Journal of Research Administration
Society of Research Administrators International

FORMULATION AND EVALUATION OF SELF DOUBLE EMULSIFYING DRUG DELIVERY SYSTEMS OF TAMOXIFEN

Shafiya Samreen[1], Venu Madhav Katla[1]*, Somnath De[2], Naga Raju K[3], Naga Haritha P[4], Sridhar Babu G[5]

[1] MPharmacy Student, Department of Pharmaceutics, St. Pauls College of Pharmacy, R.R District, Telangana, India- 501510.

[1*] Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R.R District, Telangana, India-501510.

[2] Professor, Department of Pharmacology, St. Pauls College of Pharmacy, R. R District, Telangana, India-501510.

[3] Associate Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R. R District, Telangana, India-501510.

[4] Assistant Professor, Department of Pharmaceutics, St. Pauls College of Pharmacy, R. R District, Telangana, India-501510.

[5] Professor, Department of Pharmaceutical Chemistry, Sri Shivani College of Pharmacy, Warangal, Telangana, India-501510.

ABSTRACT

Indeed, the instability of multiple emulsions poses a challenge for commercial use. However, their capacity to enhance oral absorption, especially for medications with high solubility and limited permeability, highlights a promising avenue for pharmaceutical applications. Balancing stability concerns with enhanced drug delivery remains a key focus in this area of research. Optimizing the formulation of a SDEDDS by incorporating water-in-oil (w/o) surfactants that attract water emulsion is a promising strategy. This approach can lead to enhanced stability, particularly in the context of testing solubility for drugs like Tamoxifen across various solvents. Such advancements contribute to the development of more effective DDS . The construction of a pseudo-ternary phase diagram is a valuable tool for the micro-emulsion zone's identification. By adjusting oil, surfactant, and co-surfactant concentrations eight distinct formulations were created. This systematic approach aids in understanding the optimal composition for achieving stable micro-emulsions in pharmaceutical or industrial applications. Formulation F7, optimized through Zeta potential, particle size, and in vitro drug release analysis, demonstrated favorable results with a 93.69±3.72% release within 12 hours. Additionally, stability studies revealed that the preparation remained stable over a three-month period, indicating promising characteristics for potential application and storage

Keywords: Tamoxifen, Olive oil, Surfactants, FTIR studies, In vitro drug release studies

1. INTRODUCTION

Certainly, the versatility of LBDDS allows for precise targeting of medication administration enhancing therapeutic efficacy while minimizing side effects. These systems offer a versatile platform accommodating a range of molecular weights, from small to large, and are instrumental in enhancing the efficacy of bioactive agents [1, 2]. Addressing the challenges associated with poorly water-soluble drugs is crucial for formulation scientists, who work towards improving both solubility and bioavailability to enhance the effectiveness of these medications. The size-dependent properties exhibited by LBDDS have indeed captured considerable attention, highlighting their potential for precisely controlled drug release and prompting increased interest in their utilization. Certainly, the clear advantages of higher biocompatibility and versatility in lipid-based drug delivery systems contribute significantly to their prominence, paving the way for more effective and patient-friendly pharmaceutical solutions. Pharmaceutical formulation using these methods is commercially feasible across a spectrum of delivery routes, encompassing topical, oral, pulmonary, and parenteral administration. Their adaptability makes them valuable tools in pharmaceutical development. Absolutely, lipid formulations offer versatility in addressing diverse product requirements, considering factors such as disease condition, administration route, cost, stability, toxicity, and efficacy. Modifying these formulations allows tailoring to specific needs within the pharmaceutical or medical context. Indeed, lipid-based carriers have demonstrated both safety and efficiency, making them appealing candidates for formulating various pharmaceuticals, vaccines, diagnostics, and nutraceuticals. Their versatility contributes to their widespread application in diverse medical and healthcare contexts. [3]. Certainly, LBDDS have become increasingly significant, particularly for enhancing by the drugs with poor water solubility, contributing to increased solubility and improved bioavailability, ultimately enhancing therapeutic outcomes. Certainly, the versatility of LBDDS is evident in their capacity to be administered through diverse routes, offering a flexible and comprehensive approach to meet various drug delivery requirements4,5. Absolutely, Certainly, the oral route maintains its preference for drug delivery due to its non-invasiveness, cost-effectiveness, and lower risk of side effects compared to invasive methods like injections, making it a widely favored and patient-friendly option. This method is especially convenient for chronic therapies, making it the most straightforward and practical option for many patients. Certainly, a methodical and logical approach to formulation strategies at the early stages of development is crucial. This helps prevent erratic relationships between in vivo and in vitro, ultimately improving the likelihood of achievement in the process of developing formulation. Several authors have contributed valuable guidelines on convenient routes and effective formulation strategies, aiding researchers in optimizing drug delivery systems [6,7,8,9].

SDEDDS are indeed described as homogeneous blends. They typically consist of natural or synthetic surfactants, solid/liquid oils, and may include hydrophilic solvents, cosolvents, or additional surfactants. SDEDDS are polydispersed systems in which droplets of the continuous phase are contained in the dispersed phase. SDEDDS is recognized for its effectiveness in improving the stability in two-emulsion systems. Better bioavailability and a sustained release of the drug are benefit of the greater stability of drug delivery application. It uses a combination of

primary and secondary surfactants that, in a mildly agitated external aqueous environment, can spontaneously produce double emulsions. The choice of SDEDDS formulations is particularly advantageous as a lipid-based system, making it well-suited for enhancing the pharmacological activity of drugs [10,11,12].

Tamoxifen competitively prevents estrogen from attaching to its receptor, which is necessary for estrogen to function in breast cancer cells. The large volume of distribution (50-60L/kg) for Tamoxifen suggests widespread distribution in body tissues. Its excretion in bile and elimination in faeces highlight the role of the liver and gastrointestinal system in its clearance. The small amounts of Tamoxifen eliminated in urine, despite its high logP (7.9), may be attributed to its affinity for phospholipids, facilitating solubilization and renal excretion. Correct, the short half-life of Tamoxifen requires frequent administration to maintain therapeutic levels in the bloodstream, ensuring its continued efficacy in the treatment of breast cancer. TAMOXIFEN dosage form is 10mg, 20mg (tablet), and 150ml (syrup). As Tamoxifen belongs to class II of the BCS which have poor solubility and elevated log P and inadequate bioavailability. In order to overcome it is better to formulate as lipid-based system to improve the pharmacological activity of the drug for this reason SDEDDS formulation is selected. [13]

The objective of this study was to develop an optimized self-double emulsifying drug delivery system (SSMED) for tamoxifen to treat breast cancer. It also plays important role in improving invitro drug release and bioavailability of the drug further.

2. MATERIALS

Tamoxifen was purchased from Hetero labs, Hyderabad. Olive oil, Tween 80, Span 80, Liquid paraffin and Labrasol were purchased from Synpharma Research Labs, Hyderabad. Analytical grade reagents were used.

2.METHODOLOGY

2.1.1 FTIR spectroscopy14

Spectra of Fourier transform infrared were obtained with a Shimadzu FT-IR spectrometer. Sample preparation involved using 200 mg of sample per 200 mg of KBr disks. Within the scanning range of 450–4000 cm-1, the resolution was 4 cm-1.

2.1.2 Solubility studies14

The Tamoxifen SDEDDS development oil solubility research set out to determine the proper oily phase. Absolutely, selecting an oil with high solubilizing potential enhances drug loading efficiency, ensuring better absorption and bioavailability for the medication. Interaction of tamoxifen with various oils and surfactants. It appears that emulsification efficiency took precedence over solubilization ability in selecting the surfactant or co-surfactant for the research, with olive oil accommodating the highest Tamoxifen concentration at 2.34 mg/ml.

2.1.3 Construction of Pseudo Ternary Phase Diagram15,16,17

The construction of pseudo-ternary phase diagrams, excluding Tamoxifen, is crucial for pinpointing areas that self-emulsify and optimizing the concentrations of Formulations for SDEDDS contain oil, surfactant, and co-surfactant. The SDEDDS series was prepared, and their ability to self-emulsify was evident assessed, contributing to the characterization of their performance. Constructing phase diagrams at surfactant:co-surfactant ratios of 1:1, 1.5:1, and 2:1 (v/v) helps analyze the system's behavior under varying conditions, offering valuable formulation insights. Increasing Span 80 concentration led to an expansion of the gel-like region, accompanied by a reduction in the self-microemulsifying region, indicating the impact of surfactant concentration on the system's characteristics. The optimal self-microemulsifying region was identified at a surfactant:co-surfactant ratio of 1:1, emphasizing the significance of this specific formulation proportion. At ratios of 1.5:1 and 2:1, drug precipitation occurred after several hours. While co-surfactants aid in microemulsion formation within a suitable concentration range, an excess of co-surfactant can compromise system stability due to the drug's high aqueous solubility, resulting in increased droplet size from expanding interfacial film. Consequently, the optimal ratio of surfactant to co-surfactant was selected.

2.1.4 Formulation Development

Examining the formulations of SDEDDS for composition and conditions of preparation

The oil phase and the lipophilic emulsifier were thoroughly mixed after being weighed in a particular ratio. The inner aqueous phase, either water or a 20 mg/mL Tamoxifen solution, was gradually dropped into the oil phase using magnetic stirring at 1000 rpm and room temperature to create the coarse water/oil emulsions. Water/oil emulsions that were fine and homogenous (10000 rpm 3 min/6 min/9 min, 13000 rpm 3 min/6 min/9 min) were generated under different homogenization circumstances. The last step was to create tamoxifen-loaded SDEDDS by dividing the water/oil emulsions proportionally using Labrasol and magnetic swirling. The type of self-emulsifying oil phase (liquid paraffin) and lipophilic emulsifiers (Tween 80 and Span 80) that are frequently utilized were investigated using microscopic morphology, volume-weighted mean droplet size, and self-emulsifying area.

Table-2.1: Ingredients of the tamoxifen SDEDDS.

Formulation Code	Tamoxifen(mg)	Olive oil (%)	Tween80 (%)	Span 80 (%)	Liquid paraffin	Labrasol
F1	20	5	20	20	10	45
F2	20	10	20	20	10	40
F3	20	15	20	20	10	35
F4	20	20	20	20	10	30
F5	20	25	20	20	10	25

F6	20	30	20	20	10	20
F7	20	35	20	20	10	15
F8	20	40	20	20	10	10

2.1.5 CHARACTERIZATION

Particle size analysis19

The SDEDDS formulations' particle size distribution following their conversion to water/oil/water multiple emulsions was determined using dynamic light scattering fitted with a He–Ne laser (k = 623 nm). The results were frequently represented by the volume-weighted mean droplet size. Results were given after Every formulation was made by tested 3 times in parallel.

Drug entrapment efficiency20

encapsulation efficiency is a critical parameter for evaluating the preparation of several emulsions being successful. In the process of generating W/O/W multiple emulsions, it is defined as the proportion of the aqueous phase marker introduced to the inner aqueous phase that stays trapped within the inner aqueous phase. This metric is crucial for evaluating the emulsions' post-storage leakage rates serve as an indicator for encapsulation stability, reflecting the ability of the system to retain the hydrophilic drug within the inner water phase after storage. encapsulation efficacy, which affects the multiple emulsion system's overall performance and quality. The best blank and Tamoxifen- loaded formulations of SDEDDS were created; the inner aqueous phase contained 20 mg/ml of Tamoxifen. With light stirring, they might Self-forming into several W/O/W emulsions, which would then be diluted with an outer aqueous phase. In short, a fresh preparation of 1 milliliter of W/O/W numerous diluted emulsions. Using 14 ml of filtered centrifuged with water in a refrigerator-cooled centrifuge at 10,000 rpm for 15 minutes at 4 °C. within order to remove the oil droplets, the the outermost lowest aqueous phase that resulted was gathered into a 1 milliliter syringe and filtrated using a 0.22 micrometer membrane filter. It was then examined using a UV visible spectrophotometer.

2.1.6 In vitro drug release study21

Tamoxifen's release from SDEDDS formulations using the Franz diffusion cell device was examined in vitro. In summary, 100 ml of different release media (e.g., phosphate buffer solution, pH 7.4) or water), were individually supplied to diffusion vessels containing the appropriate volumes of blank and Tamoxifen-loaded SDEDDS formulations. Considering Tamoxifen's tendency toward thermal instability, the release medium's temperature was kept at 25The stirrer was set at 100 rpm and the temperature was within ± 0.5 °C. The sample was then taken out in 2 ml increments and immediately replaced with new medium at predefined intervals. The disclosure profiles were created after determining the cumulative release of tamoxifen from the SDEDDS formulations. We performed three separate analyses for every formulation.

2.1.7 Drug release kinetics22

Kinetics modelling was conducted by the kinetics of zero order, first order, and higuchi order, krosmeyer order Kinetic and finally plot the graphs.

2.1.8 Stability studies23

The stability of freshly made SDEDDS formulations and those that were stored at room temperature for 30 days were investigated by tracking changes in yield, oil droplet size, microscopic morphology, and a number of other characteristics over time. Encapsulation stability may be shown by the post-storage leakage rates of the emulsions, as the fraction of the hydrophilic medication that is supplied to the inner water phase and remains trapped inside after storage.

3.RESULTS AND DISCUSSION

3.1 Studies of drug-excipient compatibility (FT-IR):

The drug's compatibility with the selected lipid and other excipients was evaluated using the FTIR peak matching technique. The lack of peak appearance or disappearance in the drug-lipid mixture confirmed that the medication, lipid, and other components did not interact chemically.

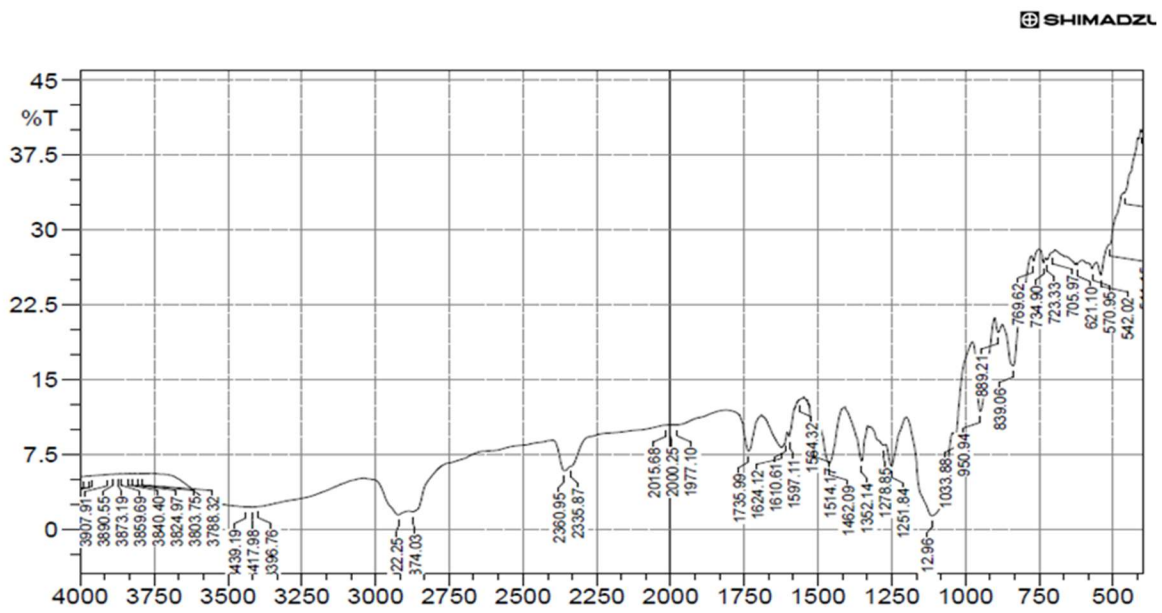


Figure-3.1: FT-IR Sample for Tamoxifen

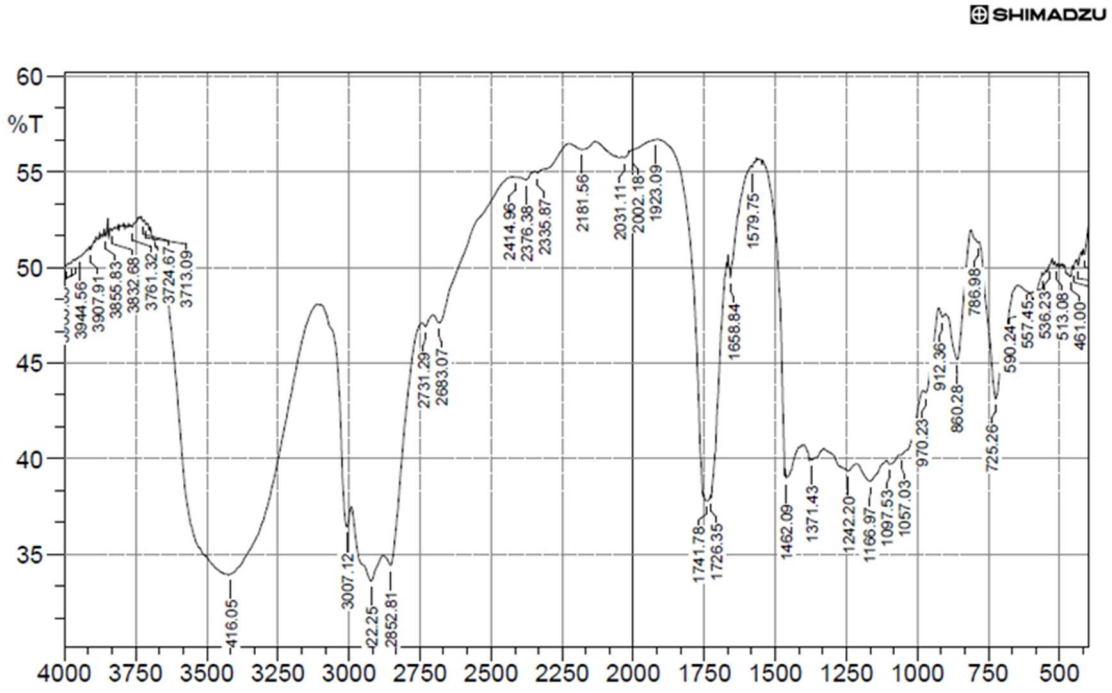


Figure-3.2: FT-IR Sample for drug and excipient physical mixture

Tamoxifen's and drug excipients' mixtures' infrared spectra were shown respectively. In In the current investigation, it has been noted that the medication and the polymers employed do not interact chemically. Your observation of the drug's IR spectra's primary peaks remains unchanged. Polymer and drug mixture suggests that there are no physical interactions or bond formations between them. Absolutely, reinforcing the integrity of the pure drug and affirming compatibility with the mixture's excipients is fundamental for maintaining the efficacy and safety of the medication.

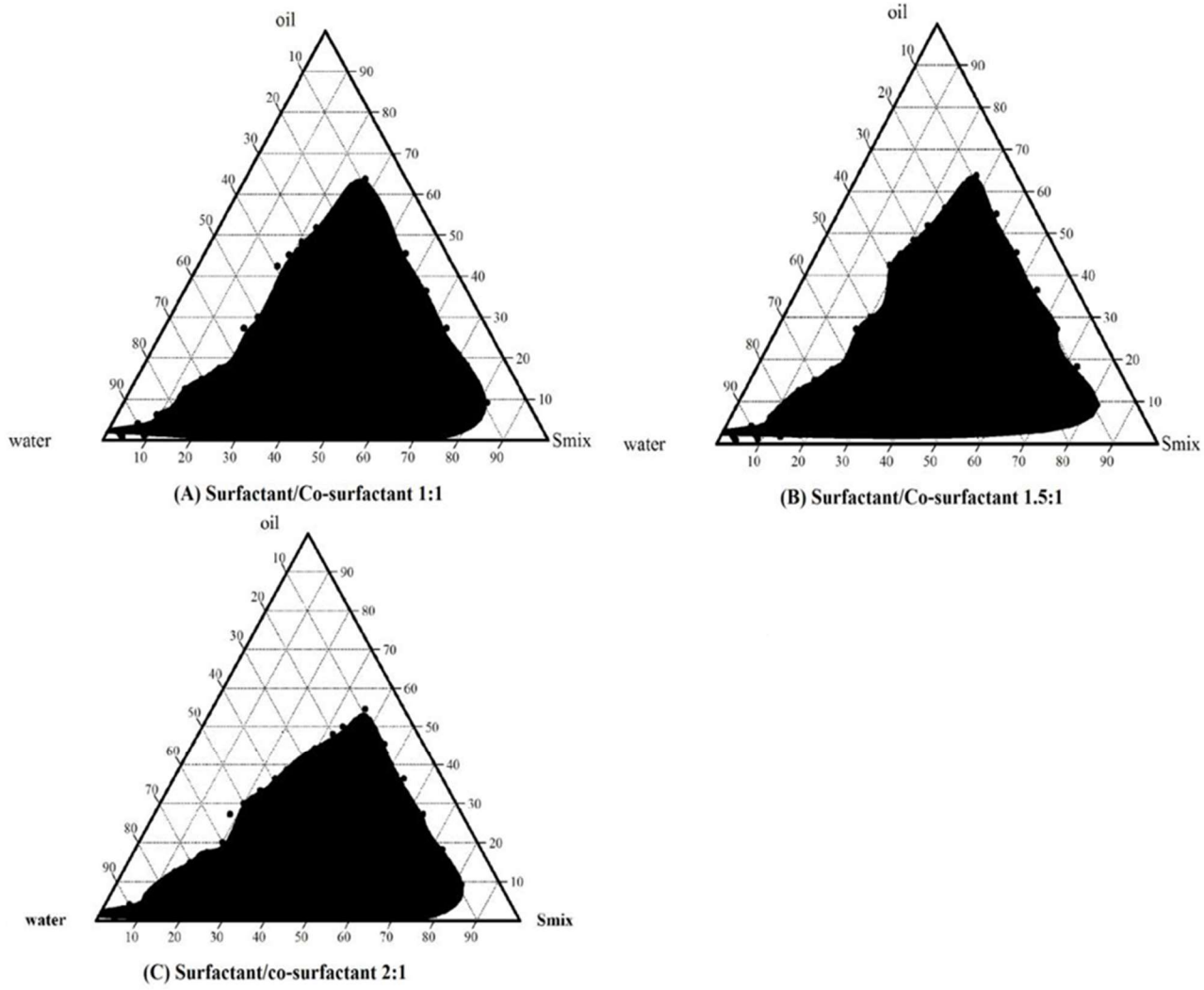
3.2 Solubility Studies

Table 3.2: Tamoxifen's Solubility in Co-Surfactants, Oils, and Surfactants

Drug	Role in SDEDDS	Solubility Average* (mg/ml)
sunflower oil	Oil	2.34±0.22
Sesame oil	Oil	1.97±0.13
Castor oil	Oil	2.22±0.23
Olive oil	Oil	2.33±0.25
Polysorbate 80	Surfactant	73.45±0.04
Span 80	Surfactant	62.65±0.14
Labrosol	Cosurfactant	32.86±1.03

Propylene glycol	Cosurfactant	8.84±0.37
Liquid paraffin	Cosurfactant	9.43±0.49

3.3 Pseudo Ternary Phase Diagram



• Figure 3.3:(A) co-surfactant:surfactant ratio: 1:1 (B)co-surfactant: surfactant 1.5 :1 ratio& (C)co-surfactant: surfactant 2 :1 ratio ,Water, hydrocarbon, cosurfactant, and surfactant are shown in the pseudoternary phase diagram of the system.

Evaluation Parameters:

3.4 Entrapment Efficiency:

Table 3.4.1: All Formulations of drug entrapment efficiency

F-No.	DEE
F1	76.93±0.03
F2	80.26±0.04
F3	69.16±0.02
F4	80.17±0.13
F5	79.87±0.135
F6	79.16±0.13
F7	81.30±0.04
F8	78.94±0.125

3.5 Determination of Particle Size and zeta potential

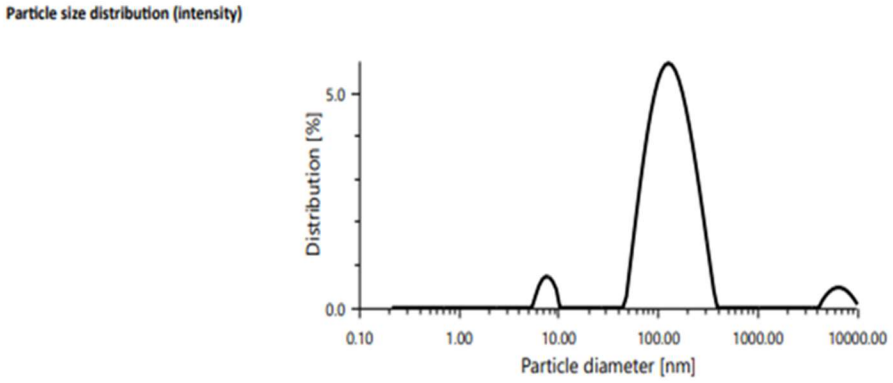


Figure 3.5.1: Particle size of optimized formulation

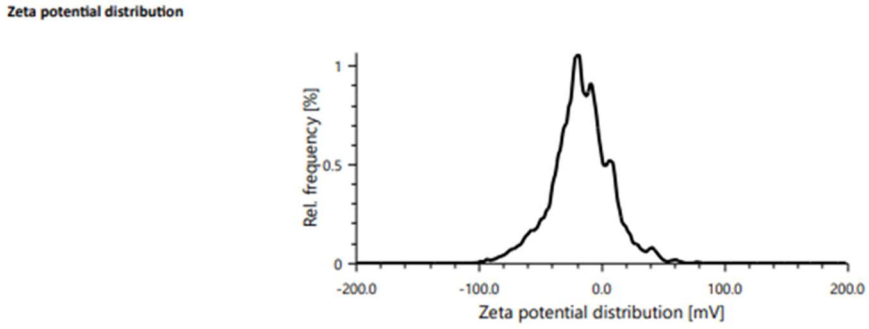


Figure 3.5.2: Zeta potential of optimized formulation

Table-3.5.1: Evaluation Studies of particle size and Zeta potential SDEDDS

FNo.	Particle Size (nm)	Zeta Potential
F-1	100.22±0.14	-29±0.6
F-2	108.52±0.16	-18±0.3
F-3	102.33±0.07	-23±0.5
F-4	114.52±0.06	-19±0.3
F-5	120.62±0.18	-29±0.6
F-6	116.52±0.02	-17±0.3
F-7	103.79±0.09	-23±0.4
F-8	101.36±0.13	-28±0.5

3.6 In vitro drug release studies:

Table3.6.1: Total percentage of drug release from different formulations of the Self-Double Emulsifying Drug Delivery System (SDEDDS).

Hours	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
0	0	0	0	0	0	0	0	0
1	10.42±0.2	11.86±0.2	13.32±0.8	14.14±0.35	13.38±0.13	15.09±0.44	18.56±0.46	14.80±0.42
2	22.61±0.4	23.1±0.5	27.48±0.5	21.65±0.4	22.19±0.25	24.21±0.45	23.28±0.12	23.15±0.08
3	35.65±1.04	36.41±0.6	36.8±1.04	32.31±0.5	33.49±0.21	32.4±0.14	38.93±0.04	32.45±0.12
4	48.28±0.08	44.57±0.7	43.35±0.6	47.31±0.7	45.95±0.12	44.4±0.01	42.48±0.07	44.31±0.7
6	54.12±0.23	56.64±0.12	55.34±0.04	57.92±0.04	50.31±0.8	53.59±0.04	50.63±0.09	56.96±0.15
8	69.47±0.14	66.32±0.14	68.64±0.01	64.02±0.7	65.43±0.17	68.14±0.04	68.35±1.05	65.12±0.32

10	75.59±0.4	73.2±0.07	75.86±0.25	72.37±0.07	72.12±0.25	73.88±0.04	79.18±1.04	76.44±0.44
12	89.54±0.04	90.25±0.04	91.27±0.04	90.25±0.09	89.39±0.11	91.47±0.08	93.69±0.25	92.87±0.42

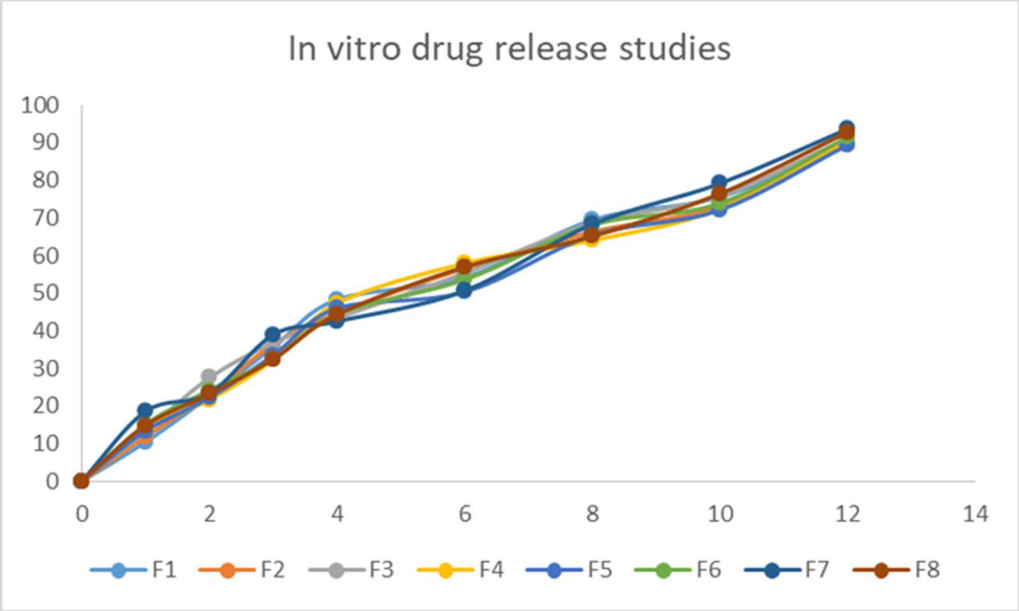
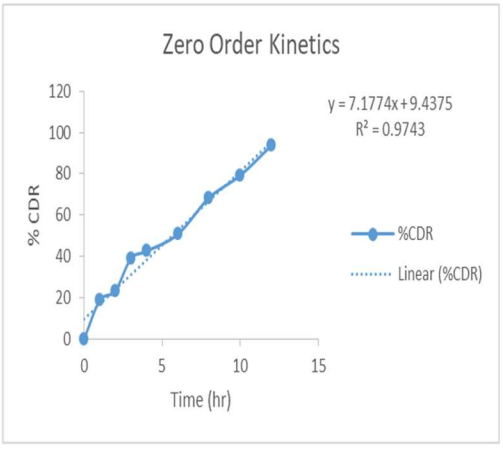
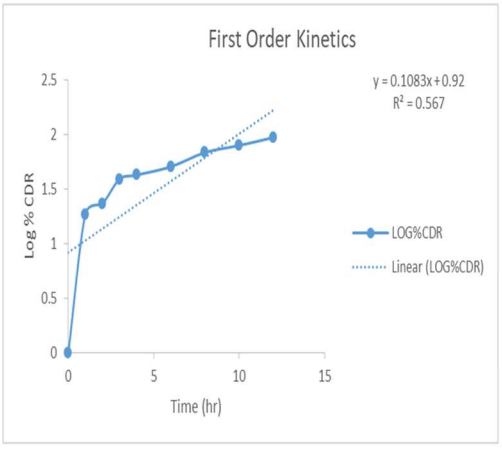


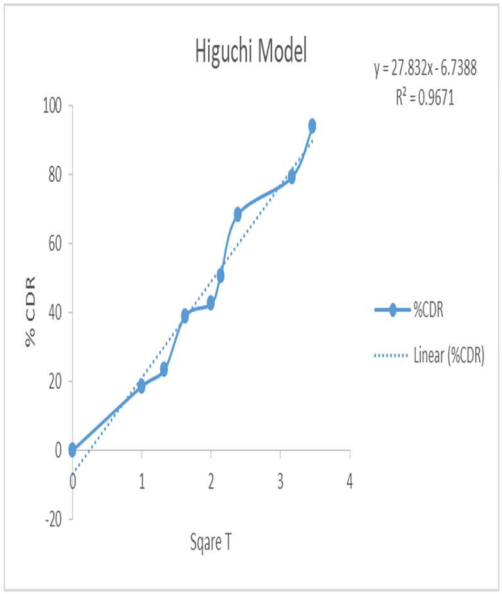
Figure 3.6.1: In vitro studies of (F1-F8) formulations

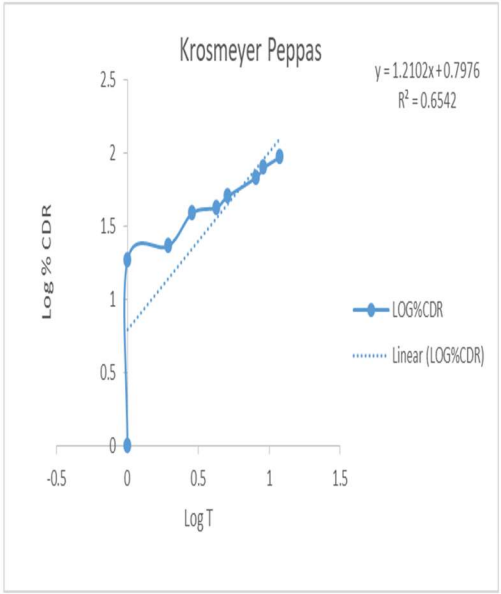
It seems like formulation F7, across all three batches, consistently released the drug over a 12-hour period with a cumulative percentage release of 93.6%.

3.7 Kinetic modelling of drug release In-vitro release tests were conducted on all eight formulations of produced Tamoxifen, with the aid of dissolving apparatus.









Kinetic modelling of drug release

There were several attempts to fit the in-vitro release values into quantitative models. outlines of Peppas, Higuchi matrix, first order, and zero order. Zero order release kinetics have greater regression values. As a result, the release kinetics of all Tamoxifen SDEDDS follow zero order.

3.8 Stability studies

Stability studies:

Table 3.8.1 : Stability studies of optimized composition F7.

Code of Preparation	Considerings	First release	1st Month	2nd Month	3rd Month	Boundaries Based on Provisions
F7	250C/60% RH% Release	94.68	93.47	92.900	91.99	Not more than 85 %
F7	300C/75% RH% Release	94.68	93.6	92.77	91.67	
F7	400C/75% RH% release	94.68	93.48	92.59	91.46	

Conclusion

We successfully created the Tamoxifen loaded SDEDDS formulations for the current study. The Tamoxifen release profiles obtained from the best formulations of SDEDDS. After 12 hours, the cumulative release of tamoxifen was approximately 90%, resulting in a prolonged release in 7.4 phosphate buffer release media. The release of Tamoxifen that was inadequately entrapped allowed us to conclude that the SDEDDS formulations were stable and did not experience an early burst release. The study indicates a promising outcome, with Tamoxifen's cumulative release from SDEDDS formulations achieving balance within 12 hours, aligning with previous research. The noteworthy stability of the optimal formulation over a three-month period at room temperature further strengthens the potential viability of the studied formulations.

REFERENCE

1. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Advanced drug delivery reviews. 2012 Dec 1;64:24-36.

2. Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Advanced drug delivery reviews. 2003 Feb 24;55(3):329-47.

3. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Advanced drug delivery reviews. 2002 Nov 1;54:S131-55.

4. Gershkovich P, Wasan KM, Barta CA. A review of the application of lipid-based systems in systemic, dermal/transdermal, and ocular drug delivery. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2008;25(6).

5. Pavelić Ž, Škalko-Basnet N, Filipović-Grčić J, Martinac A, Jalšenjak I. Development and in vitro evaluation of a liposomal vaginal delivery system for acyclovir. Journal of controlled release. 2005 Aug 18;106(1-2):34-43.

6. BENAMEUR H. Liquid and semi-solid formulations for enhancing oral absorption. Bulletin Technique Gattefossé. 2006;99:63-75.

7. Pouton CW, Porter CJ. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Advanced drug delivery reviews. 2008 Mar 17;60(6):625-37.

8. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nature reviews Drug discovery. 2007 Mar;6(3):231-48.

9. Dahan A, Hoffman A. Rationalizing the selection of oral lipid based drug delivery systems by an in vitro dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs. Journal of controlled release. 2008 Jul 2;129(1):1-0.

10. Hanpramukkun N, Kongmuang S, Chansiri G. The stability of clindamycin phosphate in w/o/w multiple emulsions. Int J Pharm Sci Tec. 2009;3(2):1-7.

11. Silva-Cunha A, Grossiord JL, Seiller M. Multiple emulsions: Pharmaceutical potentiality. Multiple Emulsions: Structure, Properties and Applications, Editions de Sante, France. 1999:279-312.

12. Taelman MC, Loll P. Multiple emulsions in cosmetics. ICI Surfactants, Reprint, RP112 E. 1994;94:1994.

13. Franckum J, Ramsay D, Das NG, Das SK. Pluronic lecithin organogel for local delivery of anti-inflammatory drugs. International journal of pharmaceutical compounding. 2004 Mar 1;8(2):101.

14. van der Graaf S, Schroën CG, Boom RM. Preparation of double emulsions by membrane emulsification—a review. Journal of Membrane Science. 2005 Apr 1;251(1-2):7-15.

15. Matsumoto S, Koh Y, Michiure A. Preparation of w/o/w emulsions in an edible form on the basis of phase inversion technique. JOURNAL OF DISPERSION SCIENCE ANDTECHNOLOGY. 1985 Dec 1;6(5):507-21.

16. Wakerly MG, Pouton CW, Meakin BJ. Evaluation of the self-emulsifying performance of a non-ionic surfactant-vegetable oil mixture. J Pharm Pharmacol. 1987;39(6):b70.

17. Shima M, Tanaka M, Fujii T, Egawa K, Kimura Y, Adachi S, Matsuno R. Oral administration of insulin included in fine W/O/W emulsions to rats. Food Hydrocolloids. 2006 Jun 1;20(4):523-31.

18. Matsumoto S, Koh Y, Michiure A. Preparation of w/o/w emulsions in an edible form on the basis of phase inversion technique. JOURNAL OF DISPERSION SCIENCE ANDTECHNOLOGY. 1985 Dec 1;6(5):507-21.

19. Garti N, Aserin A. Pharmaceutical emulsions, double emulsions, and microemulsions. Drugs and the pharmaceutical sciences. 1996;73:411-534.

20. YOSHIOKA T, IKEUCHI K, HASHIDA M, MURANISHI S, SEZAKI H. Prolonged release of bleomycin from parenteral gelatin sphere-in-oil-in-water multiple emulsion. Chemical and Pharmaceutical Bulletin. 1982 Apr 25;30(4):1408-15.

21. Dickinson E, McClements DJ. Advances in food colloids. Springer Science & Business Media; 1995.

22. van der Graaf S, Schroën CG, Boom RM. Preparation of double emulsions by membrane emulsification—a review. Journal of Membrane Science. 2005 Apr 1;251(1-2):7-15.

23. Singh SK, Prasad Verma PR, Razdan B. Glibenclamide-loaded self-nanoemulsifying drug delivery system: development and characterization. Drug development and industrial pharmacy. 2010 Aug 1;36(8):933-45.