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International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Supersaturable Self-nanoemulsifying Drug Delivery System of Irinotecan–preparation and *In-vivo* Evaluation

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ARTICLE INFO

Article history:
Received: 02 October, 2022
Revised: 22 October, 2022
Accepted: 28 October, 2022
Published: 30 November, 2022

Keywords:
Bioavailability, Irinotecan, Pharmacokinetic studies, Precipitation inhibitor, S-SNEDDS.

DOI:
10.25004/IJPSDR.2022.140619

ABSTRACT

Irinotecan (CPT-11) is a camptothec in derivative with low oral bioavailability due to active efflux by intestinal P-glycoprotein receptors. Hence, no potent oral formulation is marketed for irinotecan till date and its oral ingestion continues to remain a challenge. This study investigates the potential of supersaturated self-nanoemulsifying drug delivery systems (S-SNEDDS) to improve the bioavailability of poorly water-soluble drugs compared to conventional SNEDDS. Developed formulation comprising of canola oil – caproic acid – propylene glycol revealed particle size of 128.23 nm with PDI 0.137, zeta potential value of -23.45 mV and drug content of 99.32% with spherical shape and smooth surface. A maximum drug release of 99.96% in 60 minutes was observed for formulation F12 hence chosen for screening precipitation inhibitor (PI).The F12 containing 2% HPMC as PI was found to show high release profile. The Fourier transform infrared (FTIR) and Scanning electron microscopy (SEM) studies did not indicate any drug excipient interaction and confirm nanosized particles that are stable. Furthermore, pharmacokinetic studies demonstrated marked improvement of 2.78 fold in wistar rat's plasma as well as higher oral bioavailability through SNEDDS when compared to pure drug. Hence this approach may be effectively utilized, to replace pre-existing intravenous therapy with enhanced oral bioavailability.

Introduction

The ever-increasing number of poorly water-soluble compounds emerging from modern drug discovery programs requires scientists to break new ground in the field of drug delivery. Amongst these approaches, lipid and surfactant-based drug delivery systems, in particular self-nanoemulsifying drug delivery system (SNEDDS), are promising delivery options that have attracted much attention both academically and commercially.[1] SNEDDS consist of a mixture of oil, surfactant, co-surfactant and co-solvent.[2] The co-administered drug is dissolved in the mixture forming an isotropic SNEDDS pre-concentrate. Hence, the often rate-limiting dissolution step of crystalline compounds is avoided. Upon contact with aqueous medium and following gentle agitation, the pre-concentrate spontaneously generate ultrafine oil/water nanoemulsions.[3]

It is speculated that the improved *in-vivo* performance of drugs could be attributed to the small size of the emulsion droplets, the generation of mixed micelles during the digestion of the SNEDDS facilitating drug solubilization, and the possible inhibition of P-glycoprotein by some of the excipients.[4] To prevent the precipitation of the drug and to reduce the dosing frequency, suitable precipitation inhibitors can be used (maintains super saturation 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). The liquid formulation is converted into solid dosage form (by the use of adsorbents) to improve the stability.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Irinotecan, [7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy camptothecin (CPT11)] a potent inhibitor of topoisomerase-I is metabolized to an active metabolite [7-ethyl-10- hydroxycamptothecin (SN-38)] with the help of carboxylesterases.CPT-11 is oxidized to the inactive metabolite 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecin (APC) through cytochrome-P450-3A (CYP3A), a camptothecin (CPT-11) derivative with clinical uses in the treatment of brain tumor and colorectal cancer (Fig. 1), also revealed potential a potential applications in the treatment of other neoplastic disorders such as cervix cancer, non-small cell lung carcinoma, brain as well as pancreatic malignancies. However, with the major drawback of being inactivated P-gp induced efflux system, no oral formulation exists for this drug till date and the issue of low oral bioavailability as well as alteration of the drug by P-gp efflux system has been already reported by some of the studies. [5]

The present study is pointed to develop canola oil-based irinotecan S-SNEDDS for increasing solubility and thereby release characteristics.

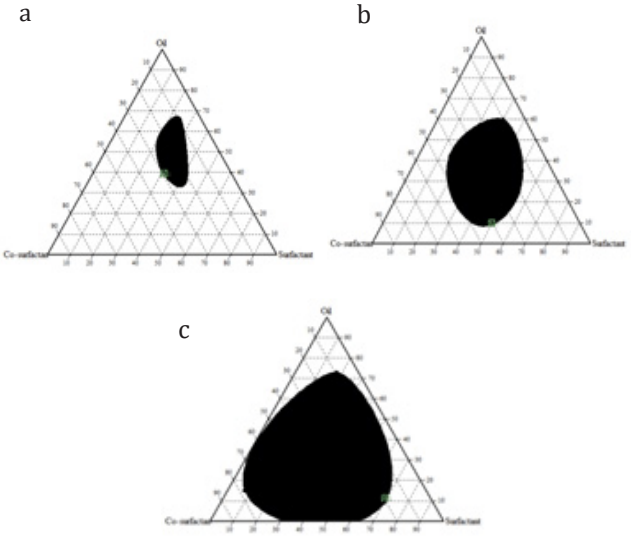

Fig. 1: Ternary phase diagram for Canola oil – caproic acid – propylene glycol with Smix in 1:1 ratio(A): 2:1 ratio(B) and 3:1 ratio(C). (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

Materials And Methods

Materials

Irinotecan is a gift sample from Hetero Labs Limited, Hyderabad, India. The oils used were purchased from local market. Surfactants and co-surfactants purchased from Gattefosse, Mumbai.

Methodology

Solubility of Irinotecan in Vehicles

An excess amount of irinotecan mixed with 1 g of vehicle in glass vials and vortexed for 10 minutes followed by shaking reciprocally for 48 hours at 25°C.The contents and allowed to stand undisturbed for 24 hours at 25°C. The contents centrifuged at 3000 rpm for 10 minutes, supernatant filtered, diluted with methanol and analysed for irinotecan spectrophotometrically at 365 nm. [6,7]

Table 1: Composition of irinotecan SNEDDS

S. No	*Formulation code*	*Irinotecan drug (mg)*	*Ratios of Oil: S_{mix}*	*Oil (Canola oil)*	*S_{mix} 3:1*	
					Surfactant (Caproic acid)	*Co-surfactant (Propylene glycol)*
1	F1	25	01:01	50	37.5	12.5
2	F2	25	01:02	33	49.5	16.5
3	F3	25	01:03	25	56.25	18.75
4	F4	25	03:01	75	18.75	6.25
5	F5	25	02:01	66	24.75	8.25
6	F6	25	02:03	40	45	15
7	F7	25	08:03	72.7	20.25	6.75
8	F8	25	07:03	70	22.5	7.5
9	F9	25	05:03	62.5	28.12	9.3
10	F10	25	04:03	57.1	31.95	10.65
11	F11	25	02:05	28.5	53.25	17.75
12	F12	25	02:07	22.2	58.2	19.4
13	F13	25	03:02	60	30	10
14	F14	25	03:04	42.6	42.6	14.8
15	F15	25	03:07	30	52.5	17.5
16	F16	25	05:02	71	21.3	7.1

Construction of Pseudo-ternary Phase Diagrams

The chosen vehicles were mixed in various ratios ranging from 1:9 to 9:1 (oil: S_{mix}). S_{mix} is the mixture of surfactant and co-surfactant prepared in defined ratios of 1:1, 2:1, and 3:1. Ternary phase diagrams comprising surfactant, co-surfactant and oil were plotted, each of them, representing an apex of the triangle. Varying ratios of oil:S_{mix} were mixed with 100 mL of water and ratios with no phase separation and turbidity were checked for the transmittance (The samples with transmittance > 90 were used for plotting pseudo-ternary phase diagram using CHEMIX software. [8]

Effect of Irinotecan Loading

Twenty compositions of varying ratios of canola oil – caproic acid – propylene glycol were taken and in 1-mL composition of each ratio were incorporated with 25 mg and 50 mg of irinotecan. Contents vortexed at 40°C and transmission determined at 365 nm. The area of nano emulsification region was identified as described above by constructing ternary phase diagrams [9].

Preparation and Evaluation of Irinotecan SNEDDS

A series of SNEDDS (F1-F16) were selected from 25 mg loaded irinotecan system and prepared as described above. [8] About 1-mL of the formulation (equivalent to 25 mg of the irinotecan) was filled in size '00' hard gelatin capsules, sealed and stored at ambient temperature (25°C) and evaluated (Table 1).[10]

Evaluations of SNEDDS

All the 16 formulations are evaluated for visual observations, time of self-emulsification, dispersibility and appearance were observed and rated according to grading system.[11,12] The turbidity of the prepared dispersions was measured using nephelo turbidity meter using 30 mL of the dispersion.[13]

The robustness, %drug content and entrapment efficiency of irinotecan SNEDDS and to dilution was studied as per the referred procedures.[14,15]

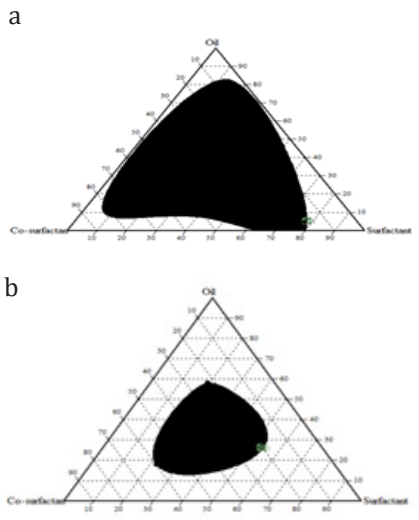

Fig. 2: Ternary phase diagram for 25 mg(A) and 50 mg(B) of irinotecan loaded in Canola oil – Caproic acid – Propylene glycol system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

In-vitro Dissolution Study

In-vitro dissolution studies performed using USP dissolution apparatus II (Lab india DS 8000, Mumbai, India). Hard gelatin capsules, size "1" filled with SNEDDS formulation were mixed with 900 mL of freshly prepared pH 7.4 phosphate buffer maintained at 37 ± 0.5°C and centrifuged at 100 rpm [16]. At pre-determined time intervals, 5 mL of samples were withdrawn and contents replaced with 5 mL of fresh medium. The samples evaluated spectrophotometrically at 365 nm.[17]

Screening for a Precipitation Inhibitor (PI)

In-vitro precipitation experiments were used to estimate the apparent drug concentration-time profile and the duration of the super- saturated state. Polymers such as microcrystalline cellulose, HPMC E50LV, HPMC AS and Poloxamer 407 were employed to stabilize the supersaturated irinotecan solution. 1 g of SNEDDS mixed with 100 mL of simulated gastric fluid (SGF) at 37°C and centrifuged. 1-mL sample withdrawn at regular time intervals and centrifuged at 3000 rpm for 3 minutes followed evaluation of drug content at 365 nm.[18]

Characterization of Optimized Irinotecan SNEDDS

The FTIR (fourier-transform infrared) spectra, the globule size and zeta potential of optimised formulation were recorded.[19]

Accelerated stability studies

All formulations filled in hard gelatin capsules were packed in HDPE screw capped bottles and kept in humidity chambers maintained at 40 ± 2°C/ 75 ± 5% RH as per ICH guidelines for Zone III and stored for 6 months. [20]

In-vivo Study [21]

Wistar rats used for the study were kept in an environmentally controlled room (temperature: 25 ± 2°C, humidity: 45–55%, 12 hours dark–light cycle). Animals were fed on a standard pelleted diet and water (ad libitum). The protocol of animal study was approved by the institutional animal ethics committee (IAEC No.1447/PO/Re/S/11/CPCSEA-55/A).

Rats divided into three groups containing six animals in each group randomly (Group A, Group B and Group C) and were administered with each sample. Group A was administered with pure drug, dispersed in 0.5% w/v of sodium carboxymethyl cellulose with gentle manual mixing, group B was administered with supersaturable-SNEDDS dispersion at a dose equivalent to 3.12 mg. Group

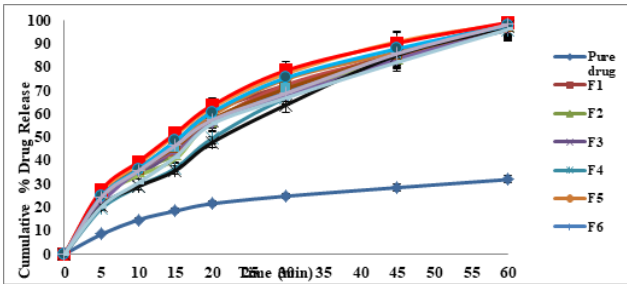

Fig. 3A: Comparative dissolution profile of irinotecan pure drug and irinotecan SNEDDS formulation (F1-F16).

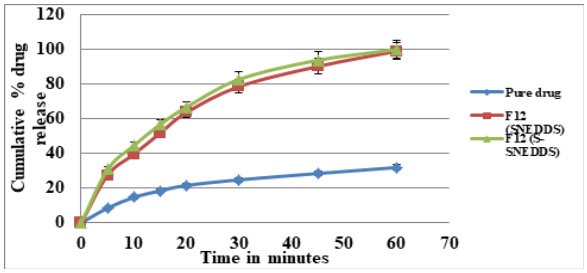

Fig. 3B: Comparative dissolution profiles of irinotecan pure drug, irinotecan SNEDDS and irinotecan S-SNEDDS.

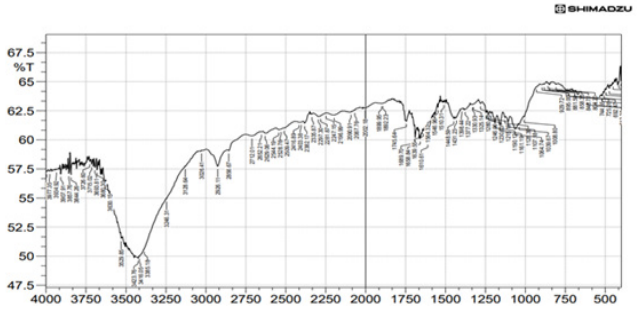

Fig. 4: FTIR spectrum of pure drug irinotecan.

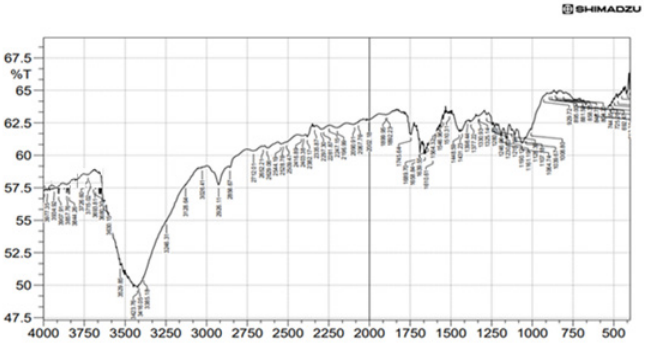

Fig. 5: FTIR spectrum of irinotecan S-SNEDDS (F12).

C was kept as control. The blood sample (300 µL) was withdrawn (femoral artery) under mild anesthesia at various time intervals and stored in blood sample tubes. The collected blood samples were centrifuged (3000 rpm for 5 minutes) to separate plasma which was stored at −20°C till further analysis was carried out.

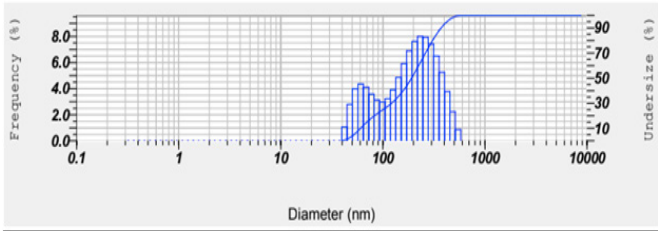

Fig. 6A: Particle size of optimized SNEDDS formulation of irinotecan (F12)

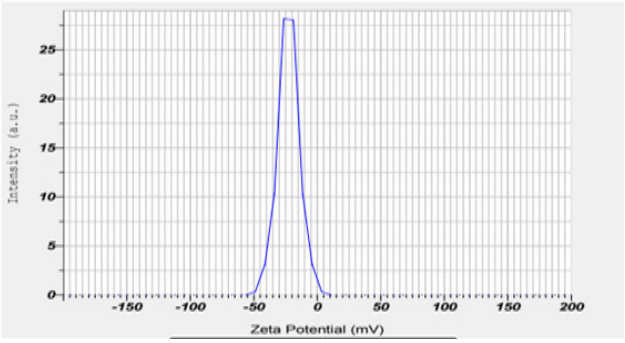

Fig. 6B: Zeta potential of optimised SNEDDS formulation of irinotecan (F12).

The data thus generated was expressed as mean ± S.D. and statistically compared using Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p < 0.05$ was considered statistically significant.

Results And Discussion

Determination of Irinotecan Solubility in Various Excipients

Canola oil was selected as oil phase due to its higher solubilization (19.54 ± 0.26 mg/mL) of irinotecan compared to other oils surfactant (caproic acid) and co-surfactant (propylene glycol) was selected for further studies due to their higher solubilizing capacity towards irinotecan.

Construction of Ternary Phase Diagrams

The region of nano emulsification was indicated as shadow area encircled by a solid line and the points indicate the compositions of the system explored. Canola oil – caproic acid – propylene glycol system with S_{mix} ratio in 3:1 exhibited larger nanoemulsification region as compared to 1:1 and 2:1 S_{mix} ratio. (Fig. 1).

Effect of Irinotecan Loading

The area of nano emulsification was considerably reduced with increase in irinotecan loading in to the canola oil – caproic acid – propylene glycol system with 3:1 S_{mix} ratio hence for the stability reasons of the SNEDDS, system

Table 2: The % drug content and % entrapment efficiency values

Formulation code	*%Drug content*	*% Entrapment Efficiency*
F1	97.61 ± 1.21	97.76 ± 1.43
F2	98.21 ± 1.19	98.37 ± 1.51
F3	98.95 ± 1.65	98.93 ± 1.69
F4	95.80 ± 1.59	95.75 ± 1.43
F5	96.53 ± 1.19	96.48 ± 1.22
F6	98.03 ± 1.49	98.08 ± 1.67
F7	95.93 ± 1.78	95.88 ± 1.53
F8	96.14 ± 1.15	96.09 ± 1.79
F9	96.85 ± 1.66	96.80 ± 1.73
F10	97.40 ± 1.45	97.39 ± 1.35
F11	98.81 ± 1.13	98.76 ± 1.39
F12	99.32 ± 1.62	99.27 ± 1.95
F13	97.21 ± 1.89	97.16 ± 1.84
F14	97.97 ± 1.39	97.91 ± 1.70
F15	98.47 ± 0.72	98.52 ± 0.54
F16	96.07 ± 1.39	95.91 ± 1.70

Table 3: Storage at 40 ± 2° C/75 ± 5% RH for 6 months

Retest time for optimized formulation F12 (S-SNEDDS)	*% Drug content*	*Entrapment efficiency (%)*	*In-vitro drug release (%)*
0 days	99.32 ± 1.50	99.27 ± 0.50	99.96 ± 0.93
30 days	99.06 ± 0.15	99.01 ± 0.39	99.63 ± 0.37
60 days	98.72 ± 0.96	98.82 ± 1.60	99.32 ± 1.26
90 days	98.41 ± 0.48	98.47 ± 1.72	98.97 ± 0.67
180 days	98.09 ± 0.75	98.05 ± 0.41	98.75 ± 0.24

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

Table 4: Mean pharmacokinetic parameters of irinotecan pure drug and irinotecan optimized supersaturable SNEDDS

Pharmacokinetic parameters	*Irinotecan Pure drug*	*Irinotecanoptimized supersaturable SNEDDS*
C_{max}(ng/mL)	1605.44 ± 2.31	4569.31 ± 1.22
AUC_{0-t}(ng. h/mL)	4956.938 ± 1.36	13234.235 ± 0.97
AUC_{0-inf}(ng. h/mL)	5240.2 ± 0.64	14595.01 ± 1.26
T_{max}(h)	1.5 ± 0.72	1.0 ± 0.53
t ½ (h)	4.07 ± 0.02	1.73 ± 0.05
ke	0.15683	0.36848

containing 25 mg of irinotecan was chosen for formulation of irinotecan SNEDDS and further studies (Fig. 2).
From the results it was found that canola oil concentration in the range of 22–75% w/w, caproic acid in the range of 18–59% w/w and propylene glycol in the range of 6–19% w/w in 3:1 of oil: S_{mix} ratio with 25 mg loaded irinotecan drug produced the SNEDDS having the transmittance > 90, with good stability.

Evaluation of SNEDDS

Visual observations indicated that at higher levels of surfactant, the spontaneity of the self-emulsification process was increased. The formulations that have low turbidity (<20) gave a transmittance values of more than 90 indicating rapid and spontaneous emulsification within 1-minute, hence it gives a good correlation between transmittance and turbidity values. All the formulations were found robust towards dilution with water, 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer with drug precipitation within 24 hours of storage. The drug content of all formulations ranged between 95.80 ± 1.59 to 99.32 ± 1.62% with maximum value exhibited by F12 The entrapment efficiency of all formulations varies between 95.75 ± 1.43 to 99.27 ± 1.95 % with maximum value displayed by F12 (Table 2).

In-vitro Dissolution Tests

The formulations F1-F16 released more than 60% of drug within 30 minutes, whereas, pure drug released 31.92% of drug in 60 minutes. Formulation F12 exhibited highest drug release of 99.06% in 60 minutes.

In-vitro Evaluation of Precipitation

The HPMC AS displayed superior inhibition with highest drug concentration (421.61 µg/mL after 60 minutes). *In-vitro* dissolution studies for S-SNEDDS of formulation F12 with 2% HPMC AS precipitation inhibitor was studies. Comparative dissolution profiles of irinotecan pure drug, irinotecan SNEDDS and irinotecan S-SNEDDS which indicates the release of drug from irinotecan S-SNEDDS was highest with 99.96% at the end of 60 minutes (Fig. 3).

Drug Compatibility Study by FTIR

The pure irinotecan spectrum showed the main characteristic bonds at 692.47 cm^{-1} (C-F bending) 1039.67 cm^{-1} (C-O stretching), 1190.12 cm^{-1} (C-F stretching), 1280.78 cm^{-1} (C=O stretching), 1448.59 cm^{-1} (aromatic stretching), 1639.55 cm^{-1} (amide stretching), 1689.7 cm^{-1} (C=C stretching), 1745.64 cm^{-1} (C=0 stretching), 3026.41 cm^{-1} (C-H stretching), 3250.16 cm^{-1} (O-H stretching), 3319.6 cm^{-1} (N-H stretching).The presence of prominent characteristic peaks in FTIR of SNEDDS confirming the compatibility between drug and excipient.(Fig. 4,and 5)

Globule Size and Zeta Potential

The particle size for the optimized formulation of S-SNEDDS (F12) was found to be 128.23 nm with PDI 0.137 and the zeta potential value of -23.45 mV. This might be due to the addition of precipitation inhibitor HPMC AS (in S-SNEDDS) which formed a physical barrier around oil droplets and prevented aggregation to give a smaller sized nanoemulsion. S-SNEDDS was found to have comparably higher zeta potential than plain SNEDDS and thus was more stable. (Fig. 6a,6b)

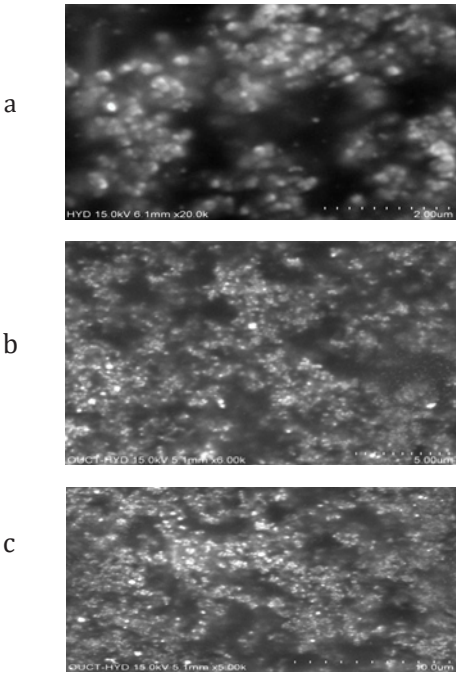

Fig. 7: SEM images of optimized formulation of irinotecan SNEDDS F12 (a, b & c)

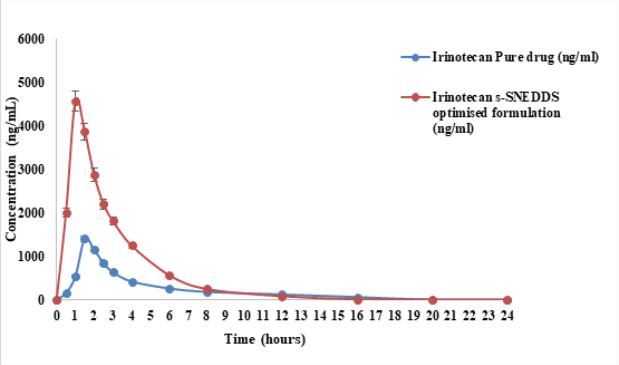

Fig. 8: Mean plasma concentration-time profiles for irinotecan pure drug and irinotecan optimized supersaturable SNEDDS formulation in rats (n=6).

SEM Studies

The formulation appeared as spherical and smooth surfaced and analysis of globule size was in accordance with these results with size of all droplets less than 100 nm (Fig. 7).

Accelerated Stability Studies

No visible physical changes were observed in all the formulations withdrawn from the humidity chambers. The samples were assayed for %entrapment efficiency, %drug content and *in-vitro* drug release and the results are shown in Table 3.

In-vivo Pharmacokinetic Studies

Fig. 8 depicts the plasma concentration–time curve in wister rats after a single oral dose of irinotecan optimized supersaturable SNEDDS formulation against irinotecan pure after a single oral dose of irinotecan optimized supersaturable SNEDDS formulation. Irinotecan plasma concentrations in rats administered with the optimized supersaturable SNEDDS formulation were considerably greater than those in rats treated with the pure medication at all time periods.

The supersaturable SNEDDS C_{max} of 4569.31 ± 1.22 ng/mL was significantly higher ($p < 0.05$) than the pure drug's C_{max} of 1405.54 ± 0.54 ng/mL. Both the SNEDDS formulation and the pure medication had T_{max} of 1.00 ± 0.53 and 1.50 ± 0.72 hours, respectively. Because it shows the entire integrated area under the blood concentration time profile and shows the entire quantity of drug reaching the systemic circulation following oral delivery, The AUC is a critical metric for determining pharmaceutical bioavailability from dose form. When compared to pure medication (5240.2 ± 0.64 ng h/mL), the $AUC_{0\text{-infinity}}$ for supersaturable SNEDDS formulation was greater (14595.01 ± 1.26 ng. h/mL). When compared to the pure drug, higher drug concentrations in the blood suggested improved systemic absorption of Irinotecan from the improved supersaturable SNEDDS formulation (Table 4). The pharmacokinetic data was subjected to statistical analysis to test the significant differences between the pharmacokinetic parameters of two formulations. The data indicated that there was significant difference in C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, between irinotecan pure drug and irinotecan optimized supersaturable SNEDDS formulation. The broader application of SNEDDS has been often restricted due to solubility limitations of lipophilic compounds in common excipients used in lipid and surfactant-based drug delivery systems ultimately requiring the administration of multiple units of SNEDDS.

Conclusion

The current study has shown that supersaturated SNEDDS are a feasible approach to increase the drug load in SNEDDS and to increase the bioavailability of irinotecan. Super-SNEDDS contained drug loads up to twice of the drug's equilibrium solubility and were physically stable for about 3 months. In a pharmacokinetic study in rats, the super-SNEDDS showed considerably higher bioavailability.

Thus, the developed irinotecan S-SNEDDS can be used as an effective approach for the management of cancer with relatively low drug dose with enhanced solubility and drug release.

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HOW TO CITE THIS ARTICLE: Shekhar MC, Sandhya P, Nirmala P. Supersaturable Self-nanoemulsifying Drug Delivery System of Irinotecan – preparation and *In-vivo* Evaluation. Int. J. Pharm. Sci. Drug Res. 2022;14(6):811-817. **DOI:** 10.25004/IJPSDR.2022.140619