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Formulation and Evaluation of Cinnarizine Loaded Solid Lipid Nanoparticles

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ABSTRACT

The present study aimed to Develop and evaluate solid lipid nanoparticles of cinnarizine using different lipids (Tristearin, Glycerol monostearate, Compritol) by using Hot homogenization followed by ultrasonication method by employing Tween 80 as surfactant and Soyalecithin as Stabilizer. The Physicochemical compatibility of the drug and excipients were carried out by performing FT-IR Spectroscopic analysis. The solid lipid nanoparticles were evaluated for Particle size, Polydispersity Index, Zeta potential, Drug content, Entrapment efficiency, Invitro drug release, and Release kinetics studies. The particle size range from 38.56 to 326.5nm, PDI of all formulations was good within the range of 0.158 to 0.596, Zeta potential from -17.3 to -27.8 Mv, Entrapment efficiency was in the range of 78.38% to 95.77%, Cumulative percentage drug release from cinnarizine nanoparticles varied from 57.86 to 89.66%, The cumulative percentage drug release of optimized formulation F2 showed good release after 24 hrs (89.66%). The release kinetic studies of Optimised formulation showed that the release was First order and the release mechanism was Anomalous diffusion (non – Fickian) Type.

INTRODUCTION:

Solid lipid nanoparticles (SLNs) are introduced as a carrier system for poorly water-soluble drug and cosmetic active drugs. Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are synthesized from synthetic/natural polymers and suited to optimize drug delivery and reduce toxicity. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents, and their stability in the nanometer size.[1]They have some limitations due to their high cost and scarcity of safe polymers with regulatory approval. To overcome this limitation polymeric nanoparticle lipid is used as an alternative carrier. These nanoparticles are known as solid lipid nanoparticles (SLNs). Solid lipid nanoparticles are also referred to as "zero-dimensional" nanomaterials.[2]

Solid lipid nanoparticles (SLNs) are particles made from solid lipids, with a mean diameter in the range from 50 to 1000 nm. It has become one of the most active areas of research in the field of drug delivery because of their ability to deliver drugs to the right place, at appropriate times, and in the right dosage. They have received considerable attention over the past 20 years due to their advantages compared to other drug delivery systems. [3]

Cinnarizine is an H1-receptor antagonist that is widely used in the treatment of motion sickness, vomiting, and vertigo. It is also used as cerebral blood flow improvement in the management of various peripheral and cerebral vascular disorders.

Chemically, it is a piperazine derivative which has a short half-life (4 to 6 hours). [4] The present study aimed to develop solid lipid nanoparticles of Cinnarizine to achieve sustained release of drugs and thereby increases the efficiency of treatment.

MATERIALS AND METHODS:

MATERIALS:

Cinnarizine was purchased from Yarrow chemicals, Mumbai. Tristearin was purchased from Sasol, Germany. Compritol was obtained from Gattefose, France. Glyceryl monostearate was purchased from lab Fine Chem Industries, Mumbai. Methanol, Tween 80, and Chloroform were purchased from SD fine Chem limited, Bengaluru. Soy lecithin and Poloxamer were obtained from HI Media laboratories Pvt Ltd, Bengaluru. All the reagents used were of

analytical grade.

METHODS:

Preparation of solid lipid nanoparticles of Cinnarizine

The SLNs were prepared by hot homogenization followed by the ultrasonication method. In this method, solid lipid nanoparticles were prepared using lipids (tristearin, glyceryl monostearate, compritol). Briefly weighed lipids[TS, GMS, CM] was first melted in a boiling tube by heating and then soya lecithin was added and then the drug was incorporated into the boiling tube containing Lipid –Lecithin which was then maintained at 5°C above the melting point of Lipid. Simultaneously in another beaker tween 80 was dissolved in water and heated to a temperature equal to that of lipid phase, then the aqueous phase was transferred slowly into the lipid phase while homogenizing the mixture at 20,000 rpm for 15 minutes, and then immediately placed in a probe sonicator at 75% amplitude for 25minutes.[5]

Table No. 1: Formulation design of SLNs using lipids Tristearin, GMS and Compritol

Formulation No	Drug (mg)	TS (mg)	GMS (mg)	CM (mg)	Tw80 (mg)	Soy (mg)	Water (mg)
F1	10	50			25	25	10
F2	10	100			50	50	10
F3	10	200			100	100	10
F4	10		50		25	25	10
F5	10		100		50	50	10
F6	10		200		100	100	10
F7	10			50	25	25	10
F8	10			100	50	50	10
F9	10			200	100	100	10

Drug: Cinnarizine; TS-Tristearin; GMS-Glycerol monostearate; CM-Compritol; TW80-Tween80; Soy-Soy lecithin

Evaluation of cinnarizine solid lipid nanoparticles

Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR Spectroscopic Analysis was carried out to check the compatibility between drug and excipients used. The pure drug, excipients and physical mixture of drug and excipients were analyzed by FT-IR spectroscopic analysis and the spectra were recorded by scanning in the wavelength of 500 – 4000 cm-1 in FT-IR Spectrophotometer.

The samples were analyzed by FT-IR spectroscopic analysis were:

A) Pure Drug (Cinnarizine)

B) A physical mixture of Drug + Tristerin

C) A physical mixture of Drug + GMS

D) A physical mixture of Drug + Compritol

Particle size analysis:

The particle size was determined by dynamic light scattering, using a Malvern system, with vertically polarized light supplied by an argon-ion laser (Cyonics) operated at 40 mW**.** Experiments were performed at a temperature of 25.0 ± 0.1 ºC at a measuring angle of 90º to the incident beam.[6]

Zeta potential:

Zeta potential was measured using *Malvern zeta sizer* nanoparticles were diluted with distilled water and placed in a clear disposable zeta cell at 25 °C. The sample was subjected to two zeta runs to determine both size and potential.[7]

Polydispersity index:

Polydispersity Index; a parameter calculated from a Cumulants analysis of the DLS-measured intensity autocorrelation function. Polydispersity index is determined by the same instrument *i.e* Malvern zeta sizer.[7]

Drug Content

About 0.2ml of drug-loaded solid lipid nanoparticles were added into 5ml of methanol in a centrifuge tube and vortexed for 15 minutes. The solution was then centrifuged at 5000 rpm for 30 mins and the supernatant was collected. The drug content in the supernatant was analyzed by UV spectrophotometer of Cinnarizine at 252 nm. Drug content was calculated using the following formula.[8]

$$Drug\ content = \frac{Practical\ amount\ of\ the\ drug\ obtained}{Theoritical\ amount\ of\ drug\ added} \times 100$$

Percentage of drug entrapment efficiency (%DEE)

About 2 ml of drug-loaded SLNs were taken and placed in the outer chamber of the centrisart device and the sample recovery chamber was placed on the top of the sample. The unit was centrifuged at 5000rpm for 20 minutes. The SLNs along with encapsulated drug remains in the outer chamber and the aqueous phase was moved into the sample recovery chamber through the filter membrane (molecular weight cut-off 20,000 Daltons). The resulting aqueous phase was analyzed by a UV spectrophotometer for Cinnarizine 252.20nm. The entrapment efficiency was calculated by using the following relationship.[9]

$$\%DEE = \frac{\text{Total amount of the drug} - \text{Amount of the drug in aqueous phase}}{\text{The total amount of the drug}} \times 100$$

***In-vitro* drug release study**

In-vitro Drug Release Studies were performed by *Franz diffusion cell. A volume of* 2ml of drug-loaded SLNs was placed in the donor compartment and the receiver compartment was filled with 22ml of diffusion medium consists of phosphate buffer of pH 7.4 maintained at 37±1°C in Franz diffusion cell. The rpm of the magnetic bead was maintained at 50 rpm. An aliquot of 2ml of samples was withdrawn from the receiver compartment through the side tube at predetermined intervals. The samples were analyzed for drug content by UV spectrophotometer at 252.20nm. An equal volume of the diffusion medium was replaced in the receiver compartment after each withdrawal to maintain the sink condition. From the data obtained, the percentage of drug release was calculated and plotted against the function of time to study the pattern of drug release. Obtained in vitro drug release data was processed into kinetic models to study the mechanism of drug release.[8]

Drug release kinetics

Different kinetic models such as zero-order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs. time), Higuchi model (cumulative percentage of drug released vs. square root of time), Korsmeyer-Peppas model were applied to interpret the drug release kinetics from the formulations. The best-fit model was decided based on the highest regression values (r2) of obtained release data of formulations.

RESULTS AND DISCUSSION:

Preparation of standard graph of Cinnarizine using phosphate buffer at pH 7.4

The standard graph of Cinnarizine using phosphate buffer of pH 7.4 was plotted from 2 to 16 µg/ml concentration. The absorbance was measured at 252.20 nm by using a UV µ spectrophotometer and a standard graph shown in Fig 1. The regression equation obtained is y =0.0574x- 0.0134 and R^2 = 0.9993.

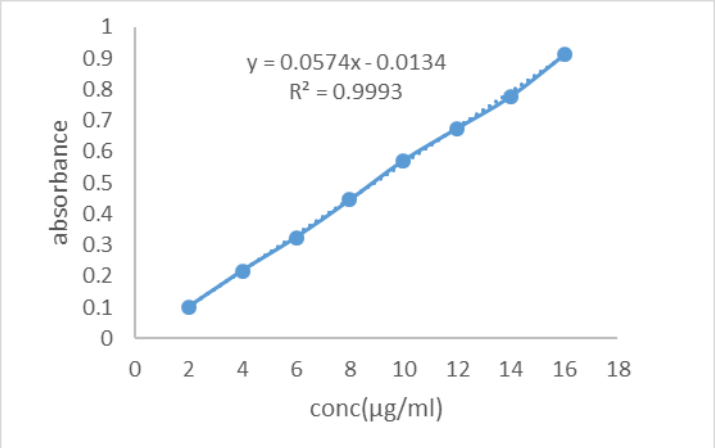
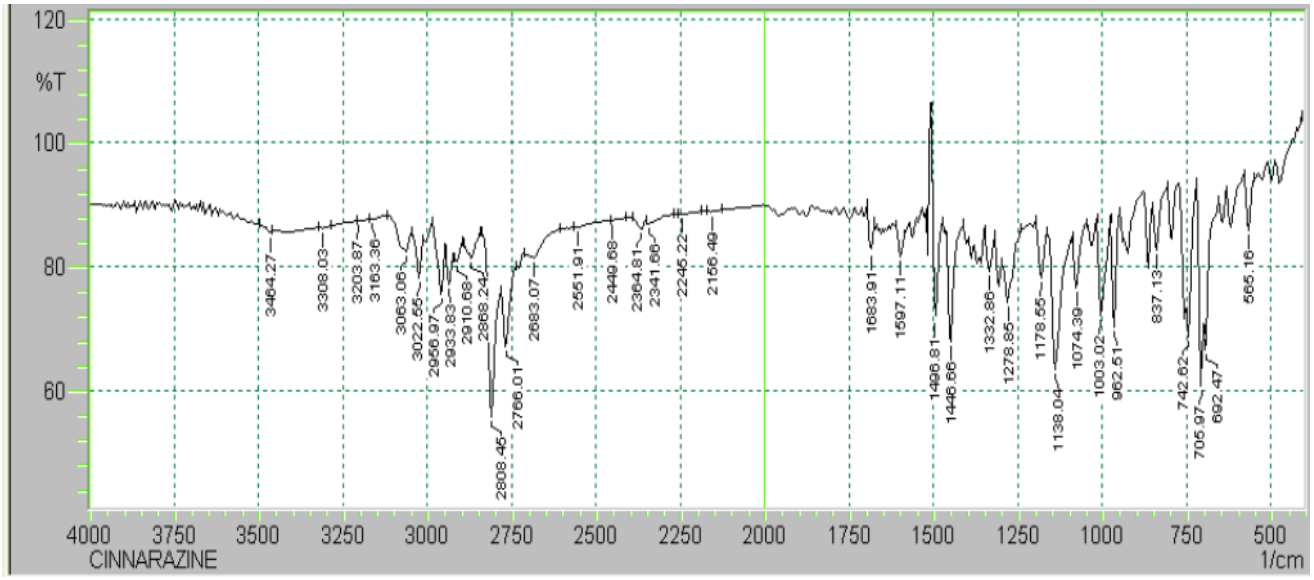


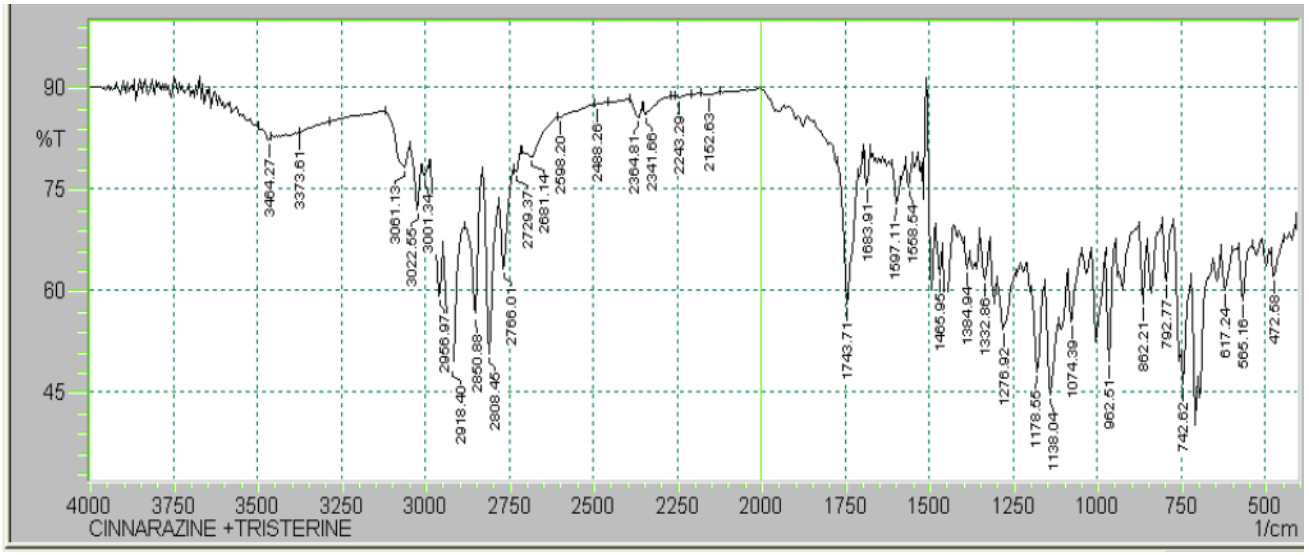
Figure No. 1: The standard graph of Cinnarizine using phosphate buffer of pH 7.4

FTIR

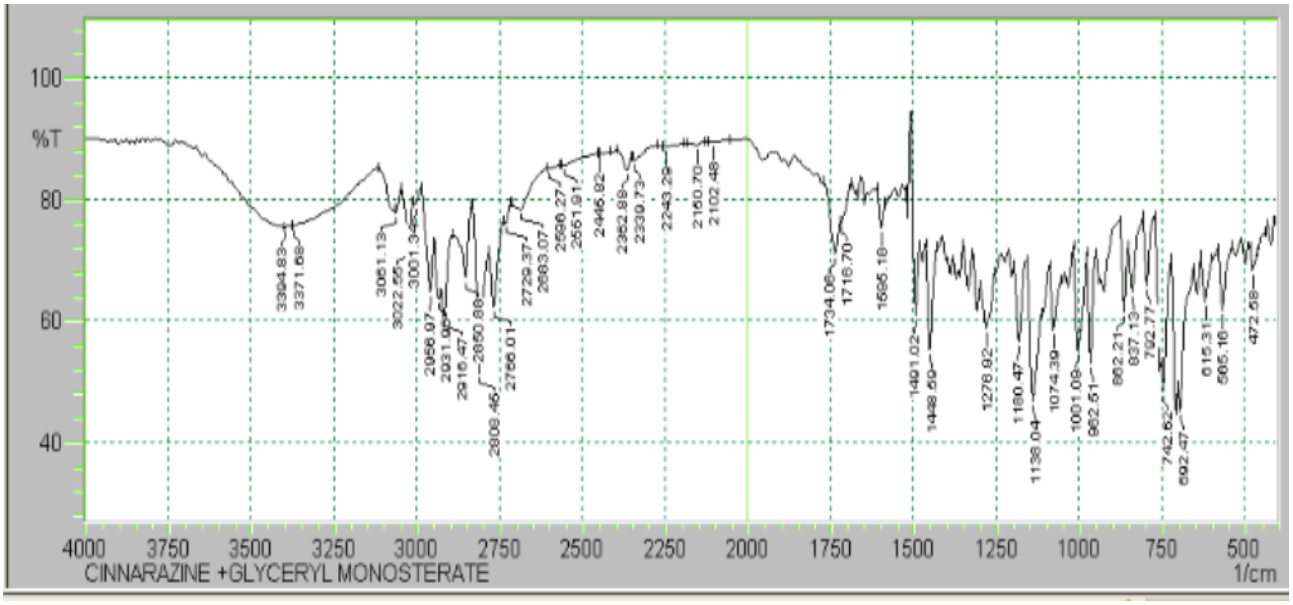
Drug-lipid interactions were studied by FTIR spectroscopy. The spectra obtained from the FTIR spectroscopy study are shown in fig 2. Wavenumbers of peaks of corresponding functional groups of Cinnarizine are shown in Table 2.



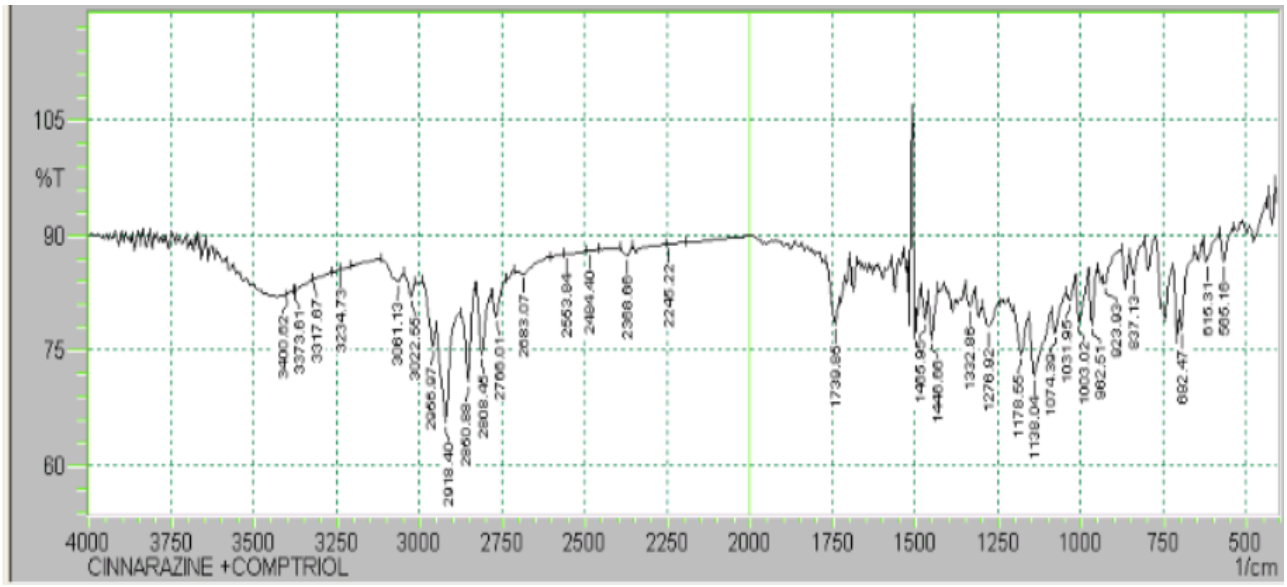
A) Pure drug



B) A physical mixture of drug and Tristearin



C) Physical mixture of drug and Glycerol monosterate



D) A physical mixture of drug and Comritol

Figure No. 2: FTIR spectra of A) Cinnarizine; B) Physical mixture of Cinnarizine and Tristearin; C) A physical mixture of Cinnarizine and GMS; D) Physical mixture of Cinnarizine and Compritol

Table No. 2: Functional group and their wave number by FTIR of pure drug and its physical mixtures

Compound Name	Functional groups	Characteristic peaks (cm-)		Observed peaks (cm-1)	
		Stretching	Bending	Stretching	Bending
Cinnarizine	C−H, Aromatic (Monosubstituted)	3067 – 3025		3063.06	
	C−H Alkane	2962 – 2853	1340	2808.45,2766.01	1332.86
	CH2, Alkane		1485-1445		1446.66
	C-H, Alkene, Disubstituted -Cis	3040-3010	690	3022.55	692.47
	C=C, Aromatic cis		1600		1597.11
	Characteristic Peaks of monosubstituted benzene		2000-1667		1683.91
	Piperazine ring N, N disubstituted		1400-1500		1446.66 1496.81
Cinnarizine+Tristearin	C−H, Aromatic (Monosubstituted)	3067 – 3025		3061.13	
	C−H Alkane	2962 – 2853	1340	2808.45,2766.01	1332.86
	CH2, Alkane		1485-1445		1465.95
	C-H, Alkene, Disubstituted -Cis	3040-3010		3022.55	
	C=C, Aromatic cis		1600		1597.11
	Characteristic Peaks of monosubstituted benzene		2000-1667		1683.91 1743.71
	Piperazine ring N,N disubstituted		1400-1500		1465.95
Cinnarizine+Glycerol monostearate	C−H, Aromatic (Monosubstituted)	3067 – 3025		3061.13	
	C−H Alkane	2962 – 2853	1340	2808.45,2766.01	1332.86
	CH2, Alkane		1485-1445		1448.59
	C-H, Alkene, Disubstituted -Cis	3040-3010	690	3022.55	692.47
	C=C, Aromatic cis		1600		1595.18
	Characteristic Peaks of monosubstituted benzene		2000-1667		1716.70 1734.06
	Piperazine ring N, N disubstituted		1400-1500		1448.59 1491.02
Cinnarizine+Compritol	C−H, Aromatic (Monosubstituted)	3067 – 3025		3061.13	
	C−H Alkane	2962 – 2853	1340	2808.45,2766.01	1332.86
	CH2, Alkane		1485-1445		1446.66 1465.95
	C-H, Alkene, Disubstituted -Cis	3040-3010	690	3022.55	692.47
	Characteristic Peaks of monosubstituted benzene		2000-1667		1739.85
	Piperazine ring N, N disubstituted		1400-1500		1446.66 1465.95

Particle size, PDI and Zeta potential

Particle Size of Cinnarizine SLNs prepared with lipids Tristearin, GMS, and Compritol using tween 80 as a surfactant were in the range 38.56 to 326.5 d.nm. PDI of all the formulations was good within the range of 0.198 to 0.596. The zeta potential ranges from -17.3 to -27.8mV were shown in Table 3. Similarly, Cinnarizine SLNs of optimized formulation F2 range of particle size 60.83d.nm with 0.434 PDI and –25.8mV zeta potential are shown in fig .3 and fig.4 sizes were in nano range and zeta potential obtained was optimum for good stabilization.

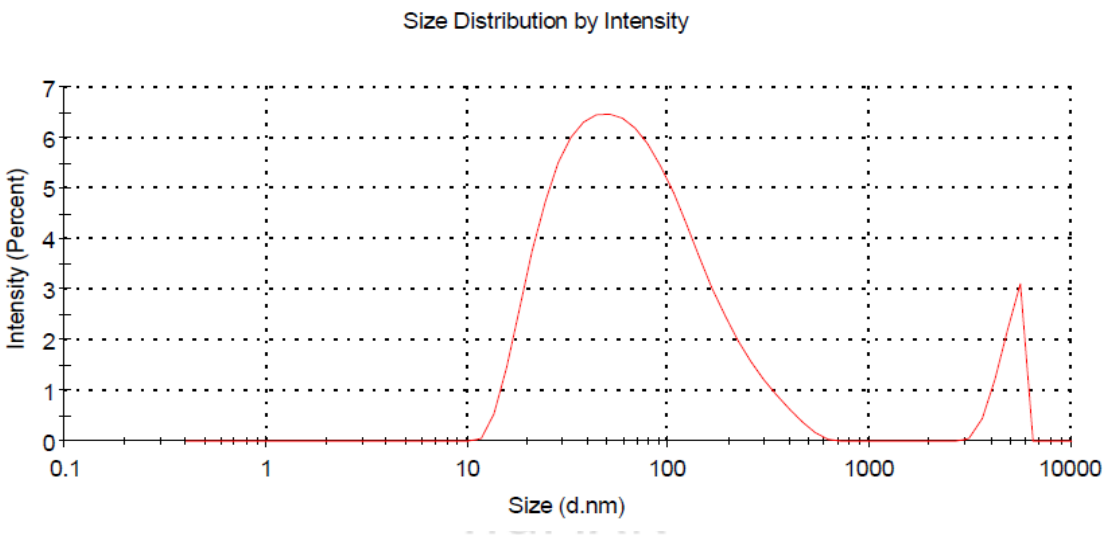


Figure No. 3: Size distribution profile of optimized formulation F2

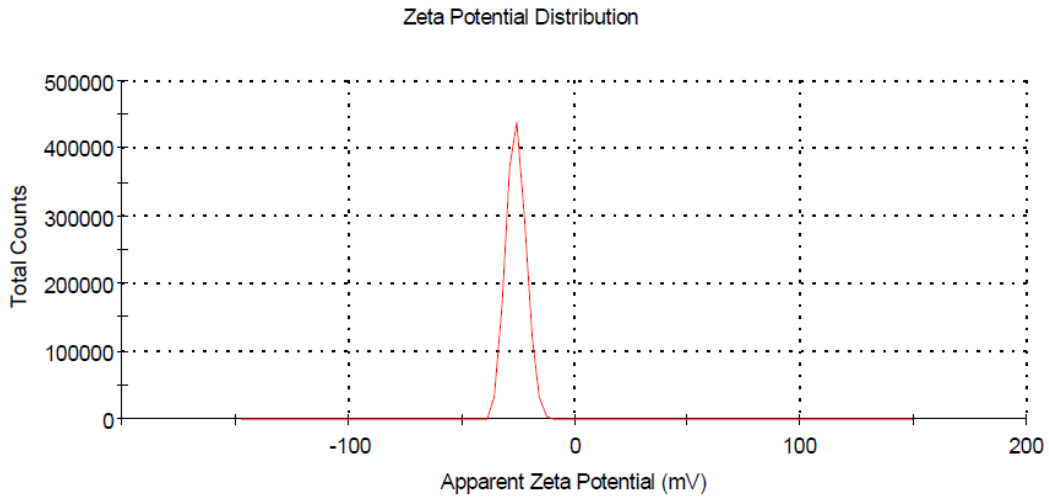


Figure No. 4: Zeta potential profile of optimized formulation F2

Table No. 3: The particle size, PDI and zeta potential of Cinnarizine prepared with Tristearin, GMS and Compritol using Tween 80.

Formulation No	Particle size (d. nm)	PDI	Zeta potential (mV)
F1	38.56	0.294	-21.2
F2	60.83	0.434	-25.8
F3	103.8	0.596	-20.6
F4	137.7	0.198	-25.5
F5	156.7	0.258	26.6
F6	295.5	0.286	-19.4
F7	140.8	0.578	-24.3
F8	195.6	0.586	-27.8
F9	326.5	0.384	-17.3

Drug Content and Entrapment Efficiency

The drug content of formulations was carried out by extraction with methanol as mentioned in the methodology section. The drug content results were ranged between 92.44 to 99.72%. The average percentage entrapment efficiency of Cinnarizine SLNs was good in the range of 78.38 to 95.77% and the loading efficiency was found to be in the range of 4.31 to 17.75% was shown in Table 4.

Table No. 4: Drug content and Entrapment efficiency of all formulations

Formulation No.	Drug Content	Amt of drug in Aqueous phase	Amt of drug in Lipid phase	Entrapment Efficiency	Loading Efficiency
F1	95.91	1.123	8.877	88.77	17.75
F2	99.72	0.984	9.016	90.16	9.01
F3	96.68	0.423	9.577	95.77	4.78
F4	94.38	1.923	8.077	80.77	16.15
F5	93.18	1.688	8.312	83.12	8.31
F6	92.44	1.102	8.898	88.98	4.44
F7	98.71	2.162	7.838	78.38	15.67
F8	93.61	1.988	8.012	80.12	8.01
F9	92.78	1.368	8.632	86.32	4.31

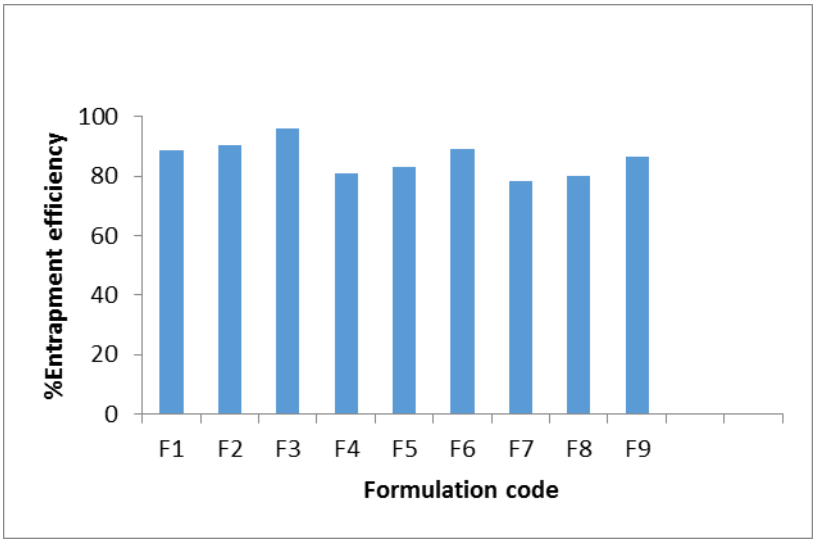


Figure No. 5: Percentage entrapment efficiency of all formulations

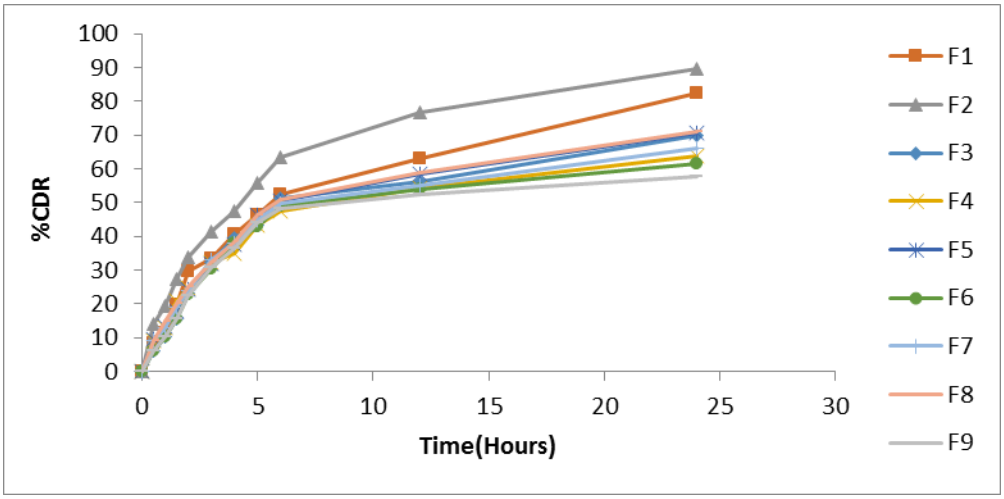
Release studies

The drug release from the nanoparticles was studied by Franz diffusion method. The cumulative percentage release of Cinnarizine of all formulations i.e. F1 to F9 varied from 57.86 to 89.83% depending upon the drug, surfactant, and the type of lipid used. Table 5 and fig 6 show the percentage of cumulative drug release of all the formulations.

The experiment showed that the drug release from F2 formulations showed maximum drug release at 24 hrs.

Table No. 5: % Cumulative drug release for all formulations after 24 hrs

Formulation No	%CDR @24 hrs
F1	82.31
F2	89.66
F3	69.98
F4	63.68
F5	70.80
F6	61.54
F7	66.19
F8	70.95
F9	57.86



% Cumulative Drug Release of F1 and F9

Figure No. 6: *In-vitro* drug release profiles of Cinnarizine SLN formulations prepared with three different lipids.

Release kinetics

In-vitro release data obtained from various formulations were fitted to various kinetic models to explore the kinetics and mechanism of drug release. R^2 values for zero-order kinetics were ranged from 0.621 to 0.862 and for the first-order kinetics ranged from 0.704 to 0.963 and for the Higuchi model ranged from 0.818 to 0.948. The regression values for First order is greater than zero and Higuchi kinetic models. The regression value for Korsmeyer – peppas ranged from 0.889 to 0.962. Data were fitted to First-order better with higher R^2 values, which indicate the drug release was first order. Since, the n value obtained from Korsmeyer – peppa's model was more than 0.5.

Hence the mechanism of drug release from these SLNs was Anomolous (non - Fickian) diffusion mechanism. The regression values of the formulations are listed in Table 6. The kinetic models of optimized formulation F2 are shown in fig 7.

Table No. 6: The regression values of kinetic models of different formulations of Cinnarizine

Formulation No	Regression Factor			Korsmeyer – Peppa's	
	Zero Order	First Order	Higuchi Model	R^2	n values
F1	0.862	0.961	0.948	0.933	0.618
F2	0.780	0.963	0.932	0.962	0.511
F3	0.730	0.862	0.896	0.916	0.658
F4	0.728	0.728	0.897	0.933	0.525
F5	0.758	0.879	0.915	0.947	0.561
F6	0.663	0.763	0.851	0.904	0.634
F7	0.718	0.833	0.890	0.931	0.552
F8	0.756	0.879	0.916	0.946	0.552
F9	0.621	0.704	0.818	0.889	0.624

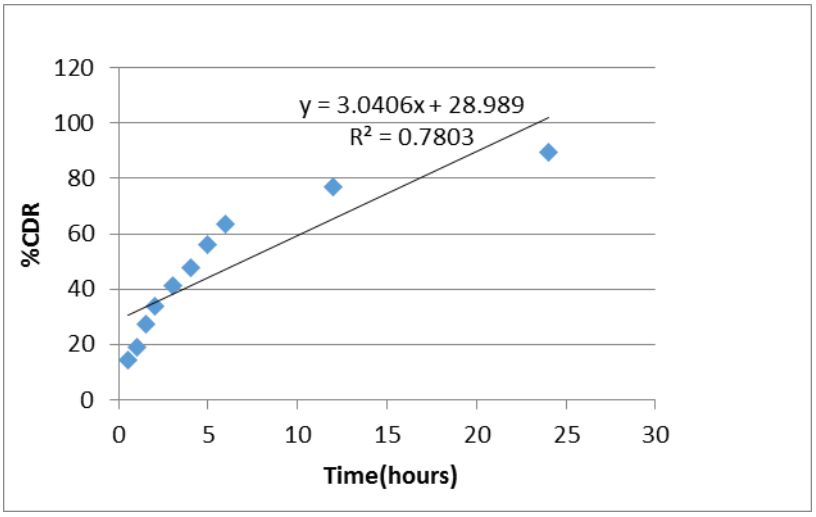


Figure No. 7: Zero order kinetics of optimised formulation F2

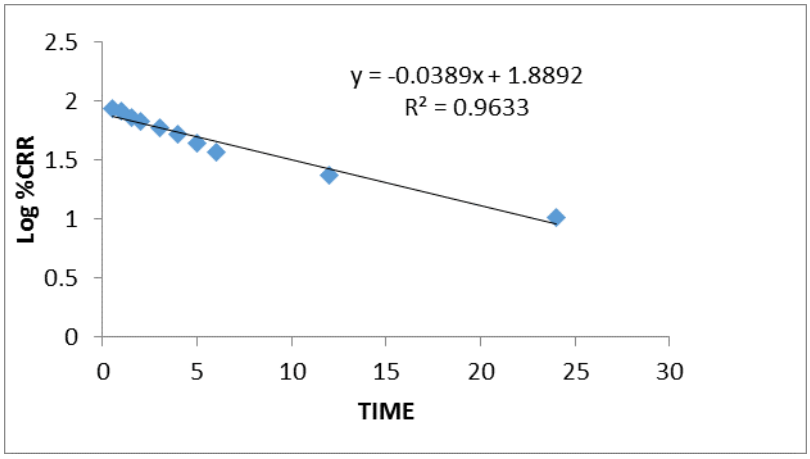


Figure No. 8: First order kinetics of optimized formulation F2

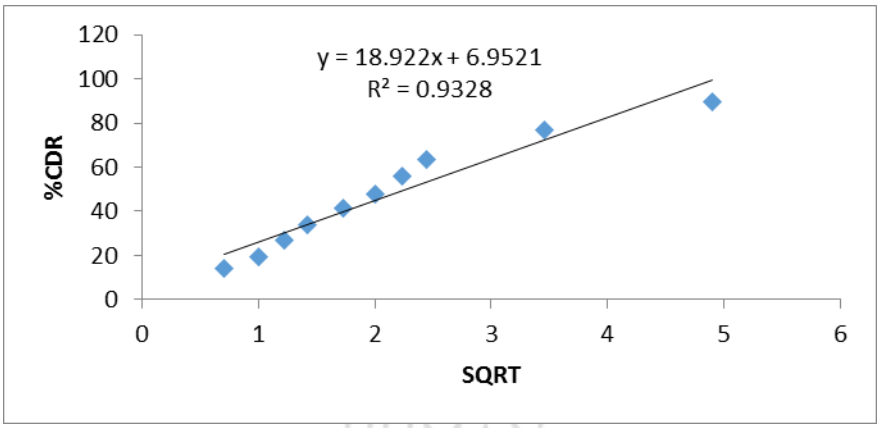


Figure No. 9: Higuchi model of optimized formulation F2

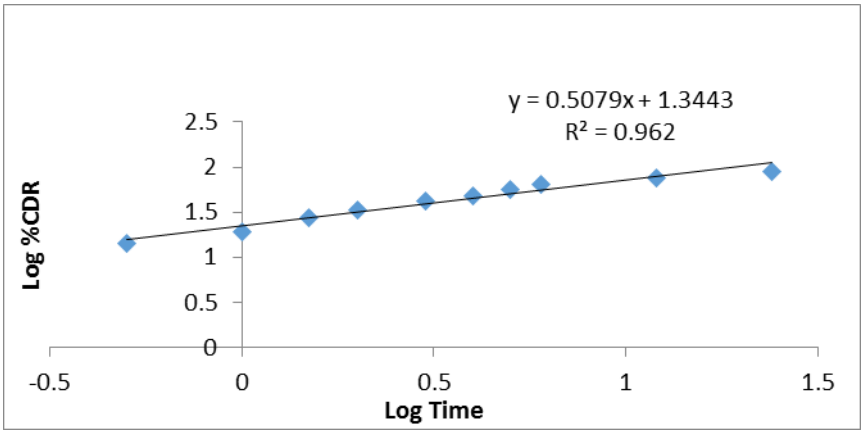


Figure No. 10: The Peppas model plot of optimized formulation F2

CONCLUSION:

SLNs containing Cinnarizine were prepared successfully using three lipids tristearin, GMS, and Compritol by hot melt homogenization technique. The FTIR study revealed that there is no interaction between drug and selected lipids. In vitro release studies confirmed that the suitable percentage of drug released from the formulation F2 which indicates Tristearin and tween80 as a surfactant in the concentration of 1.0%. Also, the developed SLNs have a good particle size, PDI, and zeta potential with good entrapment efficiency. Release kinetics studies showed that Cinnarizine released from the nanoparticles follows Anamalous diffusion (non – Fickian) Type. Based on the observations, it can be concluded that the formulated solid lipid nanoparticulate delivery system of Cinnarizine using widely accepted and pharmacologically safe lipids were capable of exhibiting sustained release properties for 24 hours. Thus SLN formulations may reduce the frequency of dosing, thereby minimizing the occurrence of side effects, improve bioavailability, and increase the effectiveness of the drug.

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