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Formulation And Evaluation of Self Nano emulsifying Drug Delivery System of Poorly Water Soluble Drug

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Abstract:
Nano-emulsion is a relatively new and fascinating field of research that aims to take advantage of appealing qualities of components to increase oral administration, such as cinnamon oil's usage in diabetic disease management. The Self-Nano Emulsifying Drug Delivery System (SNEDDS) offers a lot of promise for enhancing the solubility and bioavailability of medicines that are poorly soluble. So an effort was made to increase the solubility, dissolving rate, and bioavailability of cinnamon oil utilizing SNEDDS. Cinnamon oil's solubility was tested in a variety of vehicles, including oils, surfactants, and co-surfactants. Based on the solubility, a pseudo-ternary phase diagram was created to determine the most effective self-emulsification zone. For the manufacture of SNEDDS, oleic acid (oil), Tween 80 (surfactant), and propylene glycol (co-surfactant) were chosen. In comparison to Km 1 and Km 2, Km=3 was chosen for the preparation of SNEDDS of cinnamon oil because it shows the best Nano emulsion region. The pseudo ternary phase diagram was produced with the medication present to determine the emulsification range and to assess the effect of cinnamon oil on the phase's emulsification behavior. The main feature of these systems is their ability to produce an oil in water (o/w) emulsion or micro emulsion after dilution by an aqueous phase with modest agitation. The improved formulation was next tested for thermodynamic stability, rheology, percent transmittance, cloud point, drug content, FTIR, particle size distribution, and zeta potential to ensure that the created SNEDDS formulation was stable.

Keywords- Cinnamon oil, SNEDDS, solubility, surfactant, improving bioavailability.

Introduction:

The low bioavailability and considerable intra- and intersubject variability are typically linked with the oral administration of weakly water soluble medicines. One of numerous ways used to increase the oral bioavailability of poorly water soluble drugs intended for oral delivery is the use of lipid and surfactant-based formulation[1]. Self-Nano-Emulsifying drug delivery system (SNEDDS) are isotropic mixtures of active drug, oil, surfactant and usually one or more hydrophilic co-solvent or co-emulsifiers that on contact with aqueous medium upon mild agitation. SNEDDS have proven to be a viable method to boost oral systemic bioavailability of poorly water soluble medicines. . Most of the nanoparticle systems have been developed for the delivery of poorly water soluble drugs for enhances their bioavailability in the GI-tract. Nano-emulsion is preferred drug delivery system because of their stability and possibility of easy oral

administration to improve drug self-emulsification[2].
SNEDDS is a promising method for BCS class 2 or 4 and medicinal compounds with low aqueous solubility. It is best suited for lipophilic drugs, as the ensuing emulsification allows for faster dissolution and absorption[4]. SNEDDS, which have been demonstrated to significantly improve oral bioavailability with further development of this technology, can be used to administer hydrophobic medicines orally. SNEEDS will continue to enable novel applications in drug delivery and solve problem associated with the delivery of poorly soluble drugs. Cinnamon has been given generally recognized as safe status by the FDA[5].

Material & Method:
Cinnamon oil was purchased from Sanket enterprises, Essential oils/fine chemicals/Aromatic chemicals, Jogeshwari (East), Mumbai. Tween 80, Propylene glycol and Oleic acid were supplied from Molychem, Mumbai. All another material & chemical used were of analytical reagent grades.

Selection and Screening of Potential Nano-Emulsion Component (Surfactant, Co-Surfactant and Oil):
It is notable that an increasing proportion of new studies recognize the benefit associated with employing pharmaceutically acceptable surfactant, co-surfactant and oils. To develop a Nano-Emulsion system for oral administration of poorly water soluble cinnamon oil, suitable oil, surfactant and co-surfactant need to be chosen. Surfactants employed in SNEDDS formulation have been demonstrated to boost bioavailability through a variety of processes, and the addition of a co-surfactant has been proven to expand the Nano-Emulsion zone. Oil was selected on the basis of good solubilizing capacity for cinnamon oil as well as ease of emulsification from solubility study oleic acid showed good solubilizing capacity for cinnamon oil (33.00 ± 0.4359) amongst the other oil investigated. In case of surfactant and co-surfactant, Tween 80 (14.43 ± 0.05) and propylene glycol (20.98± 0.02) have a good solubilizing capacity, from the solubility study oleic acid, Tween 80 and propylene glycol were selected for cinnamon SNEDDS formulation as oil, surfactant and co-surfactant respectively.

Construction of Pseudo Ternary Phase Diagram:
For the improvement of SNEDDS formulations, pseudo ternary phase diagrams were used to identify the Nano-emulsion region and optimize the concentration of the selected vehicles. The optimum ratio of excipients concentrations was determined using phase diagram studies, which provided the area of the Nano-emulsion region. Based on the findings of solubility tests, oil, surfactant, and co-surfactant were chosen for Nano-emulsion formulations. For the phase diagram investigation of cinnamon SNEDDS, nine different potential combinations of surfactant mixture to oil at different Km values (1, 2 and 3) were employed. No distinct conversion of water in oil (w/o) to oil in water (o/w) was observed the boundary layer of w/o Nano-Emulsion was determined in each phase diagram. Components used for construction of pseudo ternary phase diagram are oleic acid (oil phase), Tween 80 (surfactant), propylene glycol (co-surfactant) and distilled water (aqueous phase)

Km – 1 (1:1)

Table no. 1 Composition of Oleic acid, Tween 80, Propylene glycol and Water at Km 1:1

Sr. No.	S mix : oil	Composition expressed as % w/w		
		Oil	S mix	Water
1	1:9	75.4	6.9	17.7
2	2:8	72.3	11.4	16.3
3	3:7	68.1	18.9	13.0
4	4:6	55.6	26.1	18.3
5	5:5	48.0	32.6	19.4
6	6:4	41.5	35.1	23.4
7	7:3	38.7	39.0	22.3
8	8:2	17.2	33.7	49.1
9	9:1	14.8	28.2	57.0

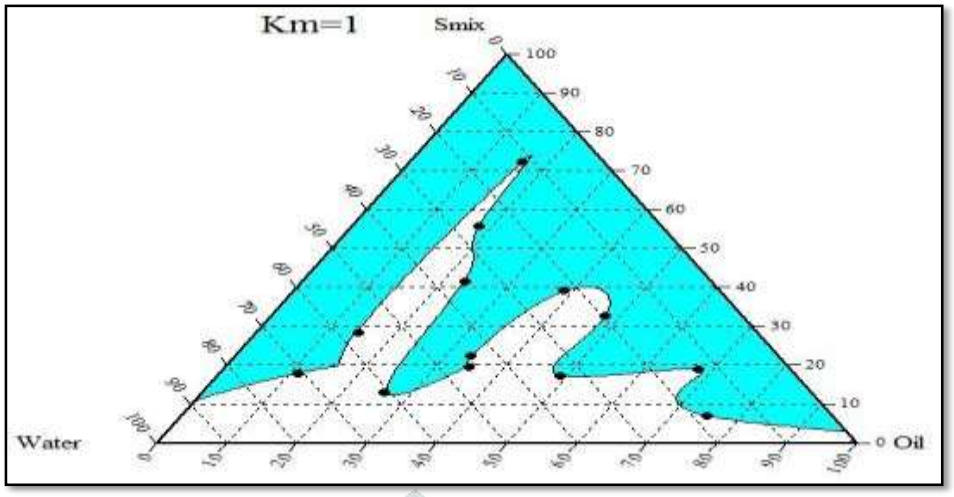

Fig.1. Pseudo Ternary Phase Diagram of Oleic acid: Tween 80: PropyleneglycolKm – 2(2:1)

Table no.2: Oleic acid: Tween 80: Propylene glycol: Water at Km = 2

Sr. no	S mix : oil	Composition expressed as % w/w		
		S mix	Oil	Water
1	1:9	8.5	82.4	9.1
2	2:8	12.2	75.0	12.8
3	3:7	19.4	66.9	13.7
4	4:6	29.5	60.7	9.8
5	5:5	32.1	56.2	11.7
6	6:4	38.0	50.1	11.9
7	7:3	41.7	46.2	12.1
8	8:2	31.9	48.1	20.0
9	9:1	43.3	36.4	20.3

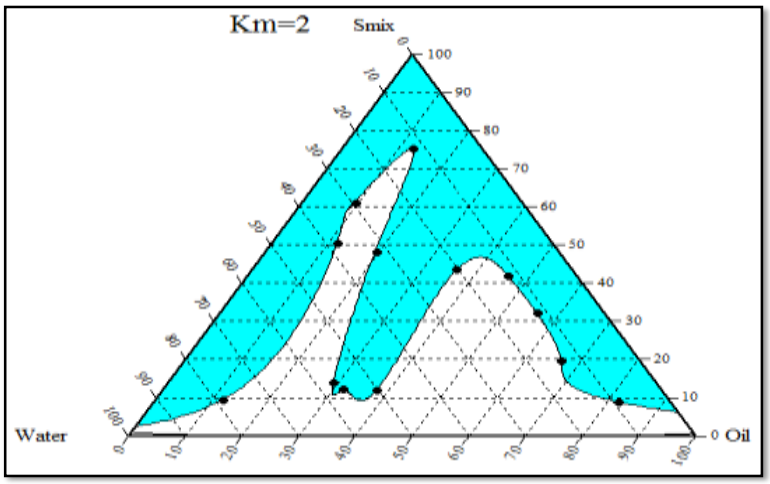

Fig. no. 2. Pseudo Ternary Phase Diagram of Oleic acid: Tween 80: Propyleneglycol

Km – 3 (3:1)

Table no. 3. Composition of Oleic acid: Tween 80: Propylene glycol: Water atKm-3

Sr.no	S mix : Oil	Composition expressed as %w/w		
		S mix	Oil	Water
1	1;9	9.0	82.0	9.0
2	2:8	18.7	71.2	10.1
3	3:7	27.4	62.0	10.6
4	4:6	30.2	58.6	11.2
5	5:5	33.3	52.9	13.8
6	6:4	37.1	51.0	11.9
7	7:3	28.6	61.0	10.4
8	8:2	26.8	63.0	10.2
9	9:1	22.9	67.1	10.0

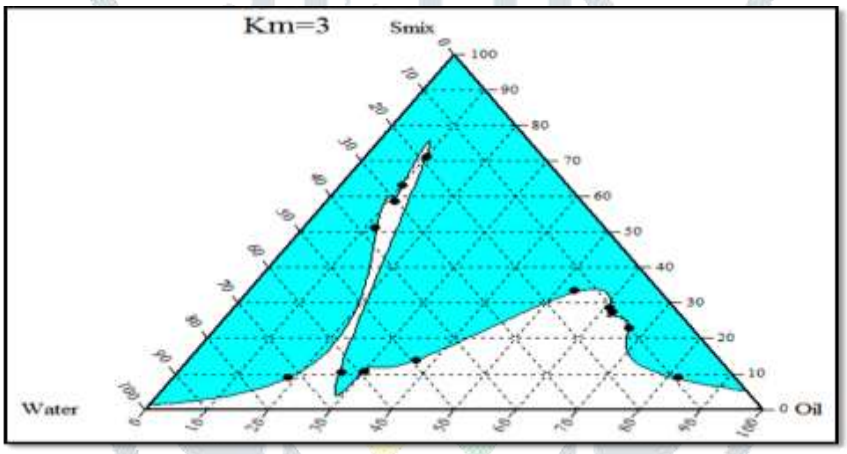

Fig. no. 3. Pseudo Ternary Phase Diagram of Oleic acid: Tween 80: Propyleneglycol.

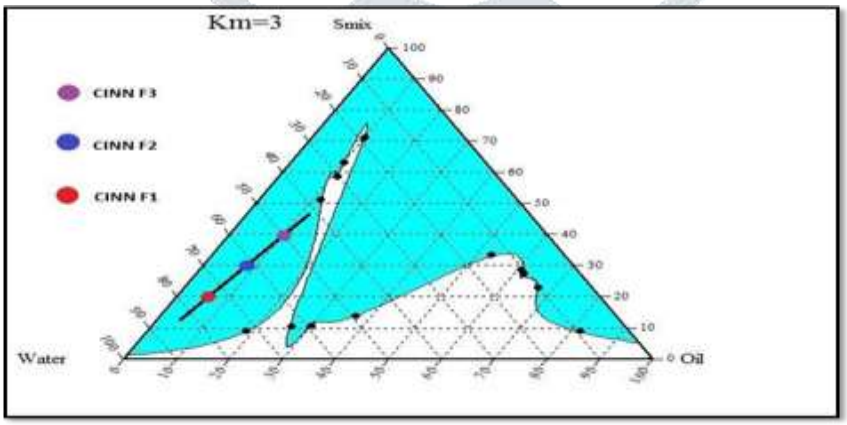

Fig. no .4. Selected Composition of Formulations Cinnamon Oil

Preparation of Liquid Self Nano Emulsifying Drug DeliverySystem (SNEDDS):

Oleic acid – Tween 20 – propylene glycol – water based system selected at final Pseudo ternary phase diagram of various surfactants and co – surfactants weigh ratio was constructed and system of highest water absorption (highest Nano emulsionregion) selected for formulation. The phase diagram at Km value

3 showed better Nanoemulsion existence region than 1 and 2.

.Table no. 4. Composition of Selected Formulation:

Formulations	Drug (mg)	Water	Formulation composition in ml	
			Oil	S mix
F 1	100	75	5	20
F 2	100	63	7	30
F 3	100	50	10	40

Evaluation of Liquid Self Nano Emulsifying Drug Delivery System:

Physical Characterization:

The visual observation was used to check the SNEDDS' organoleptic qualities, such as color, aroma, and physical appearance.

Rheological Study:

The generated formulations' viscosity was determined by using a Brookfield viscometer, which decides the consistency of nano-emulsion formulations. 1ml of each created mixture was diluted 10 times with distilled water, then the viscosity was measured using a Brookfield viscometer and any phase separation was visually examined.

Globule Size and Zeta Potential Determination:

SNEDDS formulation optimized from droplet size and PDI estimation was determined using a analyzer sz-100. These formulations were subjected to sonication prior diluted with excess (100 times) double distilled water and then examined. OR 1ml of SNEDDS was diluted with 500 ml double distilled water. This was mixed for 1 min by gentle agitation using magnetic stirrer. The zeta potential of formed Nano Emulsion were determined at room temperature by Nanoparticle analyser sz-100.

Assessment of Self Emulsification:

Emulsification time of the SNEDDS formulation optimized formulation was added drop wise to 500 ml of distilled water maintained at 37 ± 0.3 ^{0}C. A basic stainless steel dissolving basket revolving at 50 rpm offered gentle agitation. The time it takes for the emulsion to form is measured visually.

Percentage Transmittance:

The percent transmittance was measured at 229 nm using a UV – Visible spectrophotometer (Shimadzu - 1800) against distilled water after 1 ml of liquid SNEDDS was diluted to 100 ml distilled water.

Cloud Point Measurement:

The liquid SNEDDS was diluted in distilled water at a 1: 250 ratio, placed in a water bath, and the temperature was gradually increased. The cloud point was defined as the temperature at which cloudiness appeared suddenly.

Fourier Transforms Infrared Analysis:

Cinnamon sample was analyzed by Furrier Transforms Infrared spectroscopy (UV – Agilent Technology) to characterize the probable structural modification produced. The sample was analyzed in the region of 400 cm – 1 and then sample or mixture kept into sample holder for analysis. Similarly, the spectra of polymers were taken.

In Vitro Drug Release:

In vitro dissolution studies of prepared SNEDDS are carried out. The SNEDDS formulation was filed in hard gelatin capsule. In vitro drug release profile of cinnamon from SNEDDS was assessed using USP dissolution testing apparatus 1 (basket type) at 50 rpm with 900 ml as dissolution medium. Temperature was set at 37.0 ± 0.5 ^{0} C and sampling interval were fixed at 5, 10, 15, 20, 25, 30 min 5ml of sample

withdraw at each time interval and replaced with 5ml fresh phosphate buffer solution. The solution was immediately filtered through Whitman filter paper and from filtered sampled 1 ml sample was evaluated for the drug content using UV – Visible spectrophotometric method.

Table no. 5. In Vitro Dissolution Condition Employed in the Dissolution Study:

Sr. no.	Parameter	Specification
1	Dissolution medium	900 ml, phosphate buffer 6.8 p^H
2	Temperature	37± 0.5 ^{0}C
3	Rotation speed	50 rpm
4	λmax	302 nm

Result & discussion:

Physical Characterization:

Table no. 6.Organoleptic Properties of Formulation

Sr.No	Properties	To be found
1	Color	Golden – Yellow
2	Odor	Characteristic
3	Taste	Very hot aromatic taste, Pungent

Rheological Study:

The Rheological properties of the prepared formulations were evaluations were evaluated by Brookfield viscometer. This viscosities determination confirm the system is o/w or w/o. if system has low viscosity then it is o/w and high viscosity thenw/o. viscosity of prepared batches was identify by diluting 1ml sample of each batch with 10ml and 100ml of distilled water by using Brookfield viscometer.

Table no. 7. Rheological Study

Sr.no	Batch	Viscosity Cp	
		10 ml dilution	100 ml dilution
1	Cinnamon F 1	0.6357	0.4362
2	Cinnamon F 2	0.7352	0.5921
3	Cinnamon F 3	0.5361	0.3140

Globule Size Analysis and Zeta Potential Determination:

Because it determines the rate and extent of drug release as well as drug absorption, the droplet size globule size of the emulsion is a critical factor in Self Nano emulsification performance. Smaller particle size of the emulsion droplets may lead to more rapid absorption and improved bioavailability. The globule

size and zeta potential determined absorption and improve the bioavailability. The globule size and zeta potential determined using Nanoparticle analyzer sz-100. The average globule size was take in to consideration table no. 8 shows the particle size of optimized batch CINN 2 of cinnamon SNEDDS diluted with water. The average particle size obtained from optimized batch CINN 2 of SNEDDS formulation of cinnamon was found to be 178.9nm, zeta potential-23 mv and polydispersity index was found to be 0.374. zeta potential is the another property that was assessed for increased absorption of SNEDDS is the charge of oil droplets which is usually found to be negative due to the presence of free fatty acid these results indicate that the optimal cinnamon oil SNEDDS formulation produced clear nano emulsion with Nanometric size

Table no. 8 Globule Size, Zeta Potential Determination and PDI.

Sr.no	Formulation	Average particle size (droplet size/globule size)	Zeta potential	Polydispersity index(PDI)
1	Cinnamon F 1	193.7 nm	- 20 mV	0.317
2	Cinnamon F 2	178.9 nm	- 23 mV	0.374
3	Cinnamon F 3	200.3 nm	- 21 mV	0.291

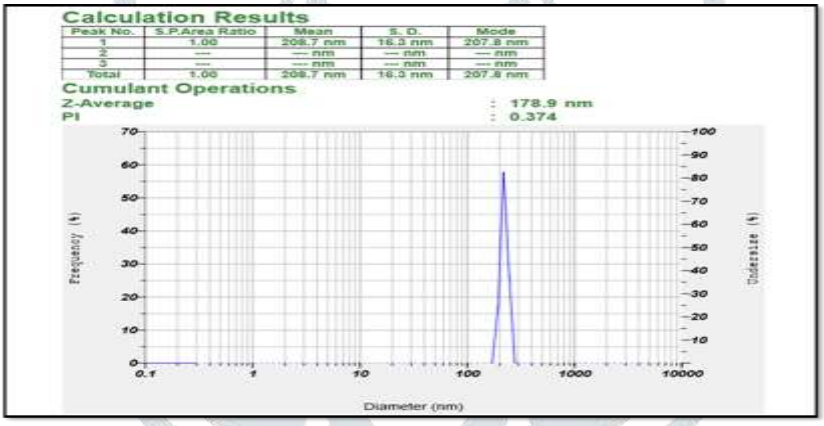

Fig no. 5. Globule Size Analysis of Optimized Batch Cinnamon F 2.

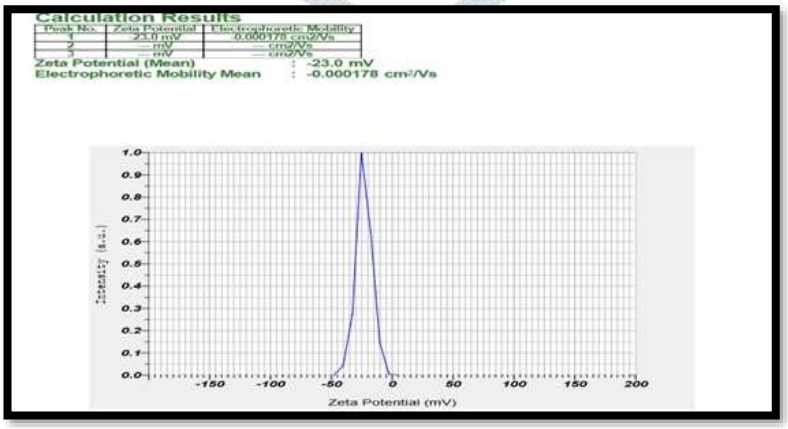

Fig no.6 Zeta Potential of Optimized Batch Cinnamon F 2.

Assessment of Self Emulsification:

Emulsification time is a major parameter that helps in the determination of emulsification rate of SNEDDS. Oil is a major factor that affect relatively because when it present in high concentration, it prevent penetration of water. While hydrophilic compound such as surfactant and co – surfactant helps in dispersion and so enhance the emulsification rate. The rate at which oil droplets of the SNEDDS

formulation dispersed swiftly and fully when subjected to water dilution under agitation might be used to measure the efficiency of Self Emulsification. The following are the emulsification times for the formulations:

Table no.9 .Emulsification Time of the Formulations

Sr.no	Formulation code	Emulsification time (sec)
1	CINN 1	58.49 ± 0.68
2	CINN 2	74.38 ± 0.30
3	CINN 3	61.57 ± 0.27

Percentage Transmittance:
The Result of percentage transmittance is shown in table no.10. The clarity of prepared NanoEmulsion was checked by transparency, measured in terms of transmittance. SNEDDS forms w/o Nano Emulsion since oil is external phase. Formulation CINN 2 has 98.03% transmittance. The result indicates good clarity of emulsion.

Table no. 10 % Transmittance.

Sr.no	Batch	% Transmittance
1	Cinnamon F 1	90.67 ± 0.30
2	Cinnamon F 2	98.17 ± 0.17
3	Cinnamon F 3	93.33 ± 0.49

Cloud Point Determination:
Cloud point of prepared Nano Emulsion was found to be higher than 80^0C, which indicate that Nano Emulsion will be stable at physiological temperature without risk of phase separation.

Table no. 11. Cloud Point Determination

Sr. no	Batch	Cloud point
1	Cinnamon F 1	More than 85°C
2	Cinnamon F 2	More than 90°C
3	Cinnamon F 3	More than 80°C

Drug content:

The drug content of the prepared formulation was shown in table no. 12.

Table no. 12. Drug content of prepared formulation

Sr. no	Batch	Percentage yield
1	Cinnamon	72.33 ± 0.54
2	Cinnamon	86.57 ± 0.72
3	Cinnamon	69.17 ± 0.68

FTIR spectra of optimized batch CINN F 2:

Drug and formulation has shown no any difference in spectra indicate drug is intact in the formulation which was shown in fig.7.

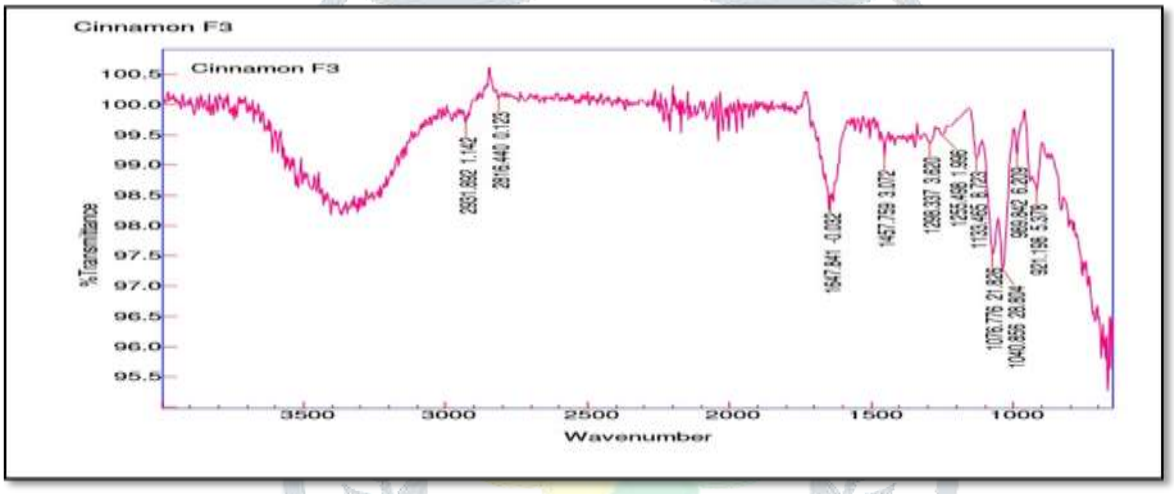

Fig. no. 7. FTIR Spectra of Optimized Batch CINN F 2

Table no.13. FTIR Spectra of Optimized Batch CINN F 2

Function group	Theoretical wave no. (cm – 1)	Peaks (cm – 1)	Indication
C = C	1680 – 1600	1647.841	Alkene
O – H	3500 – 2400	2931.892	Carboxylic acids
C – O	1300 – 1000	1255.498	Alcohol
C – H	3000 – 2850	2816.440	Alkanes

In Vitro Drug Release Study:

In vitro drug release study of prepared formulations of cinnamon oil SNEDDS was performed in phosphate buffer pH 6.8. Drug release was shown in table no. 14

Table no. 14. In Vitro Drug Release Study

Sr. no.	Batch	% Drug release
1	Cinnamon F 1	80.65 ± 0.48
2	Cinnamon F2	95.29 ± 0.68
3	Cinnamon F3	89.21 ± 0.89

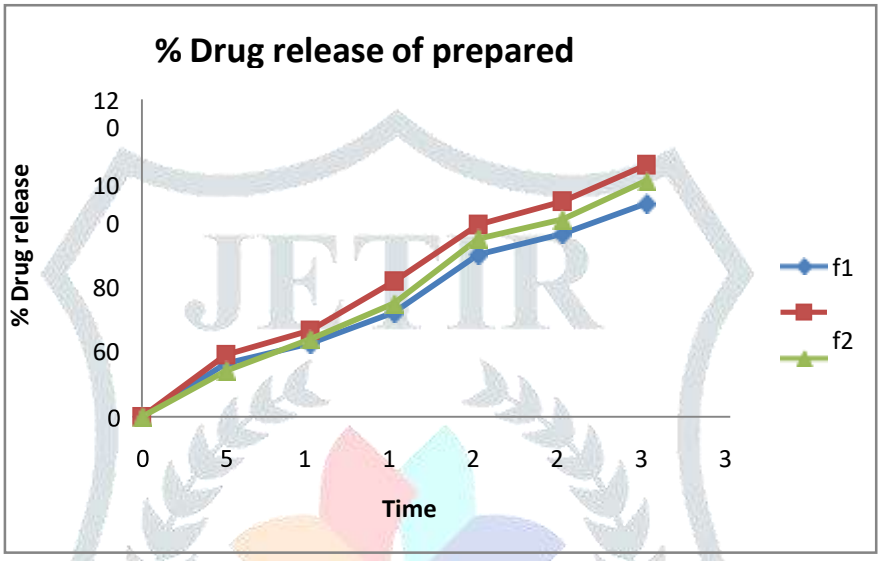

Fig. no. 8. % Drug Release of Prepared Formulation

CONCLUSION:

An attempt has been made in this study to design and assess a cinnamon self-nano emulsifying medication delivery system. Cinnamon oil is nearly water insoluble. Drug absorption is influenced by the rate of dissolution. The Nano–Emulsifying drug delivery system, which presents the drug in solubilized form in the body and bypasses the first pass metabolism in the drug absorption of SNEDDS, which are an isotropic mixture of oil, surfactant, and co–surfactant, can solve the bioavailability problem.

Pre–formulation studies and solubility studies in various oils, surfactants, and co-surfactants were carried out during the experimental activity. The compatibility and solubility of the medicine in the solvent were used to identify and screen candidate components (oil, surfactant, and co–surfactants). The influence of surfactant to co–surfactant ratio (Km) on the area of Nano Emulsion existence was investigated using a phase diagram. Km value 3 was discovered to cover the most Nano Emulsion region.

The SNEDDS was prepared by using oil: S mix ratio (3:7) the in vitro release study conducted in phosphate buffer pH 6.8 formulations was optimized by particle size and In vitro dissolution. Optimized formulation composed of Oleic acid as oil, Tween 80 as surfactant and propylene glycol as co–surfactant. Combination of all three components oil: S mix: water in the ratio 7:30:63 exhibit particle size 178.9 nm and invitro drug release 95.29 % in 30 min.

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