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FORMULATION AND EVALUATION OF SELF-EMULSIFYING DRUG DELIVERY SYSTEM USING HEPATOPROTECTIVE AGENT

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ABSTRACT

Objective: The objective of the present study was to develop self-emulsifying drug delivery system (SEDDS) of Silymarin to improve its solubility, in vitro dissolution efficiencies, and further the bioavailability)

Materials and Methods: The solubility of silymarin in various oils, surfactants, and cosurfactants was determined. Pseudotemary phase diagrams were constructed using Capryol 90, Transcuto P,Span 80 to identify the efficient self-microemulsification region. Prepared SEDDS was evaluated for emulsification time, drug content, droplet size, and in vitro dissolution.

Results and Discussion: The optimized formulation F3 had shown the smallest particle size, maximum solubility, less emulsification time, drug stability in water, and improved in vitro release. In the present study, already existed historical data were used for importing data. Optimized SEDDS Silymarin formulation (F3) prepared had shown improved in vitro release when compared to commercial formulation.

Conclusion: It was concluded that SEDDS would be a promising drug delivery system for poorly water-soluble drugs through oral route.

Keywords: Self-Emulsifying Drug Delivery System, Silymarin, Hepatoprotective Agent.

1.Introduction

SMEDDS is a mixture of lipid, surfactant, and cosurfactant, which are emulsified in aqueous medium under gentle digestive motility in the gastrointestinal tract[1]. When designing formulations for such active pharmaceutical components, about one-third of the pharmaceuticals originating from drug discovery programmes are poorly water soluble, posing a number of challenges for pharmaceutical scientists (API)[2]. S(M)EDDS are isotropic combinations of oil, hydrophilic surfactant, and/or cosurfactant, as well as a

solubilized drug. They can be enclosed in hard or soft gelatin capsules or solidified (Solid SEDDS/SMEDDS). When these formulations are diluted with water, they spontaneously create a fine oil-in-water emulsion in the case of SEDDS and a nanoemulsion in the case of SMEDDS[3]. They are easily disseminated in the GI tract, where the stomach and small intestine movement provides the moderate agitation required for emulsification. SEDDS creates coarse emulsions, whereas SMEDDS creates droplets smaller than 100 nanometers[4].

2.MATERIALS & METHOD:

Silymarin was a gift sample from Yarrow Chem Products Pvt. Ltd. Capryol 90 and Span 80 were procured from Loba Chemie Pvt. Ltd. Transcutol P were purchased from Molychem India Pvt. Ltd. All other chemicals were obtained from commercial sources.

Determination of Saturation Solubility Studies[5-6]:

The Saturated solubility studies was carried out by placing excess amount of drug in to 2 ml of solvent (Oil/Surfactant/Co-surfactant) in 5 ml glass vial with rubber closer. Vial containing Drug-solvent mixture was subjected to intense sonication for 30 min with heating. Vial was kept unstirred for 48 hours to allow equilibrium in system. Supernatant layer was and centrifuged at 2000 RPM for 10 min to sediment undissolved drug present if any. 1 ml of post centrifugation supernatant was diluted up to 10 ml with methanol and evaluated using UV-Visible spectrophotometer.

Construction of Ternary Phase Diagram[7-8]:

Selected Surfactant and co-solvent were mixed in the ratio of 1:1, 2:1 to prepare Smix. Various formulations were prepared with selected oil and each Smix where concentration of oil ranges from 10 to 90%. Transparency of resultant emulsion was observed. Transparent/Bluish appearance confirm microemulsion region and turbid appearance confirms macroemulsion region. Ranges of oil, surfactant and co-solvent, where microemulsion region, were used for further optimization.

Formulation of Silymarin SMEDDS:

The Formulations showing microemulsion region were selected. The selected Microemulsions from ternary phase diagram study were used by adding 150 mg of drug Silymarin to each formulation.

table 1.1: formulation table of smedds

Batches	Ingredients				Total (ml)
	Drug (mg)	Capryol 90 (ml)	Transcutol P (ml)	Span 80 (ml)	
F1	150	1.00	4.50	4.50	10
F2	150	2.00	4.00	4.00	10
F3	150	4.00	3.00	3.00	10
F4	150	5.00	2.50	2.50	10
F5	150	9.00	0.50	0.50	10
F6	150	1.00	6.00	3.00	10
F7	150	2.00	5.33	2.67	10
F8	150	3.00	4.67	2.33	10
F9	150	4.00	4.00	2.00	10
F10	150	8.00	1.33	0.67	10
F11	150	9.00	0.67	0.33	10

Evaluations of Silymarin SMEDDS[9-12]:

a. Appearance:

The Appearance of the prepared SMEDDS was observed visually. The prepared SMEDDS was mixed with 100 ml of water and checked for its Transparency, Colour and Clarity.

b. Emulsification Time:

The Emulsification time is the critical parameter for SMEDDS. The Emulsification time of the prepared SMEDDS should be less than 30 seconds. The Emulsification time was obtained by mixing the prepared SMEDDS in sufficient quantity of water and was allowed to emulsify on its own. The time taken by SMEDDS to completely disperse into water was measured.

c. Cloud Point Measurement:

The Cloud point is an essential factor in the SMEDDS consisting of non-ionic surfactants, and it is responsible for the successful formation of a stable microemulsion. When the temperature is higher than the cloud point, and irreversible phase separation will occur and the cloudiness of the preparation would have a bad effect on drug absorption, because of the dehydration of the polyethylene oxide moiety. Hence, the cloud point for SMEDDS should be above 37°C, which will avoid phase separation occurring in the gastrointestinal tract. The SMEDDS was diluted with water in the ratio of 1:250, and the sample was placed in a water bath with the temperature increasing gradually at 2°C intervals, spectrophotometric analysis was carried out to measure the sample transmittance using an empty glass test tube as a blank.

d. Turbidity:

The Turbidity of the prepared SMEDDS was measured by using the Turbidimeter. The SMEDDS was placed in the cuvette and later the turbidity reading was observed for all the formulation.

e. Emulsion Droplet Size:

The Emulsion droplet size was performed by using Malvern particle size analyser. The SMEDDS were dissolved in water in a ratio of 1:100, and checked for the droplet size of the Emulsion.

f. Viscosity:

The Viscosity of the prepared SMEDDS was measured by using Oswald Viscometer. The SMEDDS were dissolved in water in a ratio of 1:100, and checked for the Viscosity of the Emulsion.

g. Drug Content:

The Drug content was calculated by dissolving 1 ml of SMEDDS in 100 ml of 0.1M hydrochloric acid and the absorbance of the solution was measured at 286 nm. The absorbance of the standard solution of silymarin was also obtained and the % Drug Content was determined by using following formula;

$$\%\ Drug\ Content = \frac{Sample\ absorbance}{Standard\ absorbance} \times 100$$

h. In-vitro Drug Studies:

Studies of the drug release/diffusion from SMEDDS are directed towards the approaches that are relevant to the in-vivo condition. For in-vitro dissolution test, USP apparatus II (paddle) method was used. 0.1M HCl was used as the dissolution media. Paddle speed of 50 rpm and 900 ml of the dissolution medium were used. As soon as the paddles were rotated, membrane bag containing 1 ml of SMEDDS was introduced into each dissolution vessel containing dissolution medium. Samples were obtained at different time intervals like 0.5,1,

2, 3, 4, 5, 6, 7 and 8 hours, filtered through 0.45µ Nylon filter, diluted suitably with dissolution medium and analysed by UV spectroscopy at wavelength of maximum absorption.

3.RESULTS & DISCUSSION:

3.1 By IR Spectroscopy:

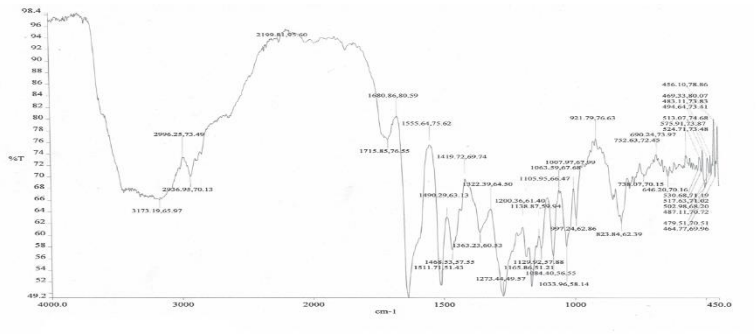

figure a : ir spectrum of obtained silymarin

The IR spectrum of the drug sample was recorded and the functional groups where interpreted as per the structure and where found to be appropriate the structure of the drug. Fig a gives the IR spectra of the pure drug, gives the interpretation of the peaks obtained in the IR spectra along with their corresponding functional groups.

The given IR spectra of Silymarin shows the principle peaks such as >C=C< Aromatic 1508 cm^{-1} -O-H Stretch 1083,1157,1269 cm^{-1} ,

-COOH Carboxylic acid 1732 cm^{-1}

indicate that above IR spectra is of Silymarin which is identified and proved. The broad intense peak that appeared at 3457 cm^{-1} was specifically due to oxygen-containing functionality of SL. The broad peak represented –OH stretching vibration mode. The distinct peaks observed at 2942 cm^{-1} and 2880 cm^{-1} were due to the presence of CH-CH stretching vibration. The reactive flavonolignon ketone showed strong intense peak at 1639 cm^{-1}. A small intense peak at 1365 cm^{-1} and 1278 cm^{-1} was due to –OH bending and C-O-C stretching, respectively. Two conjugated peaks emerged at 1509 cm^{-1} and 1467 cm^{-1} representing aromatic ring stretching vibrations. An intense peak appeared at 1731 cm^{-1} showed the presence of C-O stretch from aromatic ring structure. The in-plane vibration stretching of –C-H was observed at 1085 cm^{-1} corresponding to flavonolignans, while the peaks that appear at 996 cm^{-1} were due to benzopyran ring. The SL primarily reveals the presence of polyphenolic moiety and confirms its structural vibrational frequencies from FTIR spectra.

3.2 Selection of Wavelength:

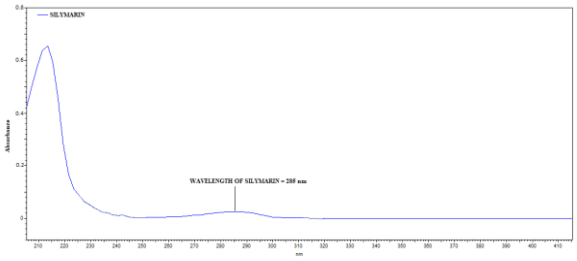

figure b: uv spectrum of obtained silymarin

Silymarin was analyzed for its UV Lambda max and it was found that maximum absorbance was observed at 285 nm. The literature value is also close to the same value that we reported.

3.3 Construction of Calibration curve in 0.1 M Hydrochloric acid:

The Calibration curve of Silymarin was constructed in 0.1M Hydrochloric acid. The obtained absorbances of corresponding concentrations were plotted and it was found to be linear. Absorbance at different concentration showed in The regression coefficient of the Silymarin was found to be 0.9959

Table A : results of calibration curve of silymarin

Sr No.	Concentration (ug/ml)	Absorbance
1	10	±0.219
2	20	±0.404
3	30	±0.561
4	40	±0.762
5	50	±0.986

*(n=3)

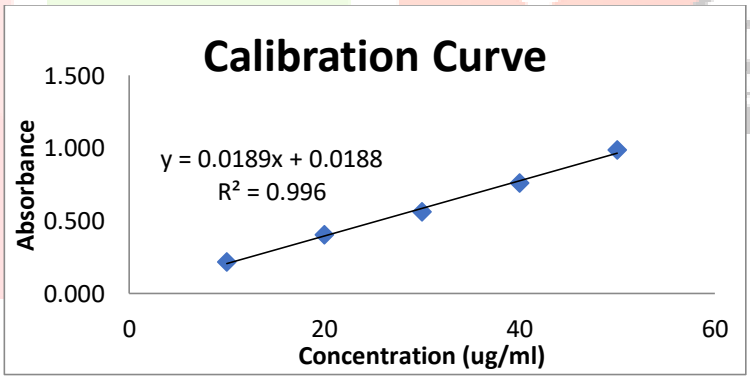

figure c : calibration curve of silymarin

Parameters	**Value**
λmax (nm)	285 nm
Beer's law limit (µg/ml)	10 – 50 µg/ml
A 1% 1cm	401.42
Correlation coefficient (r2)	0.9959
Regression Equation (y=a+bc)	Y=0.0189x+0.0188

Intercept (a)	0.0188
Slope (c)	0.0189
Limit of quantification (µg/ml)	0.82 µg/ml
Limit of detection (µg/ml)	0.31 µg/ml

The linearity projected is linear for the concentration of 10ug/ml to 50ug/ml.

Determination of Saturation Solubility:

table B : results for solubility of silymarin in different oils

Sr. No.	Oils	Solubility (ug/ml)	SD
1	Cottonseed Oil	±26.74	±2.14
2	Soybean Oil	±56.21	±3.93
3	Castor Oil	±67.08	±1.34
4	Capryol 90	±113.67	±7.96
5	Coconut oil	±73.49	±5.88
6	Linseed oil	±34.76	±1.74
7	Light Mineral oil	±21.27	±1.91
8	Olive Oil	±102.76	±5.14

*(n=3)

Solubility of silymarin was studied in 8 different oils to know and choose an oil phase for SMEDDS preparation. Eight different oils were used likewise: Cottonseed Oil, Soybean Oil, Castor Oil, Capryol 90, Coconut oil, Linseed oil, Light Mineral oil and Olive Oil. . Silymarin was found to be soluble in Capryol 90 having a solubility of 113.67±7.96 µg/ml which was higher than compared to other oils hence it was selected as Oil phase for the further studies of Ternary phase diagram. The Results of the Solubility of the Silymarin in different Oils are given in Table B.

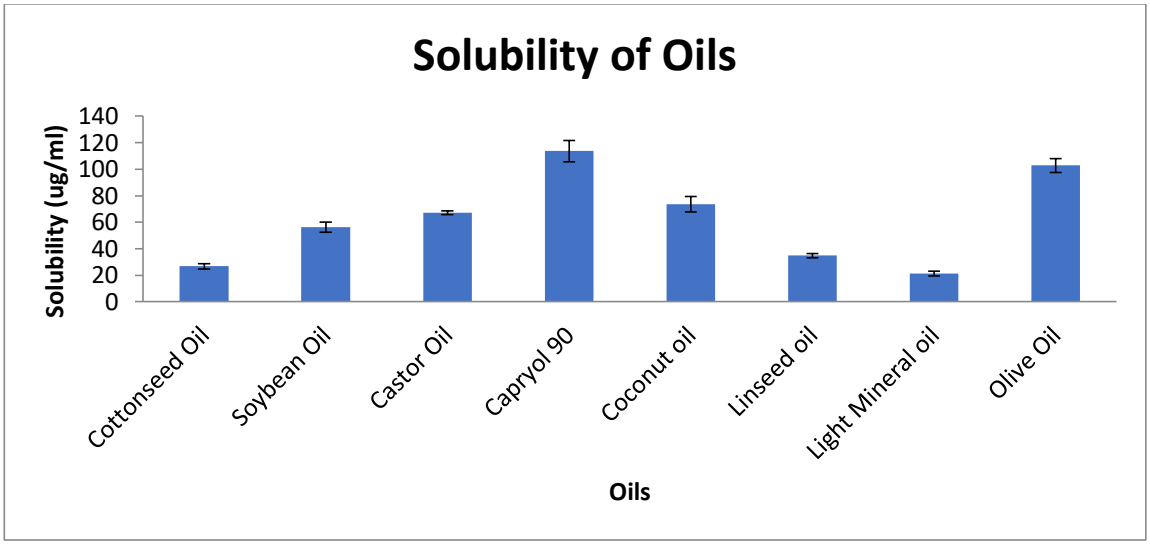

figure d : solubility of silymarin in different oils

Solubility of Silymarin in Surfactants and Co-surfactants were studied as below:

table C : results for solubility of silymarin in different surfactants/co-surfactants

Sr. No.	Surfactants/Co-surfactants	Solubility (ug/ml)	SD
1	Transcutol P	±29.81	±2.38
2	Tween 40	±6.84	±0.48
3	Tween 60	±7.67	±0.15
4	Tween 80	±12.61	±2.14
5	Propylene Glycol	±3.11	±0.25
6	Span 80	±21.95	±1.10
7	Transcutol HP	±12.05	±1.08
8	Kolliphor RH 40	±17.83	±0.89

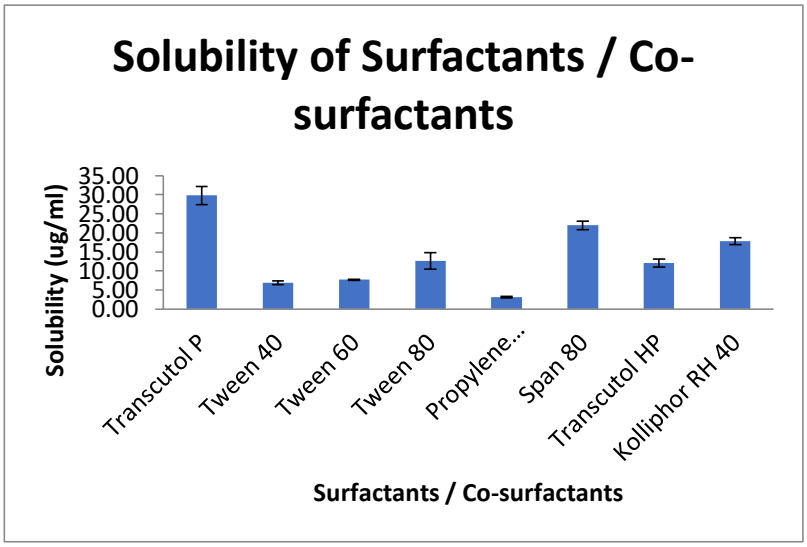

figure e : solubility of silymarin in different surfactants/co-surfactants

The Silymarin was dissolved in different surfactants and co-surfactants comprising of Transcutol P, Transcutol HP, Tween 40, Tween 60, Tween 80, Span 80, Propylene glycol and Kolliphor RH 40. The Silymarin possessed a solubility 29.81±2.38 µg/ml in Transcutol P and 21.95±1.10 µg/ml in Span 80 and hence were selected as Surfactant and Co-Surfactant in the study of Ternary Phase diagram. The Results of the Solubility of the Silymarin in different surfactants and co-surfactants are given in Table C .

6.3. Construction of Ternary Phase Diagram[13-14]:

The SMEDDS formulations that could self-emulsify under aqueous dilution and gentle agitation were identified through ternary phase diagram. The Ternary Phase Diagrams was constructed using Capryol 90 as oil phase, Transcutol P as surfactant and Span 80 as co-surfactant. The surfactant and co-surfactants were mixed in different ratios like 1:1 and 1:2. These Smix were mixed with oil in different weight ratios like 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 and titrated with aliquots of water to obtain a stable microemulsion. These stable microemulsion points were plotted on a ternary phase diagram to obtain a microemulsion region. This region was very helpful was further optimization of the SMEDDS formulation. The Results of Ternary phase diagram are given in Table D and the Figure f and g depicts the Ternary phase diagrams.

table D : results of ternary phase diagram

Smix Ratio (S:Cos)	Oil (ml)	Smix (ml)	Water (ml)	Emulification
1:1	1	9.00	5.80	Yes
	2	8.00	7.20	Yes
	3	7.00	8.10	No
	4	6.00	9.80	Yes
	5	5.00	10.90	Yes
	6	4.00	5.51	No
	7	3.00	4.10	No
	8	2.00	5.42	No
	9	1.00	6.50	Yes
2:1	1	9.00	3.00	Yes
	2	8.00	5.21	Yes
	3	7.00	6.20	Yes
	4	6.00	2.65	Yes
	5	5.00	4.35	No
	6	4.00	6.75	No
	7	3.00	2.17	No
	8	2.00	9.11	Yes
	9	1.00	9.54	Yes

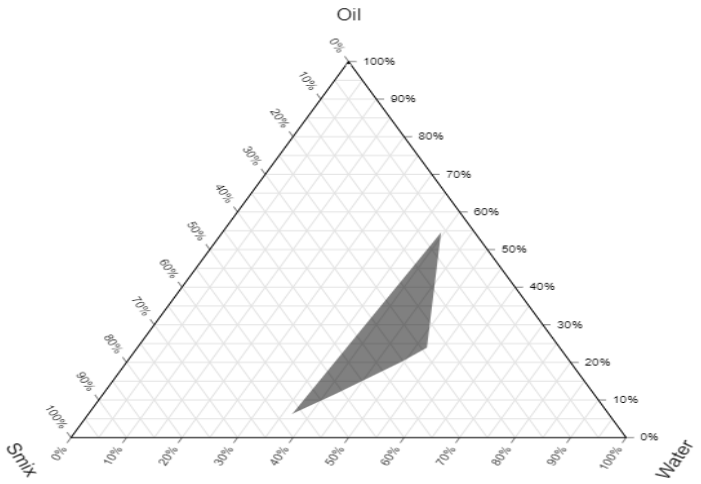

figure f: ternary phase diagram using 1:1 ratio of smix

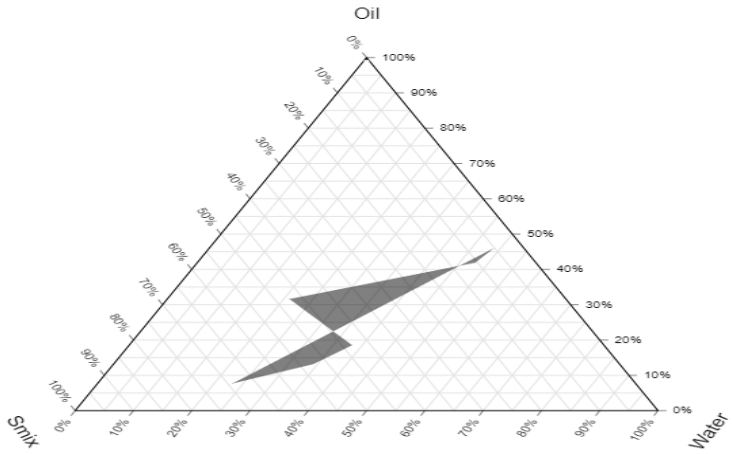

figure g : ternary phase diagram using 2:1 ratio of smix

In order to aid successful microemulsion development, it is essential to study the ternary phase behaviour of potential combinations of oil, surfactant and co-surfactant. Pseudo-ternary phase diagrams were therefore constructed to determine regions of microemulsion formation. The shaded region in the ternary diagram signifies the self-emulsification domain. Incorporation of co-surfactant, Capryol 90, within the self-microemulsifying region increased the spontaneity of the self-emulsification process. The efficiency of emulsification was good when the surfactant/co-surfactant concentration was 70% w/w of SMEDDS formulation. Moreover, the spontaneous emulsion formation was not efficient with 50% w/w of surfactant in SMEDDS. It has been reported that the drug incorporated in the SMEDDS may have some effect on the self-microemulsifying performance.

Five percent w/w of Silymarin was added to the boundary formulations and random points inside the self-emulsification area of the ternary phase diagrams and selfemulsification performance was accessed. No significant differences were found in self-microemulsifying performance when compared with the corresponding formulations with Silymarin. The prepared SMEDDS were further evaluated for its Physiochemical properties[15]

Evaluation of SMEDDS:

a. Appearance:

The appearance of all prototype was same as to be "Transparent, Slightly bluish and Clear product".

b. Emulsification time:

There was a major change in emulsification time for all prototypes. The Emulsification time ranged between 19 to 49 seconds. All within 1 minute. Thus, determining the best based on emulsification time was not the best way to short list the prototypes.

c. Cloud point Measurement:

Cloud point of each prototype was studied. Based the cloud point ranged between 28.8^{0}C to 79.6^{0}C. As the cloud point temperature has to be above 37^{o}C, formulation F4, F5, F7, F8, F11 have cloud point below 37^{o}C. Formulation F1, F2, F3, F6, F9,F10 have cloud point above 37^{o}C. Making them as the desired choice of prototype for further testing.

Table E : Results for Appearance, Emulsification time & Cloud point of SMEDDS

Batch	Appearance	Emulsification Time (seconds)	Cloud point measurement (°C)
F1	Transparent, Slightly bluish, Clear	± 24	± 65.8
F2	Transparent, Slightly bluish, Clear	± 19	± 66.7
F3	Transparent, Slightly bluish, Clear	± 22	± 79.6
F4	Transparent, Slightly bluish, Clear	± 36	± 38.5
F5	Transparent, Slightly bluish, Clear	± 38	± 37.2
F6	Transparent, Slightly bluish, Clear	± 23	± 73.5
F7	Transparent, Slightly bluish, Clear	± 41	± 29.6
F8	Transparent, Slightly bluish, Clear	± 49	± 28.8
F9	Transparent, Slightly bluish, Clear	± 21	± 67.8
F10	Transparent, Slightly bluish, Clear	± 22	± 69.4
F11	Transparent, Slightly bluish, Clear	± 36	± 30.1

*(n=3)

d. Turbidity:

table F : results for turbidity, emulsion droplet size, viscosity and drug content of smedds

Batch	Turbidity (NTU)	Emulsion Droplet Size (nm)	Viscosity (cps)	% Drug Content
F1	0	± 157	± 56.1	± 98.9
F2	0	± 163	± 67.2	± 100.4
F3	0	± 121	± 45.6	± 101.5
F4	0	± 591	± 43.9	± 98.6
F5	0	± 672	± 51.9	± 99.2
F6	0	± 189	± 53.4	± 98.7
F7	0	± 582	± 62.3	± 97.1
F8	0	± 891	± 61.9	± 98.1
F9	0	± 175	± 68.5	± 102.5
F10	0	± 155	± 49.6	± 100.9
F11	0	± 776	± 54.5	± 99.5

*(n=3)

e. Emulsion droplet Size:

The Emulsion droplet size is a critical parameter for enhancing the bioavailability of the drug. The SMEDDS were subjected to Emulsion droplet size measurement by mixing the SMEDDS with water in the ratio of 1:100 and the globule size of the emulsion was measured by using Malvern particle size analyzer. The average size of emulsion was of nanosized for all the SMEDDS preparation. Batches F1, F2, F3, F6, F9 and F10 were having size less than 200 nm. Hence, on the basis of the globule size these batches were shortlisted for the drug release studies.

f. Viscosity:

The Viscosity was measured by mixing the SMEDDS with water in ratio of 1: 100. The viscosities of all the batches were found to be less than 70 cps for all the batches. The lower the viscosity of the batch, the faster will be the drug release.

g. Drug Content Determination:

The % Drug content is a critical parameter to achieve the therapeutic efficacy. The Drug content was determined spectrometerically. The formulations were developed with the expectations of obtaining the drug content between 95-105% w/v. The % Drug content of all the SMEDDS was found to be within the specified range. The % Drug contents of F2, F3 and F10 were almost 100% w/v.

h. in-vitro drug release studies:

table G : results for in-vitro drug release

Time (hrs.)	F1	F2	F3	F6	F9	F10
0	± 0.00	± 0.00	± 0.00	± 0.00	± 0.00	± 0.00
0.5	± 3.54	± 8.37	± 12.36	± 5.36	± 8.49	± 7.26
1	± 7.67	± 13.48	± 19.38	± 11.28	± 15.21	± 15.29
2	± 13.65	± 25.37	± 30.12	± 27.08	±24.66	± 22.82
3	± 22.85	± 33.08	± 41.68	± 39.94	± 34.64	± 33.43
4	± 37.94	± 46.72	± 53.32	± 49.31	± 49.31	± 45.63
5	± 43.81	± 59.63	± 67.29	± 61.17	± 58.13	± 57.04
6	± 51.67	± 67.05	± 76.71	± 69.64	± 69.21	± 68.44
7	± 60.54	± 75.27	± 85.18	± 78.57	± 81.39	± 78.85
8	± 68.12	± 82.17	± 97.65	± 88.26	± 93.57	± 91.25

*(n=3)

The % Drug release of the optimized batch F1, F2, F3, F6, F9 and F10 were performed for 8 hours. The % Drug release was batch F1 showed to 68.12% drug release over the period of 480 minutes. The % Drug release of batches F2 and F4 was found to be 82.17% and 88.26% w/v, respectively. The % Drug release of batches F5 and F6 was found to be 93.57% and 91.25% w/v, respectively. The Batch F3 was found to have 97.65% drug release which was better than compared to other batches. From the drug release results, it was found that Smix in the ratio of 1:1 and ratio of Oil to Smix 4:6 was found suitable for the faster delivery of the Silymarin.

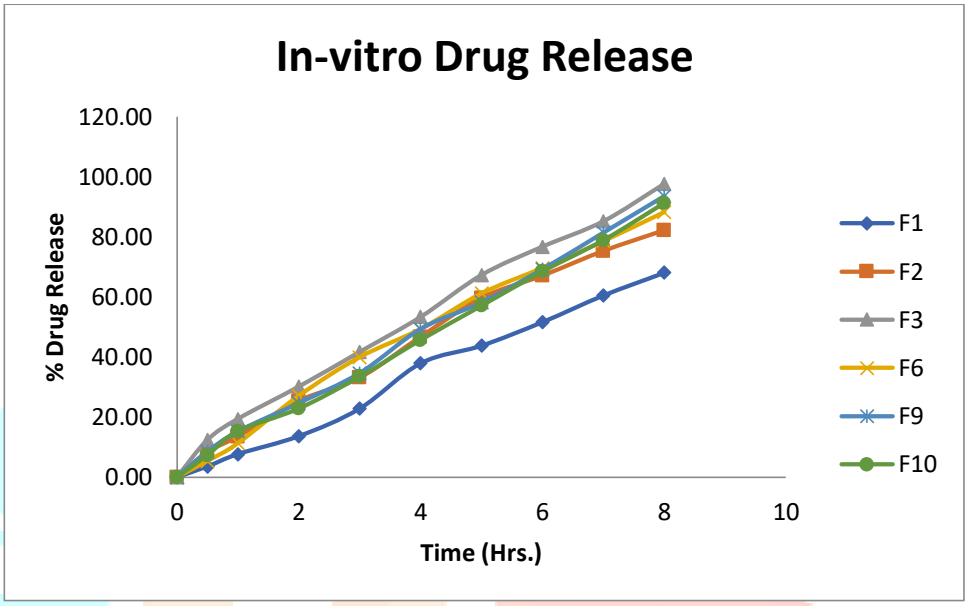

Figure h : in-vitro drug release studies of SMEDDS

The results of Batch F3 % drug release was further studied for its drug release kinetics to determine the best fit release kinetics model. The Best fit model for Batch F3 was found to be Zero Order kinetics.

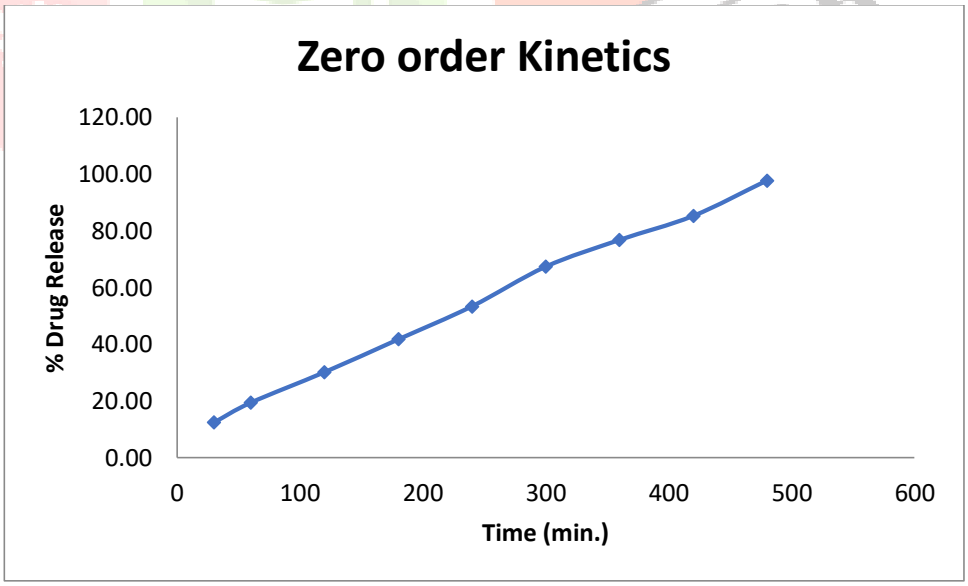

figure i: zero order kinetics of batch f3

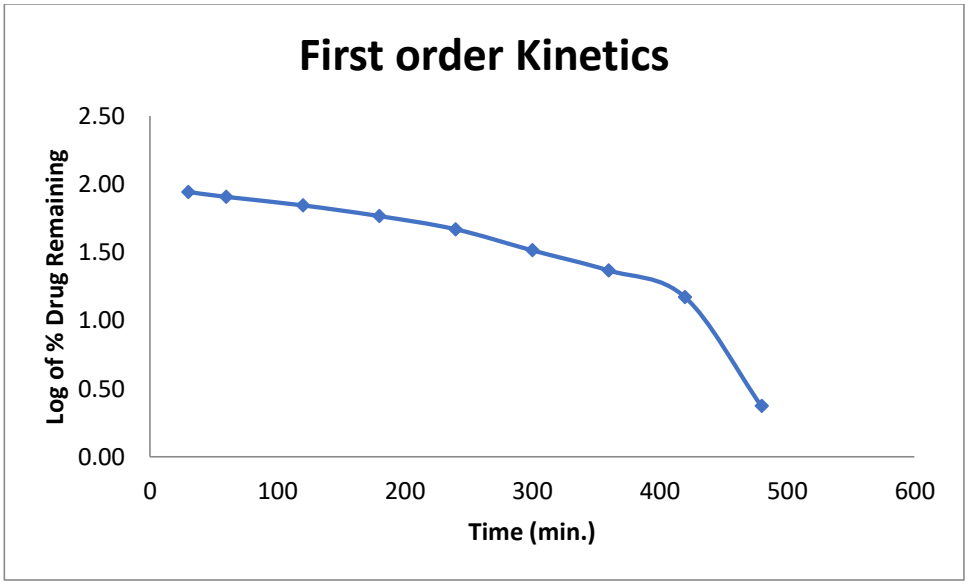

figure j : first order kinetics of batch f3

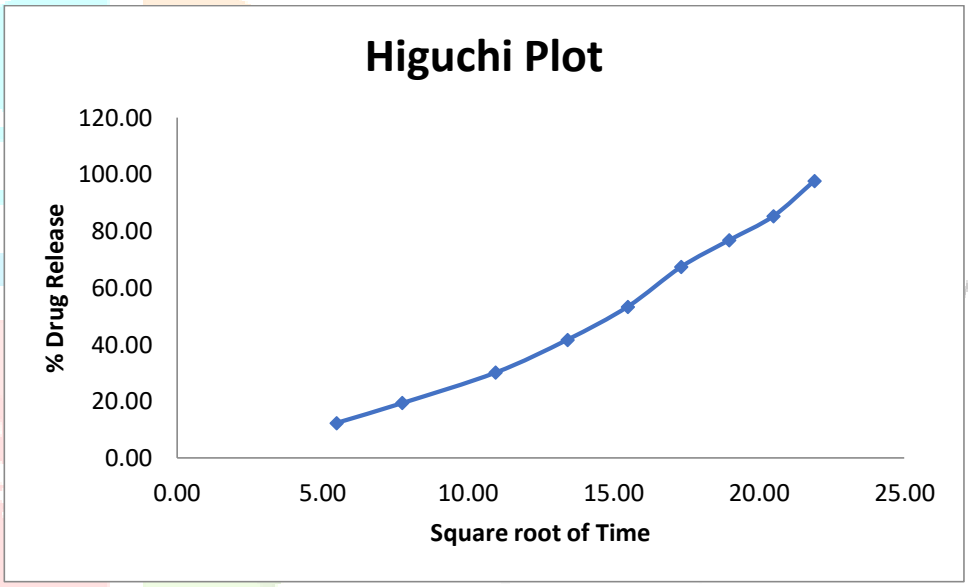

Figure k : Higuchi of Batch F3

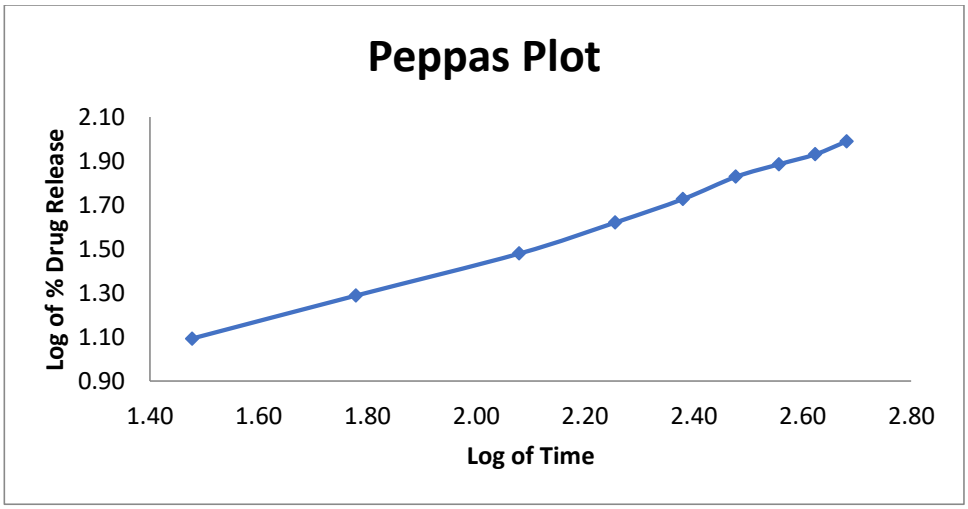

Figure l : Peppas Plot of Batch F3

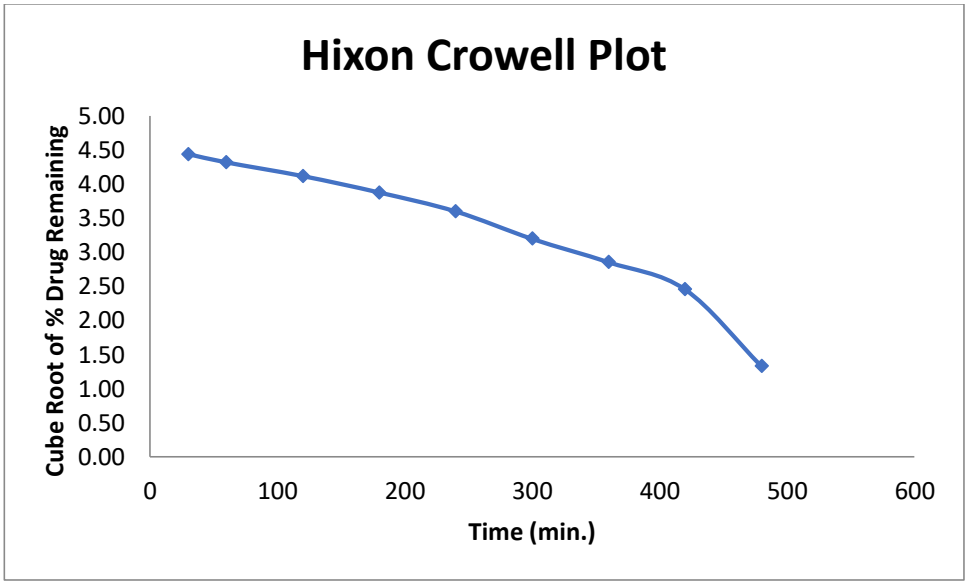

Figure m : Hixon Crowell plot of Batch F3

CONCLUSION

An attempt has been made to formulate and evaluate "Self Emulsifying drug delivery system of Silymarin" (SEDDS). Silymarin is insoluble in water and has low oral bioavailability. The absorption of the drug is dissolution rate dependent. The bioavailability problem can be overcome by the Self emulsifying drug delivery system, which presents the drug in saturated form (High energy form) and also partly /complete solubilized form to the body, which bypasses the dissolution process in the drug absorption.

Silymarin was identified by FTIR and UV absorbance. UV Calibration curve was constructed for further studies. Saturation solubility was determined in different oils and were found that silymarin was the highest soluble in Caproyl 90 with 113.67 ug/ml. Study of solubility of Silymarin in surfactants was studied as the final formulation was SMEDDS. The Silymarin possessed a solubility 29.81±2.38 µg/ml in Transcutol P and 21.95±1.10 µg/ml in Span 80 and hence were selected as Surfactant and Co-Surfactant in the study of Ternary Phase diagram. Based on the Ternary phase diagram SMEDDS formulation was made and studies on physiochemical characteristics were done. Based on Appearance, Emulsification, Cloud point, Turbidity, Emulsion droplet size, Viscosity, Drug content and In-Vitro drug release study, the ideal formulation was found to be formulation F3. The results of Batch F3 % drug release were further studied for its drug release kinetics to determine the best-fit release kinetics model. The Best fit model for Batch F3 was found to be Zero Order kinetics.

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