formulation code	Ibrutinib drug (mg)	Ratios of Oil: Smix	Oil (Crossential O94)	Smix 3:1	
					Surfactant (Croduret 40SS)	Co-surfactant (Carbitol)
1	F1	70	01:01	50	37.5	12.5
2	F2	70	01:02	33	49.5	16.5
3	F3	70	03:01	75	18.75	6.25
4	F4	70	02:01	66	24.75	8.25
5	F5	70	02:03	40	45	15
6	F6	70	05:02	71	21.3	7.1
7	F7	70	03:02	60	30	10
8	F8	70	03:04	42.6	42.6	14.8
9	F9	70	03:07	30	52.5	17.5
10	F10	70	08:03	72.7	20.25	6.75
11	F11	70	07:03	70	22.5	7.5
12	F12	70	05:03	62.5	28.12	9.3
13	F13	70	04:03	57.1	31.95	10.65
14	F14	70	02:05	28.5	53.25	17.75
15	F15	70	02:07	22.2	58.2	19.4

Table 2: Composition of supersaturable L-SNEDDS (LSS1-LSS9)

Formulation code	L-SNEDDS+PPI (%)
LSS1	L-SNEDDS+ PVP K25 (1%)
LSS2	L-SNEDDS+HPMC 50-60 (1%)
LSS3	L-SNEDDS+HPMC E4M (1%)
LSS4	L-SNEDDS+PVP K25 (2%)
LSS5	L-SNEDDS+ HPMC 50-60 (2%)
LSS6	L-SNEDDS+ HPMC E4M (2%)
LSS7	L-SNEDDS+ PVP K25 (3%)
LSS8	L-SNEDDS+ HPMC 50-60 (3%)
LSS9	L-SNEDDS+ HPMC E4M (3%)

Table 3: Composition of solid supersaturable SNEDDS (Solid S-SNEDDS) (SSS1-SSS4)

Formulation code	LSS9 (g)	Magnesium trisilicate (g)	MCC (g)	Syloid FPP (g)	Florite RE (g)	Talc (g)
SSS1	10	15	-	-	-	2
SSS2	10	-	15	-	-	2
SSS3	10	-	-	15	-	2
SSS4	10	-	-	-	15	2

Table 4: Drug content and micromeritic properties solid S-SNEDDS

Formulation code	BD (g/cc)	TD (g/cc)	Θ	CI	HR	Drug content (%)
SSS1	0.89±0.02	0.94±0.06	22˚.91±0.24	5.32±0.07	1.06±0.015	99.72±1.49
SSS2	0.82±0.04	0.88±0.04	23˚.93±0.42	6.8±0.092	1.07±0.072	99.02±0.59
SSS3	0.77±0.06	0.85±0.05	25˚.54±0.67	9.41±0.054	1.10±0.09	98.41±1.33
SSS4	0.83±0.07	0.91±0.08	24˚.91±0.82	8.79±0.02	1.10±0.023	98.77±1.28

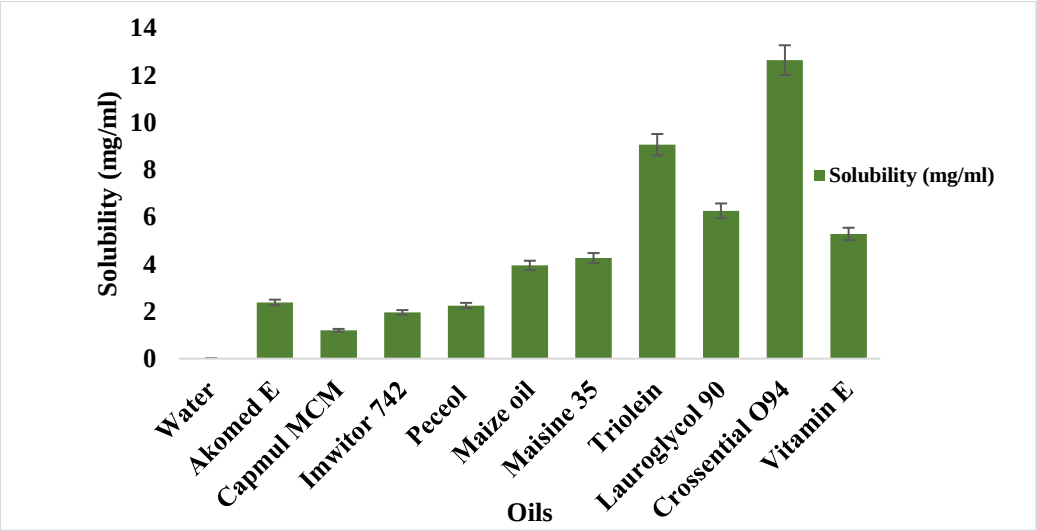
(All determinations were performed in triplicate and values were expressed as mean±S.D., n=3)

Table 5: Storage at 40±2° C/75±5% RH for 3 Months

Retest time for optimized formulation (SSS1)	% Drug content	In-vitro drug release (%)
0 days	99.72±1.49	99.67±0.82
30 days	99.40±0.51	99.25±0.91
60 days	99.04±1.28	99.02±0.34
90 days	98.74±1.83	98.68±0.42

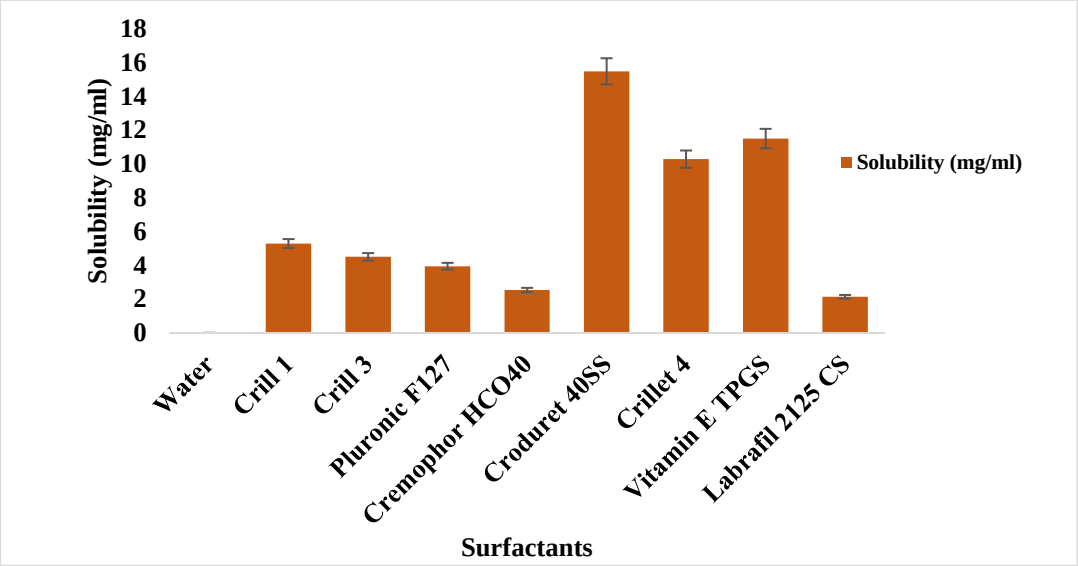
(All determinations were performed in triplicate and values were expressed as mean±S.D., n=3)

FIGURES



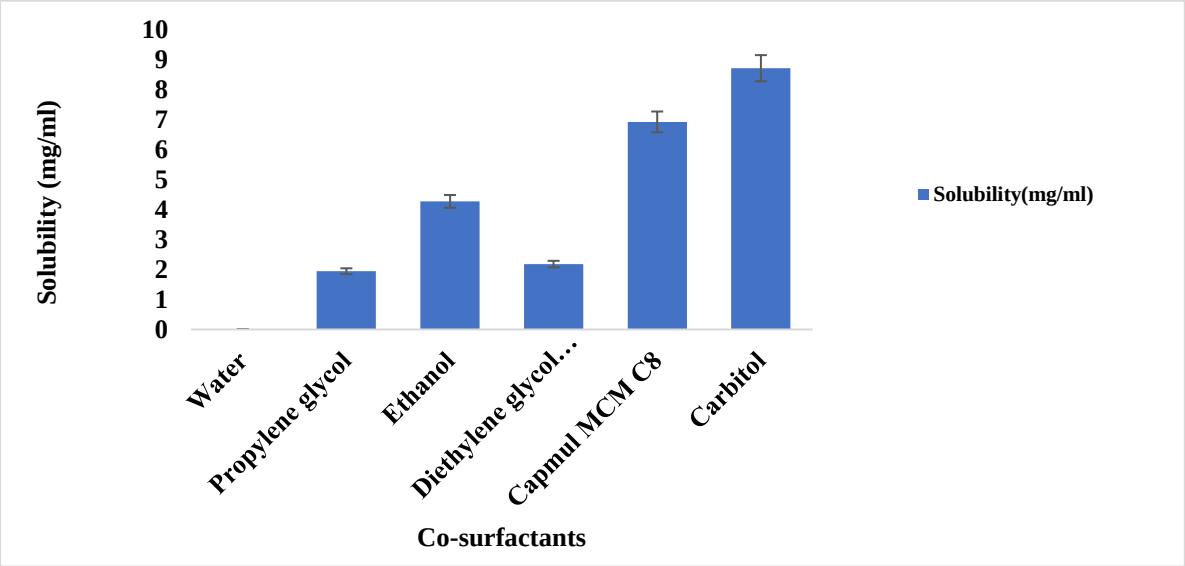
Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig 1: Solubility of Ibrutinib in various Oils



Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig 2: Solubility of Ibrutinib in various Surfactants



Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig 3: Solubility of Ibrutinib in various Co-Surfactants

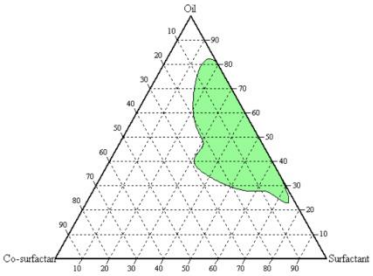


Fig. (4A).

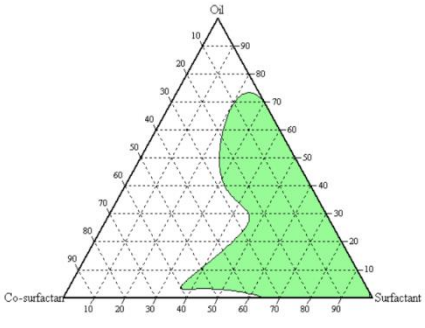


Fig. (4B).

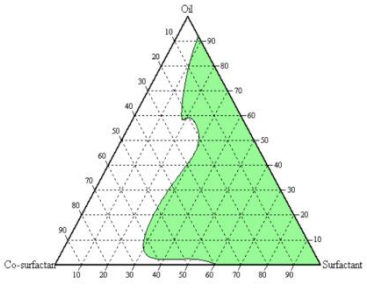
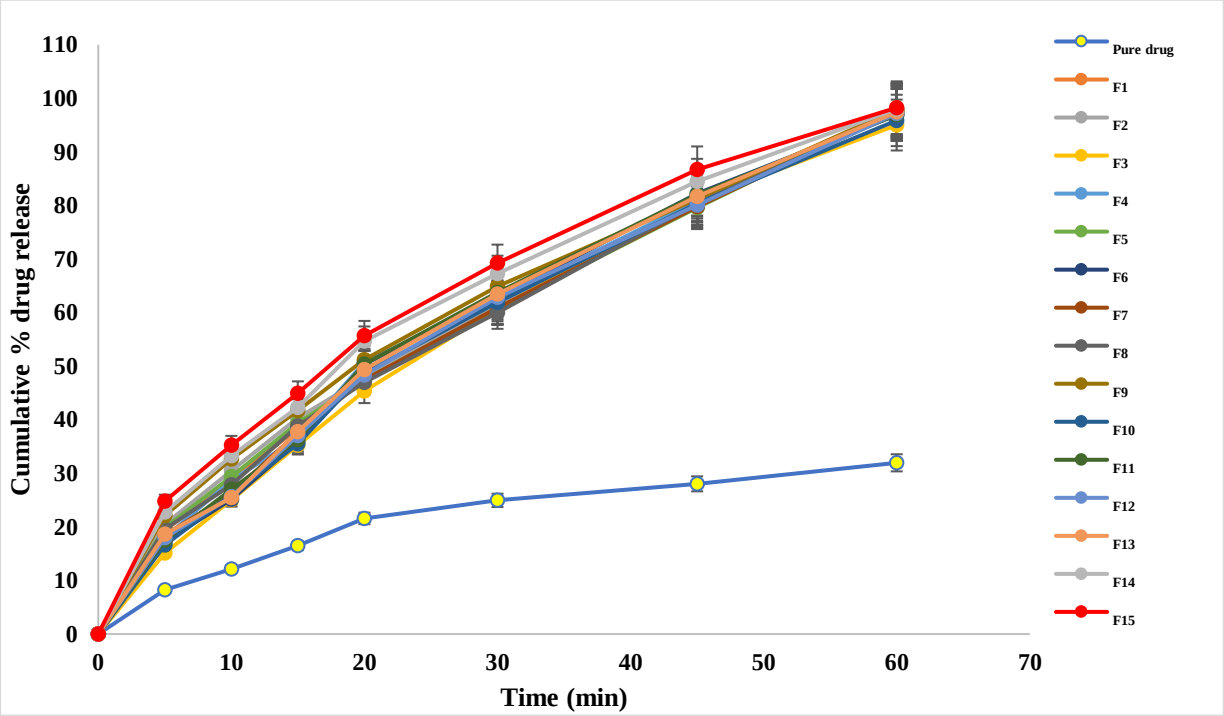


Fig. (4C).

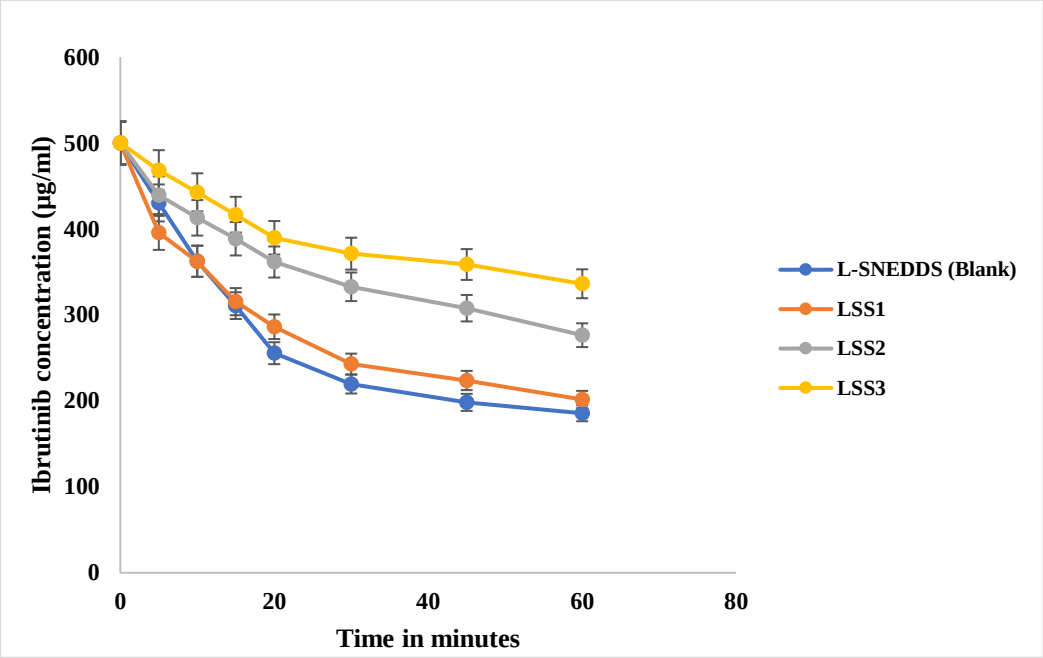
Fig 4: Ternary phase diagram for Crossential O94– Croduret 40SS – carbitol with (A)Smix in 1:1 (B) Smix in 2:1 (C) Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

Fig. (5). Ternary phase diagram for (7A) 70 mg (7B)140mg (7C) 210mg of Ibrutinib loaded in Crossential O94– Croduret 40SS – carbitol system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)



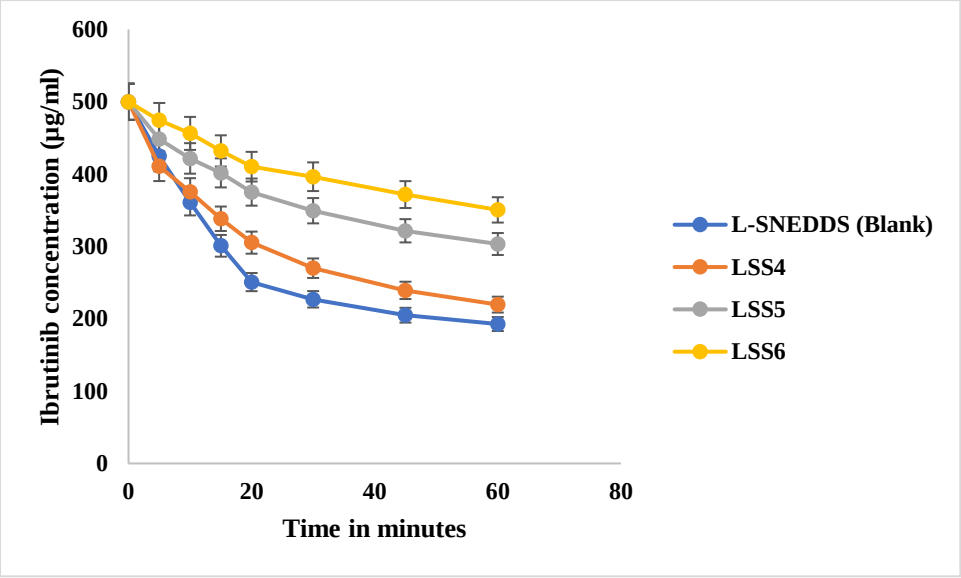
Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig 6: Comparative dissolution profile of Ibrutinib pure drug and Ibrutinib SNEDDS formulation (F1-F15)



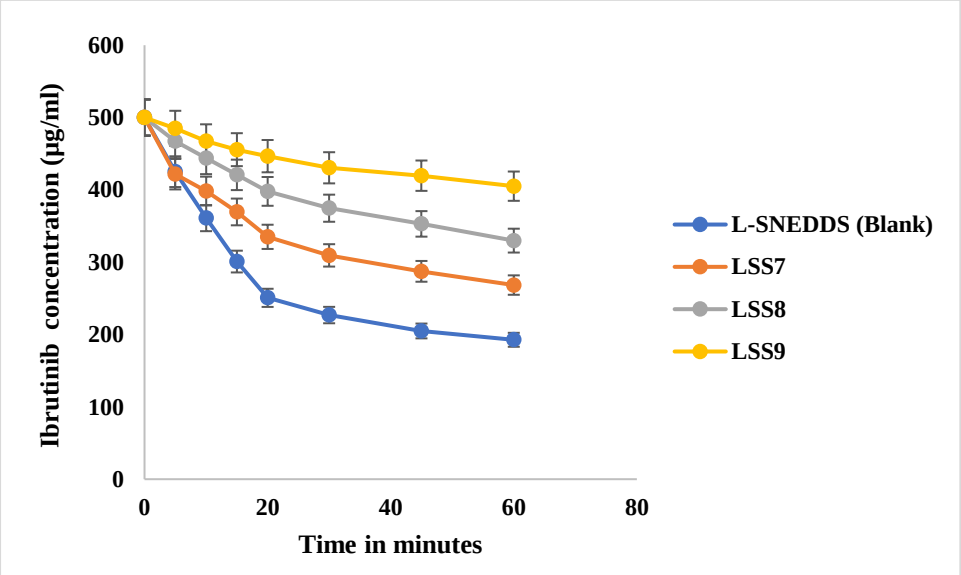
Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig 7: Invitro concentration release profiles of Ibrutinib from SNEDDS formulation without precipitation inhibitors and L-SNEDDS formulation containing different precipitation inhibitors (LSS1-LSS3)



Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig 8: Invitro concentration release profiles of Ibrutinib from SNEDDS formulation without precipitation inhibitors and L-SNEDDS formulation containing different precipitation inhibitors (LSS4-LSS6)



Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig 9: In vitro concentration release profiles of Ibrutinib from SNEDDS formulation without precipitation inhibitors and L-SNEDDS formulation containing different precipitation inhibitors (LSS7-LSS9)

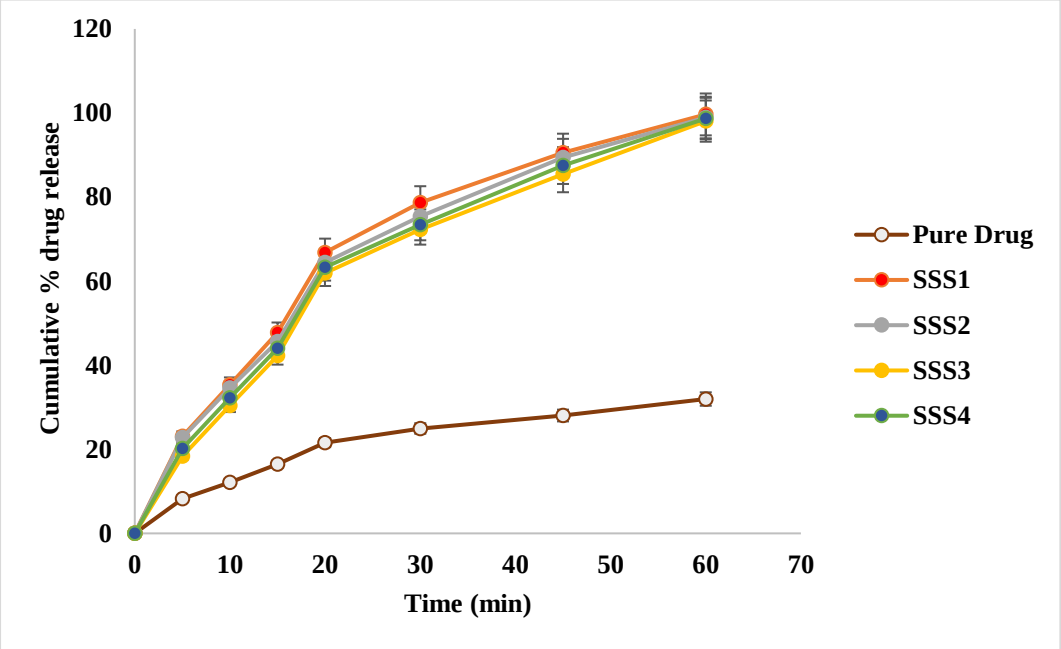


Fig 10: In-vitro dissolution of pure drug ibrutinib and ibrutinib solid S-SNEDDS (SSS1-SSS3)

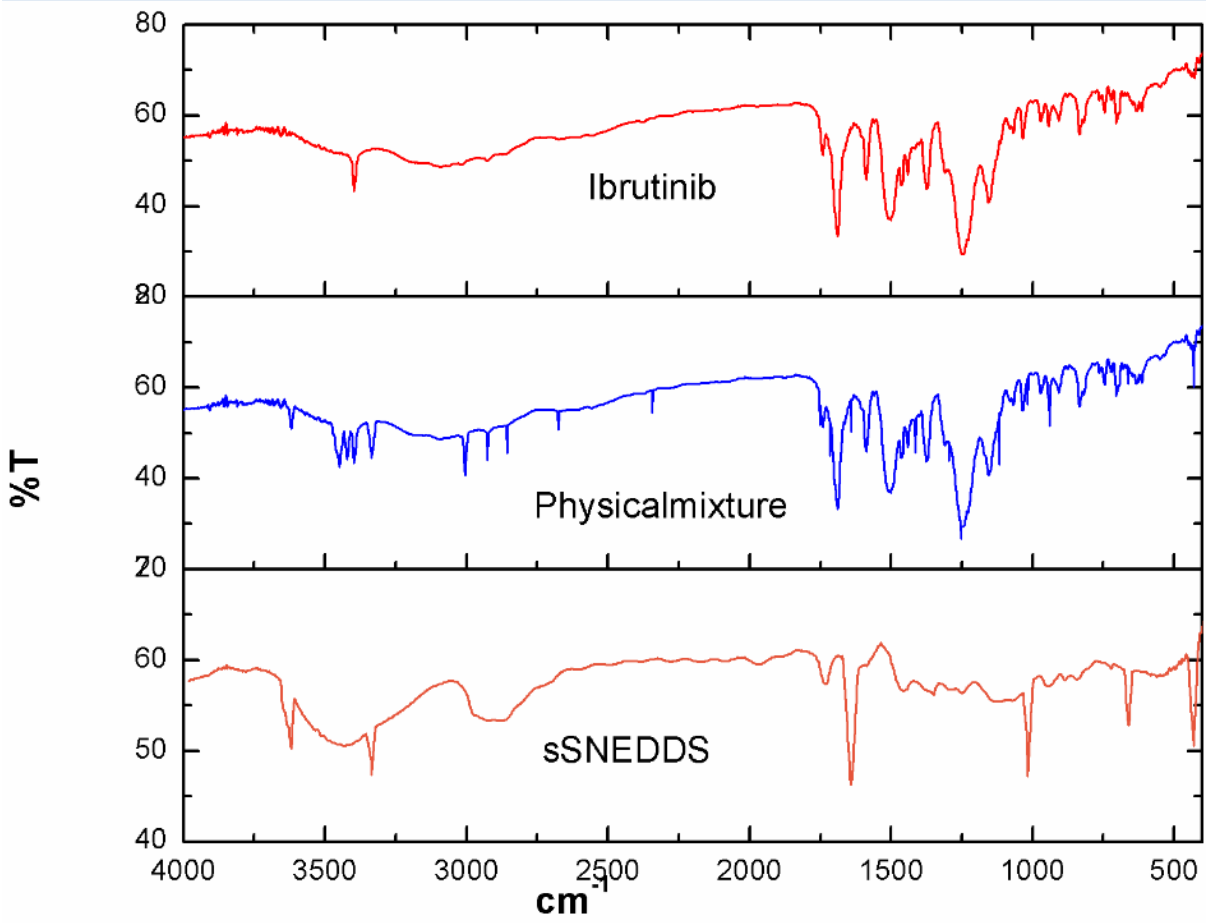


Fig 11: FTIR spectrum of ibrutinib pure drug, physical mixture and sSNEDDS (SSS1)

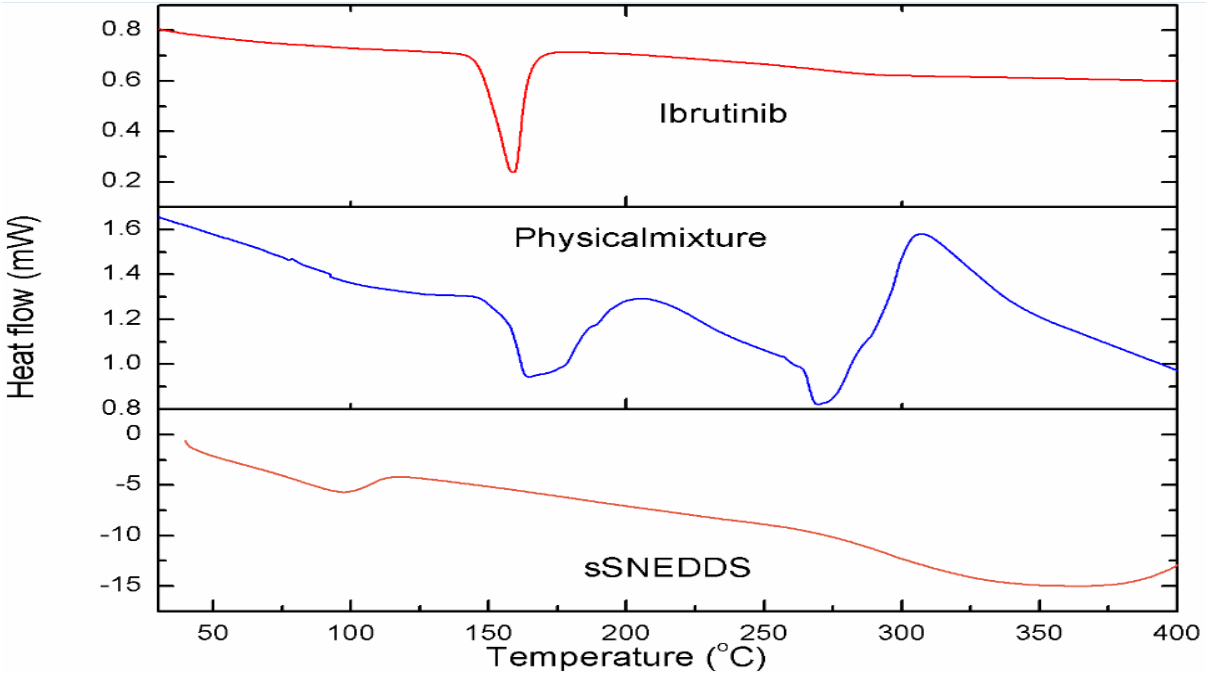


Fig 12: Differential Scanning Calorimetry (DSC) of ibrutinib and ibrutinib solid S-SNEDDS