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Original Article

FORMULATION AND EVALUATION OF SOLID-SUPERSATURABLE-SNEDDS OF IBRUTINIB

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ABSTRACT

Objective: The aim of current research is to develop a solid supersaturable self-nanoemulsifying drug delivery system (S-SNEDDS) of ibrutinib for enhancing the solubility and Bioavailability.

Methods: Crossential O 94–Croduret 40SS–carbitol are chosen based on the maximum solubility of ibrutinib and were used to construct ternary phase diagrams with S_{mix} in 3:1 ratio and 70 mg drug loading was done and evaluated for particle size, zeta potential, polydispersity index, entrapment efficiency, drug content and *in vitro* drug release. Final optimised one is characterised for FTIR, DSC, stability studies and in-vivo studies in rats. To choose a precipitation inhibitor, *in vitro* precipitation studies were carried out, and supersaturable SNEDDS were made the prepared formulations were evaluated for micromertitic properties and the final optimised one is characterized for FTIR, DSC, SEM and stability studies.

Results: Out of all formulations, F15 exhibited good results with the highest drug release of 98.25% in 60 min. LSS9 with 3% HPMC E4M as the best precipitation inhibitor (PPI) exhibited the smallest droplet size of 65.4 nm, a zeta potential of-17.7 mV, and a PDI of 0.453. SSS1 with magnesium trisilicate as an adsorbent showed best flow characteristics and the 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 3 mo. Cmax of the solid supersaturable SNEDDS 139.42±2.16 mg/l was significant ($p<0.05$) as compared to the pure drug suspension formulation 38.15±1.46 mg/l. Tmax of solid supersaturable SNEDDS formulation and pure drug suspension was 1.00±0.06 h and 1.50±0.02h, respectively. Statistically, AUC of the solid supersaturable SNEDDS formulation was significantly higher ($p<0.05$) as compared to pure drug suspension formulation.

Conclusion: Thus, this study indicated that the solid SNEDDS could be used as a potential drug carrier for ibrutinib with improved solubility and and bioavailability.

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

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INTRODUCTION

SNEDDS (self-nano emulsifying drug delivery system) is one method gaining attention due to its ability to increase the solubility of lipophilic agents. It is an isotropic mixture of oil (OL), surfactant (SF) and co-surfactant (CSF) that forms an oil-in-water nanoemulsion (o/w) with slight agitation. The choice of oil is determined by its solubility capacity and the selection of SF and CSF by their emulsification properties [1].

Solid SNEDDS provide an appealing alternative that can overcome most of SNEDDS' drawbacks while retaining all of its benefits. Changing SNEDDS to powder dosage form, by diverse solidification techniques, and subsequently to a solid oral dose form, such as a tablet, Capsules or pellets will provide the benefits of solid dose forms for example, improved patient acceptability, Stability, lower production costs, and repeatability with relation to the SNEDDS. Drug precipitation is the process by which a drug solute precipitates *in vivo* once the formulation's solubilization capability for the drug has been reduced. Supersaturable-solid SNEDDS are intended to reduce drug precipitation from Solid-SNEDDS in the gastrointestinal system. Supersaturable SSEDDS are thermodynamically stable compositions with a low surfactant content and a polymeric precipitation inhibitor. Precipitation inhibitors prevent drug precipitation by creating and sustaining a supersaturated condition *in vivo* after dilution with water [2].

The medication ibrutinib was recently licenced for the treatment of chronic lymphocytic leukaemia as a covalent inhibitor of Bruton's tyrosine kinase (BTK). This drug has been reported to have limited oral bioavailability and a wide range of first-pass effects, is pH-dependent in its solubility and is classified under BCS class II, with low solubility [3].

Thus, the present work is aimed at formulating ibrutinib supersaturable solid SNEDDS to perk up the solubility and dissolution of Ibrutinib, which is a poorly soluble drug.

MATERIALS AND METHODS

Materials used

Ibrutinib was a kind gift sample from Hetero. All the formulation excipients were purchased from Gattefosse, Mumbai.

Determination of melting point

The open capillary tube method was used to determine the drug's melting point [4].

Solubility analysis

In order to resolve the apparent solubilities of ibrutinib in various OL, SF, and CSF, spectrophotometrically at 259 nm was performed [4].

Ternary phase diagram (TPD)

The chosen vehicles from the solubility studies were blended in altered ratios that range from 1:9 to 9:1. Each apex of the triangle was represented by a TPD containing SF, CSF, and OL. CHEMIX software is used to create a pseudo ternary phase diagram [5].

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 S_{mix} in a 3:1 ratio was investigated. The transmittance of the resultant dispersions was measured using a UV spectrophotometer set to 610 nm [6]. By creating TPD, the area of nano emulsification region was found, as mentioned above [7].

Ibrutinib liquid SNEDDS preparation and evaluation

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

Table 1: Composition of Ibrutinib liquid-SNEDDS

S. No.	Formulation code	Ibrutinib drug (mg)	Ratios of oil: S_{mix}	Oil (Crossential O94)	S_{mix} 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

Characterization of liquid SNEDDS (L-SNEDDS)

The prepared L-SNEDDS were characterised for thermodynamic stability studies [8], dispersibility test [9], turbidity measurement, robustness to dilution [10], percentage drug content [11], entrapment efficiency [11], measurement of droplet size analysis and zeta potential and polydispersity index [12].

***In vitro* dissolution study**

The dialysis membrane was used to conduct *in vitro* release tests on produced ibrutinib SNEDDS. The release tests were conducted in USP XXIV dissolution device with 900 ml of 3.0% w/v Polysorbate 20 in 50 mmol phosphate buffer, pH 6.8 as the dissolution medium. The speed of the equipment is adjusted to 75 rpm, at 37±0.5 °C. The amount of ibrutinib in each dissolution sample was measured spectrophotometrically at 259 nm, as stated in the literature [13].

Preparation of liquid supersaturable-SNEDDS (S-SNEDDS)

The liquid SNEDDS was anisotropic mixture of drug ibrutinib, and SNEDDS preconcentrate [Crossential O94+Croduret 40SS+carbitol] (table 2). The formulations are designated as LSS1-LSS9 (LSS-Liquid supersaturable SNEDDS) [14].

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%)

Screening for a precipitation inhibitor

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). As part of the study, a 100 ml sample of simulated gastric fluid (SGF) was kept at 37 °C with 100 rpm stirring. To the medium, 1 gram of improved Ibrutinib SNEDDS formulation based on different polymers was added. At 5, 15, 30, 45, 60, 90, 120, 180, and 240 min, one-milliliter samples of the solution were obtained without volume replenishment, and the aliquots were centrifuged at 3000rpm for 3 min. The concentration of Ibrutinib was determined from supernatant using UV analysis at 259 nm [15].

Liquid S-SNEDDS characterization

A volumetric flask was filled with either S-SNEDDS (0.01 g) or L-SNEDDS (0.01 g) and diluted to a concentration of 50 ml with water (HPLC) using an inverted flask method. We measured the zeta potential/particle sizer at 25 °C using zeta potential/particle sizer.

Formulation 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, 1000 mg of each optimised liquid S-SNEDDS was decanted onto 1500 mg of adsorbents in a mortar and stirred for 5 min to form a homogeneous heap. A lubricant and talc (2000 mg), were added to the aforesaid material, gently mixed, and sieved through a mesh (250-mm). S-SNEDDS was created by adsorbing L-SNEDDS onto the previously described excipients. S-SNEDDS powder (equal to 70 mg ibrutinib) was packed with size "1" firm gelatin capsules and stored in glass bottles at 25 °C until utilised in the following tests [16].

Characterization of solid S-SNEDDS

Angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were used to analyse the micrometric characteristics of solid S-SNEDDS**.**

***In vitro* drug dissolution**

The dissolution tests carried out in 900 ml of polysorbate 20 in 50 mmol phosphate buffer, pH 6.8 and 100 rpm with an USP Type I dissolution apparatus (basket type). 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 quantity of medication released at every sampling point, samples were spectrophotometrically examined at 259 nm [17].

Characterization of final optimised solid S-SNEDDS formulation

Final optimised solid S-SNEDDS formulation was characterised for FTIR studies, Differential scanning calorimetry (DSC) [18].

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 acquired (DSC Q200 TA, Universal V 24.4 software, Bangalore, India) as described by Kaur *et al.* [18]

Accelerated stability studies

Optimised formulation was packed in HDPE screw-cap bottle and stored for 3 mo at 40±2 °C/75±5% RH as per ICH recommendations for Zone III [19].

Animal preparation

The bioavailability study was carried out in Himalayan rabbits (male) weighing between 1.25 and 1.50 kg. Animals were maintained at room

temperature 25°C, RH 45%, and 12 h alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. An in vivo pharmacokinetic study was conducted in accordance with the ethical guidelines for investigations in laboratory animals and approved by the Institutional Animal Ethics Committee.

The animals were divided into three groups of six animals each (group A, group B and group C). The Group A fed with pure drug ibrutinib with equivalent dose to animal body weight (8.75mg) and Group B rabbits were fed with ibrutinib SS-SNEDDS optimized formulation and with equivalent dose to animal body weight (8.75mg) while Group C was kept as control. After administration 0.2 ml blood samples were collected from the marginal ear vein at time zero (pre-dosing) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 9.0, 12, and 24 h of post-dosing and transferred to 2-ml eppendorf tubes containing sodium citrate as an anticoagulant. Blood samples were centrifuged at 6000 rpm for 15 min and the supernatant plasma were transferred to 1.5-ml eppendorf tube and kept at -20°C until analyzed [20].

HPLC Instrumentation & Conditions: The HPLC system employed was HPLC with Empower 2 Software with Isocratic with UV-Visible Detector. Optimized Chromatographic Conditions: Column: Waters ODS (C18) RP Column, 250 mm x 4.6 mm. 5µm. the Mobile Phase consisted of 0.1% Orthophosphoric Acid: Methanol in the ratio 35:65(v/v) that was set at a flow rate of 1.0ml/minute, Wave length of 287nmwith Injection volume 20µl and Run time of 09mins and Column temperature and Sampler cooler being Ambient. Vortioxetine is used as the internal standard (IS) [21]. The retention time of Ibrutinib and Vortioxetine (Internal Standard) were found to be 5.75 min and 6.08 min respectively.

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (Cmax), time to attain Cmax i.e., Tmax and t ½ values, area under plasma concentration–time curve from zero to the last sampling time (AUC0-t), area under plasma concentration–time curve from zero to infinity (AUC0-∞).

RESULTS AND DISCUSSION

Melting point

Melting point of Ibrutinib range between 149-158 °C complies with the standard reported value. The reported value is 155 °C.

Estimation of Ibrutinib solubility

Crossential O94oil was chosen as the OL due to its higher Ibrutinib solubilisation (12.64±0.34 mg/ml) than other oils (fig. 1). Croduret 40SS as surfactant and co-surfactant carbitol was chosen for future research because of its increased solubilizing capacity (fig. 2 and 3).

Construction of TPD

When compared to 1:1 and 2:1 S_{mix} ratios (fig. 4A and 4B), the Crossential O94–Croduret 40SS–carbitol of 3:1 S_{mix} system had a bigger nano emulsification 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 (fig 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, 3:1 oil: S_{mix} ratio with 70 mg 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.

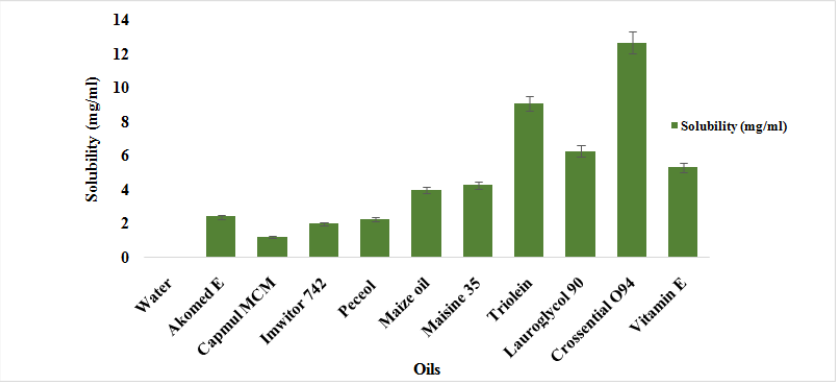


Fig. 1: Solubility of Ibrutinib in various OL, Data is given as mean±standard deviation; (n=3)

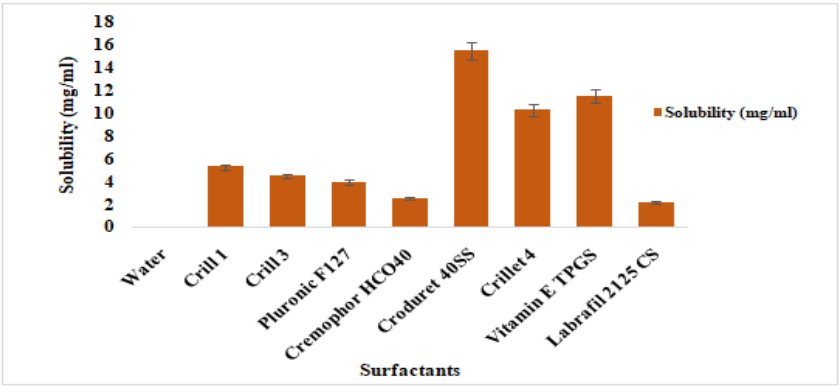


Fig. 2: Solubility of Ibrutinib in various SF, Data is given as mean±standard deviation; (n=3)

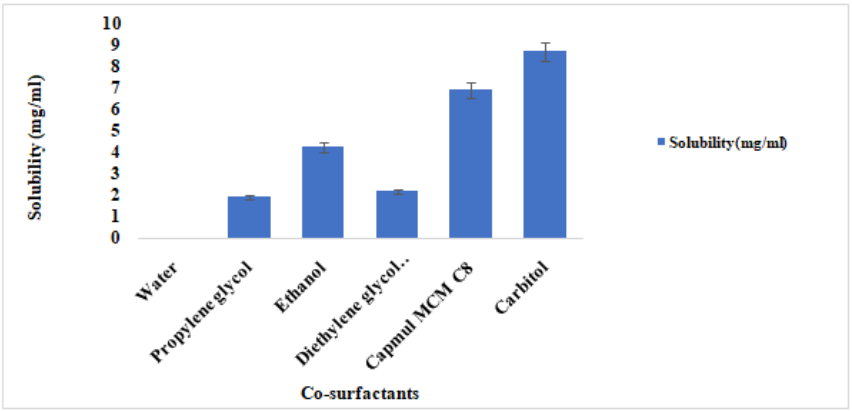
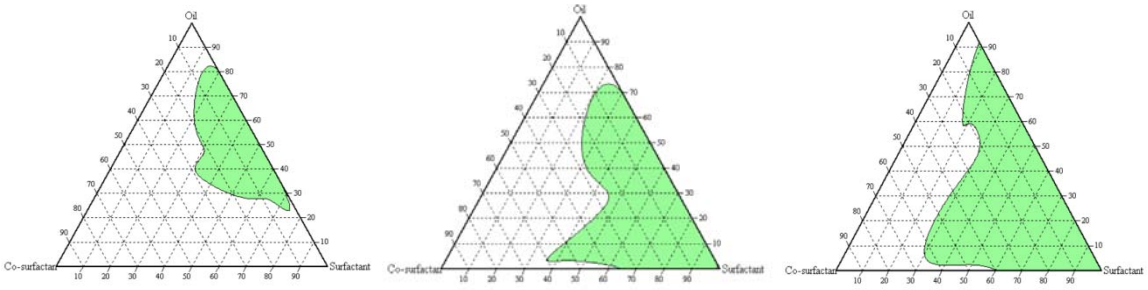


Fig. 3: Solubility of Ibrutinib in various CSF, Data is given as mean±Standard Deviation; (n=3)



4A **4B** **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

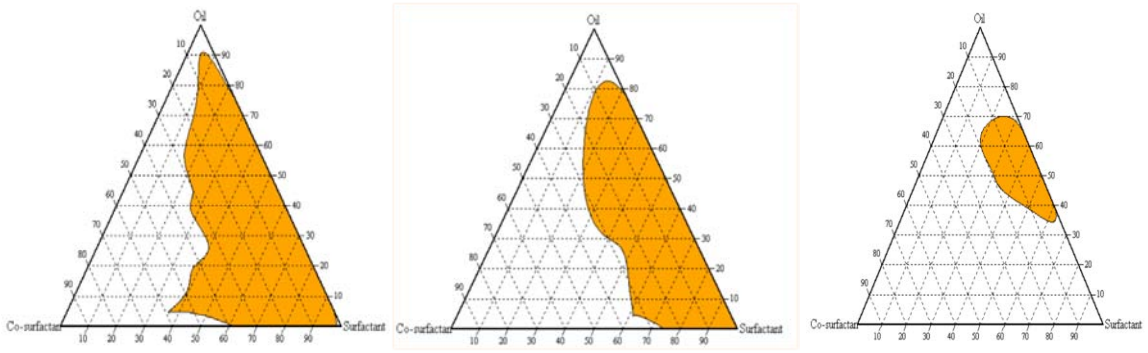


Fig. 5: Ternary phase diagram for (7A) 70 mg (7B) 140 mg (7C) 210 mg of Ibrutinib loaded in Crossential O94–Croduret 40SS–carbitol system with Smix in 3:1 ratio

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 parting or drug precipitation post 24 h 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, zeta potential and polydispersity index

The particle size of the SNEDDS was found to be between 74.5±3.17 and 159.35±1.47 nm, 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 mV. Ibrutinib particle size was decreased in comparison to prior investigations by Prasad *et al.* [20].

***In vitro* dissolution tests**

From fig. 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 min, compared to 31.92 percent in 60 min for pure drug. In 60 min, 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. Such a trend of drug release from L-SNEDDS by transporting encapsulated drugs in the form of tiny emulsion droplets towards the absorption site is beneficial in boosting bioavailability by accelerating the release of poorly water-soluble drugs [21]. Due to reduced turbidity and faster drug release among the other SNEDDS, ibrutinib SNEDDS formulation F15 was chosen as the optimal formulation.

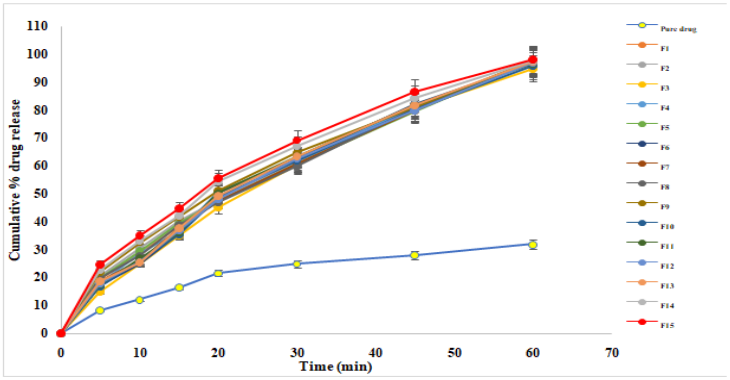


Fig. 6: Comparative dissolution profile of Ibrutinib pure drug and Ibrutinib SNEDDS formulation (F1-F15), Data is given as mean±Standard Deviation; (n=3)

Preparation of liquid supersaturable-SNEDDS (S-SNEDDS)

For the creation of supersaturable SNEDDS, F15 was used. Supersaturable self-nanoemulsifying drug delivery systems (S-SNEDDS) are an improved concept that contains a water-soluble polymeric precipitation inhibitor (PPI) that is designed to establish and sustain a meta-stable supersaturated state *in vivo* by preventing or limiting drug precipitation. Furthermore, Supersaturable-SNEDDS formulations have been shown to increase the rate and amount of oral absorption of poorly water-soluble medicines as reported elsewhere [22, 23].

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 min, and then rapidly to about 185.59 µg/ml after 60 min 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 a better release of 405.11 µg/ml in 60 min while blank L-SNEDDS showed 185.59µg/ml at the end of 60 min (fig. 7, 8, and 9).

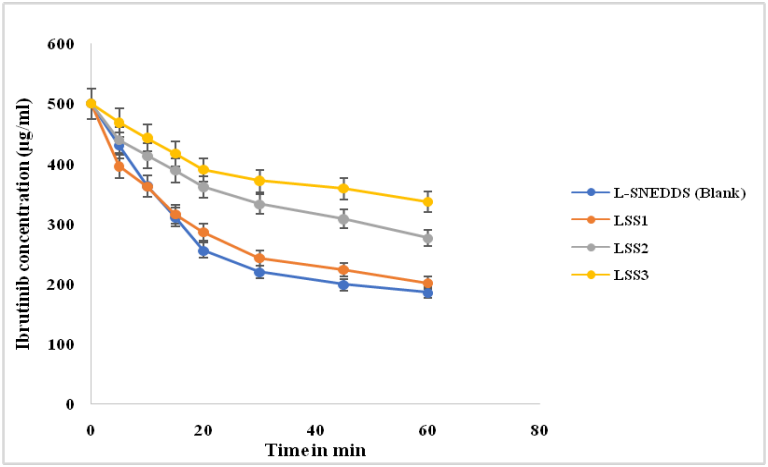


Fig. 7: *In vitro* concentration release data of Ibrutinib from blank SNEDDS and LSS1-LSS3, Data is given as mean±Standard Deviation; (n=3)

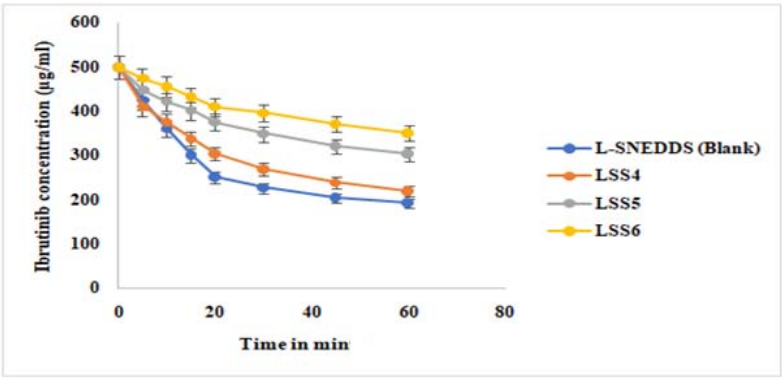


Fig. 8: *In vitro* concentration release data of Ibrutinib from blank SNEDDS and LSS4-LSS6, Data is given as mean±Standard Deviation; (n=3)

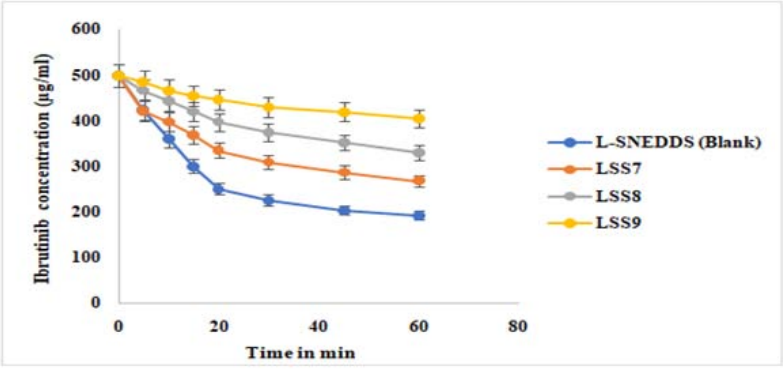


Fig. 9: *In vitro* concentration release data of Ibrutinib from blank SNEDDS and LSS7-LSS9, Data is given as mean±SD; (n=3)

Droplet size, zeta potential and PDI

With the smallest droplet size of 65.4 nm, 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

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).

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 micrometric 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

Data is given as mean±Standard Deviation; (n=3)

***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 min. 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. Fast drug dissolution from Solid supersaturable SNEDDS may be owing to the low surface free energy of the self-emulsifying systems, which favours rapid emulsification by establishing an interface between the dissolving medium and the oil as soon as possible, as reported previously in SNEDDS formulations [24-26] (fig. 10).

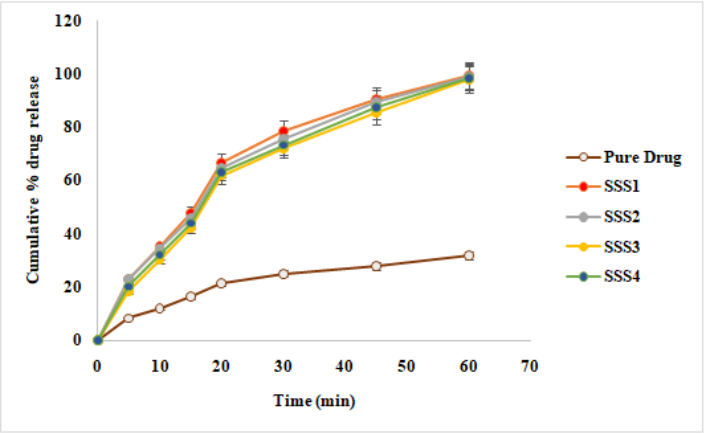


Fig. 10: *In vitro* dissolution of pure drug ibrutinib and ibrutinib solid S-SNEDDS (SSS1-SSS3), Data is given as mean±SD; (n=3)

Characterization of optimised ibrutinib solid S-SNEDDS formulation by FTIR and DSC

The FTIR spectrum of (fig. 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 was carried out by comparing FTIR of pure drug, physical mixture and optimised formulation (fig. 11). The optimised formulation shows all principal peaks present in the FTIR of pure drug, indicating the compatibility.

DSC thermogram of pure ibrutinib showed a prominent endothermic peak at 154 °C, which indicates 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 (fig. 12).

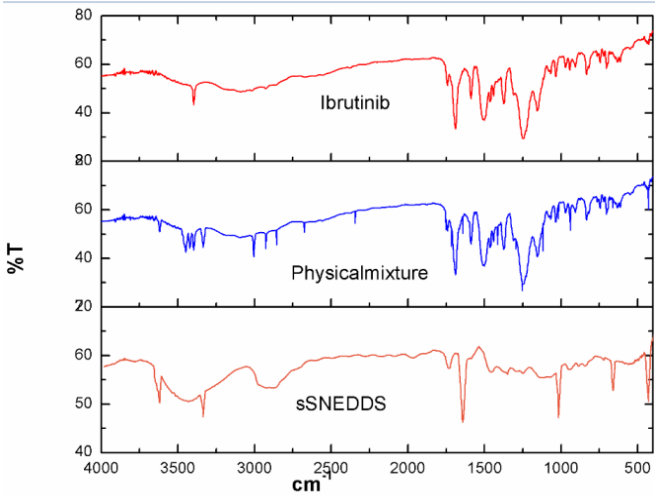


Fig. 11: FTIR spectrum of ibrutinib pure drug, physical mixture and SNEDDS (SSS1)

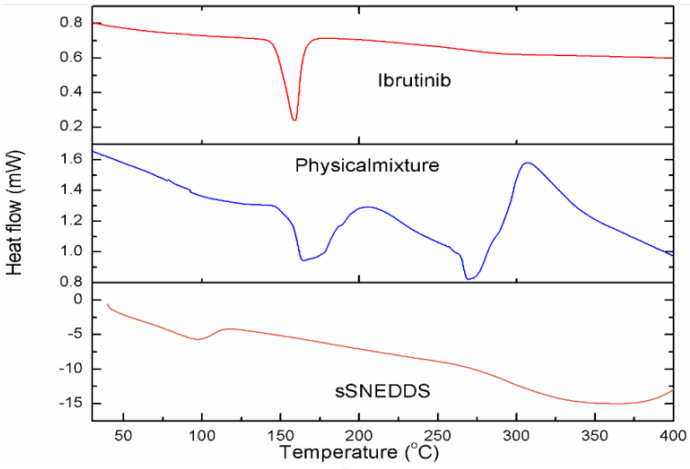


Fig. 12: Differential scanning calorimetry (DSC) of ibrutinib and ibrutinib solid S-SNEDDS

Table 5: Stability studies

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

Data is given as mean±Standard Deviation; (n=3)

***In vivo* studies**

Fig. 13 shows the plasma concentration–time curve in rabbits after a single oral dose of Ibrutinib solid supersaturable SNEDDS formulation as compared to Ibrutinib pure suspension.

Cmax of the solid supersaturable SNEDDS 139.42±2.16 mg/l was significant ($p<0.05$) as compared to the pure drug suspension formulation 38.15±1.46 mg/l. Tmax of both solid supersaturable SNEDDS formulation and pure drug suspension was 1.00±0.06 h and 1.50±0.02h, respectively. AUC0-∞ infinity for solid supersaturable

SNEDDS formulation was higher (3237.24±1.17 mg. h/l) than the pure drug suspension formulation 992.21±0.76 mg.h/l. Statistically, AUC0-t of the solid supersaturable SNEDDS formulation was significantly higher ($p<0.05$) as compared to pure drug suspension formulation. Higher amount of drug concentration in blood indicated better systemic absorption of Ibrutinib from solid supersaturable SNEDDS formulation as compared to the pure drug suspension formulation.

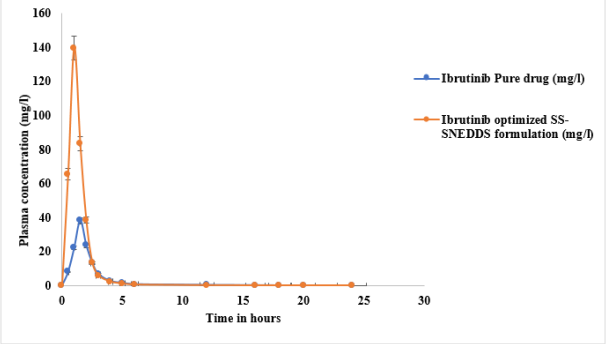


Fig. 13: Mean plasma concentration-time profiles for ibrutinib pure drug and ibrutinib optimized solid supersaturable SNEDDS formulation in rabbits (n=6)

Table 6: Mean pharmacokinetic parameters of ibrutinib pure drug and ibrutinib optimized solid supersaturable SNEDDS formulation in rabbits

Pharmacokinetic parameters	Ibrutinib pure drug	Ibrutinib– solid supersaturable SNEDDS optimized formulation
C max (mg/l)	38.15±1.46	139.42±2.16
AUC 0-t (mg. h/l)	381.72±0.67	1601.45±0.54
AUC 0-inf (mg. h/l)	992.21±0.76	3237.24±1.17
T max (h)	1.50±0.02	1.00±0.06
t 1/2 (h)	4.39±0.03	2.71±0.05

Stability studies

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

CONCLUSION

The authors report the successful development of a novel supersaturable solid-SNEDDS formulation of ibrutinib using HPMC E4M polymer as a precipitation inhibitor (LSS9). The use of magnesium trisilicate as the insert reservoir for a solid supersaturable SEDDS containing ibrutinib was optimized (SS1). During *in vitro* dissolution tests under supersaturation conditions, HPMC E4M effectively suppressed drug precipitation and maintained a stable supersaturated state. Further, the FT-IR and DSC study of the final optimised formulation (SSS1) showed no interaction of porous carriers used with the 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.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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