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FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLES OF VENLAFAXINE HYDROCHLORIDE FOR THE EFFECTIVE TREATMENT OF DEPRESSION

Sayantan Mukhopadhyay*, Jyoti Nautiyal[1] and Preeti Kothiyal[2]

***Department of Pharmaceutics, Division of Pharmaceutical Science, Shri Guru Ram Rai University, Uttarakhand, India.**

[1]Department of Pharmaceutics, Shri Guru Ram Rai Institute of Technology and Sciences, Uttarakhand Technical University, Uttarakhand, India.

[2]Department of Pharmaceutics, Division of Pharmaceutical Science, Shri Guru Ram Rai University, Uttarakhand, India.

***Corresponding Author Email: sayantan.pharmaceutics@gmail.com**

ABSTRACT

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In the present study, Venlafaxine hydrochloride-loaded solid lipid nanoparticles were successfully prepared by using modified solvent diffusion method. The SLNs were prepared by using 1.5% and 2.5% w/v of Tween 80. The prepared nanoparticles were evaluated for particle size, polydispersity index, zeta potential, surface morphology, drug entrapment and surface entrapment. The particle size of prepared nanoparticles was found in acceptable range that is from 213.2 to 635.1d. nm and PdI from 0.243-0.947. Along with this zeta potential of all the prepared nano formulations lies in the range from –11.2 to – 16.9mV. Low values of surface entrapment efficiency indicated that less amount of drug was present on the surface of drug loaded solid lipid nanoparticles and a higher amount of drug was found to be entrapped in drug loaded solid lipid nanoparticles. Finally, carbopol 940 (2%) gel was prepared by incorporating venlafaxine hydrochloride-loaded solid lipid nanoparticles into it. The prepared gel was evaluated for viscosity, spreadability, pH and drug content. Drug content of all the prepared solid lipid nanoparticulated gel was ranged from 71.94% to 88.95%. In vitro diffusion results revealed that 64.05% - 90.25% of drug released from the formulations in 24 hrs study period. In formulation FF4 and FF7, by observing the value of n it was confirmed that the anomalous transport is dominant and in remaining formulations, Super case II Transport is dominant. Therefore, it was concluded that prepared formulation was able to provide better management of depression and hence improve patient compliance.

KEY WORDS

Brain targeting, venlafaxine hydrochloride, solid lipid nanoparticles (SLN), particle size, polydispersity index, zeta potential.

1. INTRODUCTION

Targeting a drug to a particular site (either organ, tissue or cell) is the main challenge of research of pharmaceutical industry. [1] Delivery of drug to brain (CNS) is constantly a challenging and inspiring task for the scientists of research and development sector as Brain is an organ which is the most sophisticated and flexible and is very systematically protected by nature. [2][3]

Main problems associated with the delivery of drugs to CNS include:

- the poor or lack of proper knowledge about the physiology of the brain or central nervous system (CNS). [4]
- **Blood Brain Barrier:** The accessibility into the brain is prevented by a barrier which is called as ***Blood Brain Barrier (BBB)***. [3] BBB generally composed of endothelial cells which are connected by various junctions like adherens junctions (AJ) and by tight junctions (TJ). Tight junctions of the brain are mainly composed of transmembrane and cytoplasmic proteins.
- **P-glycoprotein (P-gp):** It is a type of efflux system which generally pumps out approx. all the xenobiotics along with drug molecule from CNS to blood. [5]

In order to overcome these problems, different strategies were coming into existence for the effective delivery of drug to brain by crossing BBB such as disruption of blood brain barrier, intracerebral injection, prodrugs, implants etc. [2]

There are different CNS disorders like Depression, Alzheimer's disease, and Epilepsy in which the efficacy of the treatment depends on the amount of drug reaching to its target site that is brain. [6] Depression is a mental illness with dejected mood, loss of interest, reduced energy, poor concentration and disturbed sleep or appetite. [7]

According to World Health Organization (WHO), "depression will become the second largest illness in terms of morbidity by another decade in the world, already one out of every five women, and twelve men have depression". [8] Neurohormonal and neurochemical imbalance are the main cause of depression. There are mainly three neurotransmitters present in brain that are norepinephrine (NE), dopamine (DA) and serotonin (5-hydroxytryptamine [5-HT]). Deficiency or imbalance of these neurotransmitters may responsible for depression. [9] [10]

For the effective targeting of drug to target site that is brain, colloidal system came into existence. Colloidal drug delivery systems (CDDS) are defined as the vesicular or particulate dosage form whose size is in nano range. CDDS mainly include polymeric nanoparticles, liposomes, lipid nanoparticles, multiple emulsion, nanocrystals etc. Solid lipid nanoparticulated drug delivery system is one of the Colloidal drug delivery systems for effective targeting to brain. [11] [12]

Solid lipid nanoparticles (SLNs) are the lipid-based nano formulation whose diameter is in the range from 50 to 1000nm. [13] SLNs were developed and invented in early nineties that is in 1991 and these were the first generation of lipid nanoparticles. [14] [15] Muller and Lucks were first group of researchers who patented the preparation method of SLN by making use of high pressure homogenization (HPH). [16]

Venlafaxine hydrochloride is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class. It is used for the treatment of major depressive disorder (MDD), panic disorder, generalised anxiety disorder (GAD), and social phobia. [17] Main mechanism of action of Venlafaxine hydrochloride is to inhibit the reuptake of neurotransmitter mainly norepinephrine and serotonin. [18]

Literature survey revealed that Venlafaxine hydrochloride loaded SLNs have not been reported until now. So, in the present study solid lipid nanoparticles of venlafaxine hydrochloride were prepared and evaluated for its particle size, PdI, zeta potential, surface entrapment and drug entrapment etc.

2. METHODS

2.1. Methods

2.1.1. Preparation of venlafaxine hydrochloride loaded solid lipid nanoparticles

Venlafaxine hydrochloride loaded SLN was prepared by modified solvent diffusion method. In this technique, Venlafaxine hydrochloride and monostearin ere accurately weighed and were dissolved 5ml of ethanol with heating at 60 ˚C. The prepared organic phase was then dispersed into 20 ml aqueous solution containing 2.5% w/v Tween 80 solution under mechanical stirrer at 1500 rpm for 3hrs in 60˚C water bath. The obtained dispersion was then allowed to cool in room temperature. Adjustment of pH was done by 0.1N hydrochloric acid in order to precipitate SLN. The dispersion was then centrifuged in 8,000 rpm for 15 min and the product obtained was redispersed in 20 ml Tween 80 solution. Composition of different formulations was given in **Table No. 2.1.**

Table No.2.1: Composition table of different batches of venlafaxine hydrochloride loaded solid lipid nanoparticles

Ingredients	Venlafaxine Hydrochloride (mg)	Monostearin (mg)	Ethanol (ml)	Tween 80 (%w/v)
FF_1	100	200	5	1.5
FF_2	100	300	5	1.5
FF_3	100	400	5	1.5
FF_4	100	150	5	2.5
FF_5	100	200	5	2.5
FF_6	100	250	5	2.5
FF_7	100	300	5	2.5
FF_8	100	350	5	2.5
FF_9	100	400	5	2.5
FF_{10}	100	450	5	2.5

2.1.2. Particle size, Zeta potential and Polydispersity index [19] [20]

Particle size, Polydispersity index and Zeta potential of prepared solid lipid nanoparticles was determined by using Malvern zetasizer at specific temperature that is 25°C. For this, different samples were prepared by simple diluting solid lipid nanoformulation by using the same dispersion medium as dilution medium.

2.1.3. Surface morphology studies [21] [22]

External morphology of prepared solid lipid nanoparticles was done by using Scanning Electron Microscopy (SEM).

In this methods, prepared SLNs were fixed on a stub made of aluminium with the help of an adhesive tape and then the nanoparticles were coated using gold under vaccum. Finally, the gold coated SLNs were observed by using scanning electron microscope.

2.1.4. Surface entrapment and drug entrapment efficiency [23]

For determination of entrapment efficiency, small portion of SLN dispersion (approx 5 ml) was taken and centrifuged for 20min at 18,000rpm (at 20°C). The supernatant obtained after centrifugation was separated and analysed at 270nm by using UV spectrophotometer. Finally, surface entrapment was determined from simple calculation by using absorbance and by using formula, drug entrapment efficiency was determined.

$$\textbf{\% Drug entrapment efficiency} = \frac{W_1 - W_2}{W_1} \times 100$$

W_1 = Total weight of drug used during formulation.

W_2 = Weight of drug obtained in the supernatant after centrifugation.

2.1.5. Preparation of venlafaxine HCl loaded solid lipid nanoparticulated gel [24]

For preparing gel, 2% of carbopol 940 was selected as gelling agent. 2% Carbopol 940 was slowly dispersed in 100ml water with continuous stirring for 15-20 min. Then pH of the prepared gel was checked. Finally, appropriate amount of SLN dispersion was slowly added (with continuous stirring at 1000 rpm) to prepare solid lipid nanoparticulated gel.

2.1.6. Evaluation of venlafaxine HCl loaded solid lipid nanoparticulated gel

2.1.6.1. Viscosity [24] [25]

The viscosity of prepared gel was determined by using Brookfield viscometer at temperature of 37 ± 0.5°C.

2.1.6.2. Measurement of pH [25]

For measuring the pH of the prepared carbopol gel, approx. 10gm of gel was weighed and put it into 30 ml of volumetric flask. After this, the volume was made up to 30 ml with distilled water. Finally, by using pH meter, pH of the prepared dispersion was measured.

2.1.6.3. Spreadibilty study [24] [25]

For determining the Spreadibilty of the prepared gel, approx. 0.5gm of the prepared gel was placed in a specific diameter on a pre-marked glass plate and second glass plate was then placed over the glass plate containing gel. Then a weight of 500gm was applied over the glass plate for 5 min. Finally, Spreadibilty of the gel was calculated by observing the increase in the diameter which was due to the Spreadibilty of the gel.

2.1.6.4. Drug content [26]

For the determination of drug content, approximately 1 gm of prepared nanoparticulated gel was dissolved in ethanol in 50ml volumetric flask. 5ml of the above prepared solution was diluted and volume was made up to 25 ml with the help of same solvent that is ethanol. This solution was then used to determine the drug content by measuring the absorbance at 270nm with the help of UV- Visible spectrophotometer.

2.1.7. *In vitro* diffusion study of venlafaxine hydrochloride loaded solid lipid nanoparticulated gel [22]

For *in-vitro* diffusion study, Franz diffusion cell was used for the determination of diffusion of drug from the solid lipid nanoparticulated gel. For this, phosphate buffer 7.4 was used as a receptor medium. The dialysis membrane used for the study was overnight soaked in the receptor medium which was filled in Franz diffusion cell. The prepared solid lipid nanoparticulated gel was applied in the donor compartment of Franz diffusion cell at temperature 37 °C± 2 °C and continuously stirred at 800 rpm. After 30 min, 5 ml of sample was withdrawn and immediately 5ml of fresh medium (phosphate buffer) was added to receptor chamber in order to maintain sink condition. The samples were then analysed by UV Spectrophotometer at 270nm. Finally, by using the data obtained from UV spectrophotometry, a graph was plotted between % cumulative drug release and time.

2.1.8. *In vitro* pharmacokinetic study [23]

In-vitro pharmacokinetic study of prepared solid lipid nanoparticles was determined by using different kinetic equations like zero order, first order, higuchi kinetics model, hixon crowell and Korsmeyer – Peppas Model in order to predict the release of drug **(Table No. 2.2.).**

Table No.2.2. Kinetic models and their Graphs

Kinetic Model	Graph
Zero order drug release kinetics	Between % cumulative amount of drug release and time
First order release kinetics	Between log % drug release and time
Higuchi release model	Between % cumulative drug releases and $\sqrt{t}$
Hixon crowell	Between cube root of drug remaining and time (hrs)
Korsemeyers peppas	Between log % drug release and log time(hrs)

3. RESULT AND DISCUSSION

3.1. Evaluation of venlafaxine hydrochloride loaded solid lipid nanoparticles

3.1.1. Particle size, Zeta potential and Polydispersity index

Particle size, PdI and zeta potential of venlafaxine hydrochloride loaded solid lipid nanoparticles was evaluated by using Malvern zeta sizer and was reported in **Table no. 3.1., 3.2., 3.3.** respectively.

Table No. 3.1. Particle size of venlafaxine hydrochloride loaded solid lipid nanoparticles

S.No.	Formulation Code	Particle Size	
		Size (d.nm)	% Intensity
1	FF1	310.5	81.2
		4737	18.8
2	FF2	593.2	81.9
		145.5	18.1
3	FF3	635.1	81.8
		147.7	18.2
4	FF4	213.2	94.8
		10.63	5.2
5	FF5	275.8	100
6	FF6	289.4	98.8
		5369	1.2
7	FF7	292.1	96.7
		5159	3.3
8	FF8	349.2	98.0

		69.19	2.0
9	FF9	357.2	100.0
10	FF10	379.9	100.0

Table No. 3.2. Polydispersity Index of venlafaxine hydrochloride loaded solid lipid nanoparticles

S.No.	Formulation Code	Polydispersity Index (PdI)
1	FF1	0.596
2	FF2	0.812
3	FF3	0.947
4	FF4	0.465
5	FF5	0.246
6	FF6	0.243
7	FF7	0.346
8	FF8	0.247
9	FF9	0.449
10	FF10	0.263

Table No. 3.3. Zeta potential of venlafaxine hydrochloride loaded solid lipid nanoparticles

S.No.	Formulation Code	Zeta Potential (mV)
1	FF1	- 11.8
2	FF2	-12.4
3	FF3	- 11.2
4	FF4	-12.5
5	FF5	- 12.8
6	FF6	- 13.1
7	FF7	- 13.4
8	FF8	- 14.7
9	FF9	- 15.0
10	FF10	- 16.9

From the obtained values of particle size, it was observed that formulation FF1, FF2, and FF3 (with 1.5% w/v surfactant) show particle size range from 310.5 to 635.1d. nm which indicated a wide range of particle size distribution. Apart from these, formulations FF4 to FF10 (with 2.5% w/v surfactant) show particle size range from 213.2 to 379.9 d.nm. Particle size distribution graph for prepared formulations FF4 and FF5 was shown in **Fig 3.1 and 3.2** respectively. From all the particles size values it may be concluded that if the amount of lipid increases, the particle size of the solid lipid nanoparticle also increases.

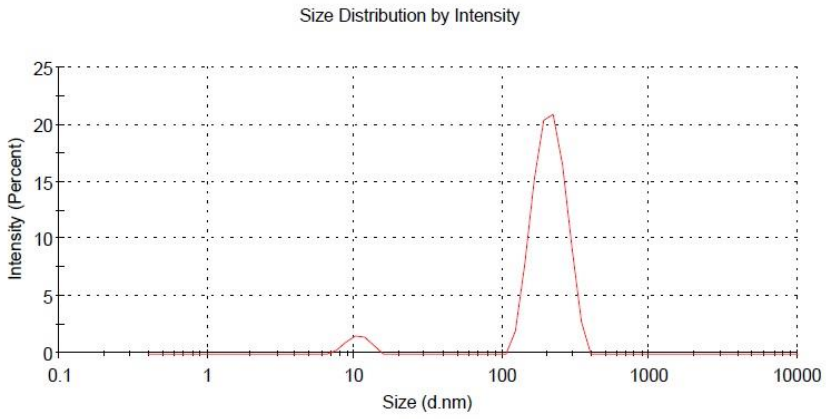

Fig 3.1. Particle Size Distribution graph of Formulation FF4

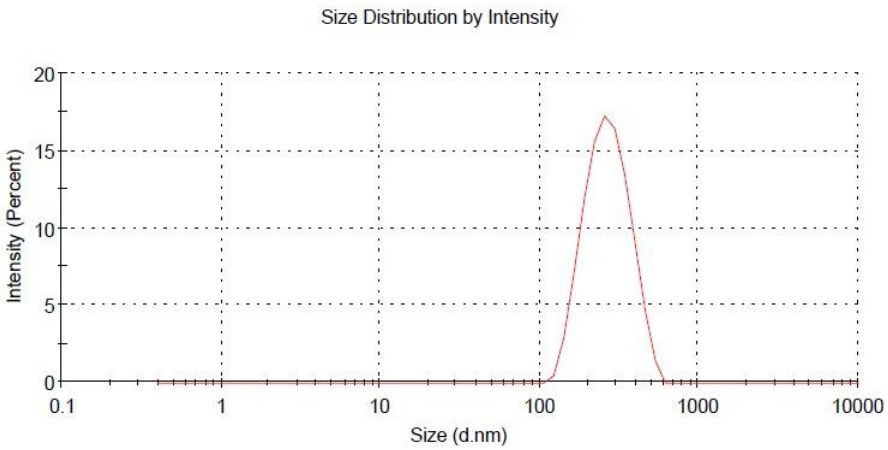

Fig 3.2. Particle Size Distribution graph of Formulation FF5

Along with this, it was also observed that amount of surfactant plays an important role in the particle size distribution and it was revealed that by increasing the concentration of surfactant, reduction in the size of particles was observed **(Fig 3.3.).** It may be due to the fact that the surfactant adsorbs on the surface of solid lipid nanoparticles and prevent the further growth of SLNs during preparation as well as it prevents agglomeration of SLN and therefore results in the formation of stabilized solid lipid nanoparticles with smaller size. The Z-average (d.nm) of all solid lipid nanoparticulated formulations ranged from 248.7 to 828 d.nm **(Fig 3.4.).**

Polydispersity index of all the formulation was reported in **Table No. 3.2.** From observed values of PdI it was revealed that most of the prepared nano formulations was mid-ranged polydisperse as they were having values ranging from 0.243-0.596. But there are two formulations FF2 and FF3 in which PdI value is 0.812 and 0.947 which indicate their polydispersity (**Fig 3.5.**).

Zeta potential of all the formulation was reported in **Table No. 3.3**. For better stability, the nanoparticles should have zeta potential less than -25mV or greater +25mv. From the experimental values obtained after evaluation, it was observed that zeta potential of all the formulations lies in the range from –11.2 to – 16.9mV which suggested that the formulations were not very stable. But the obtained zeta potential values lie within the range (that is –15mV to + 15 mV) which was reported to be effective for delivery of nanoformulation to brain. Therefore, it may be concluded that the prepared formulations may be used for further study as they were able to cross BBB and effectively reach to its target site that is brain. Zeta potential graph for prepared solid lipid nanoformulation FF4 and FF5 is shown in **Fig 3.6. and Fig 3.7.**

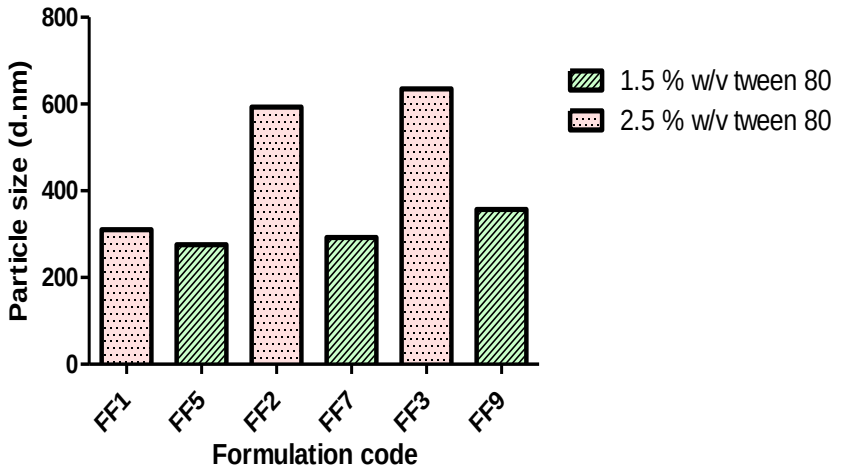

Fig 3.3. Relationship between amount of lipid used during the formulation with obtained particle size (d.nm)

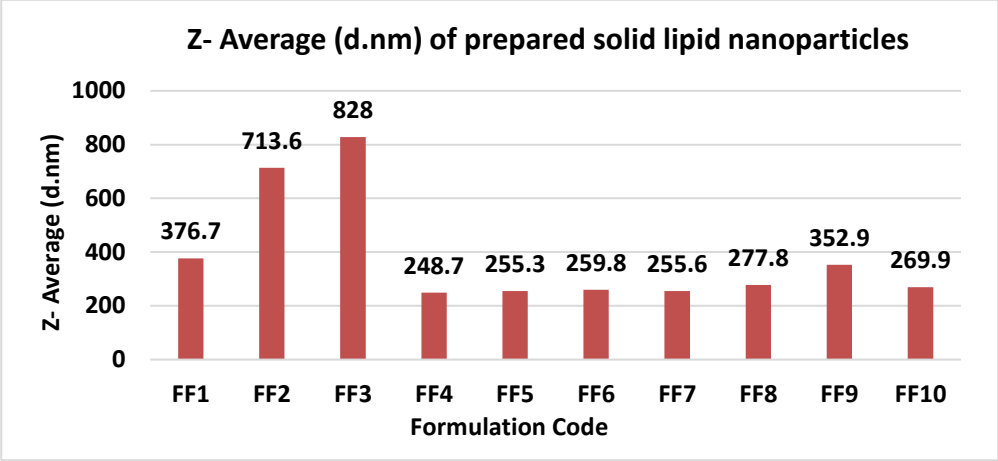

Fig 3.4. Z-Average graph of prepared venlafaxine hydrochloride loaded solid lipid nanoparticles

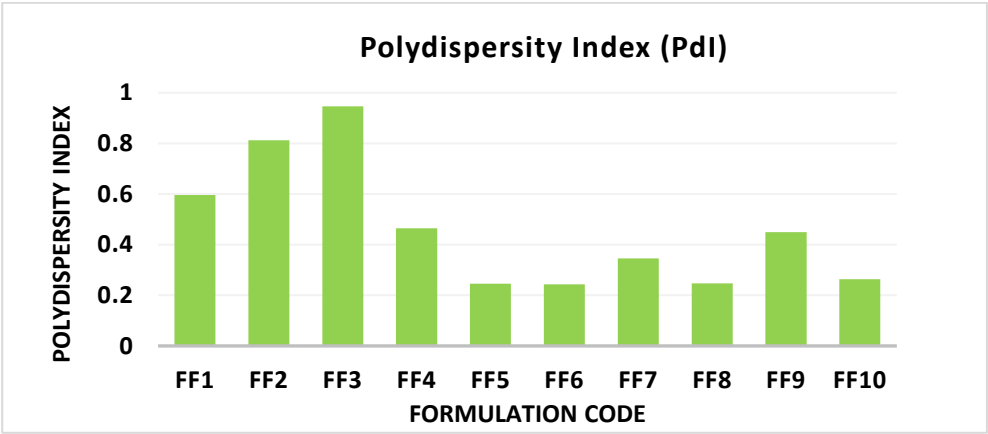

Fig 3.5. PdI distribution graph of prepared venlafaxine hydrochloride loaded solid lipid nanoparticles

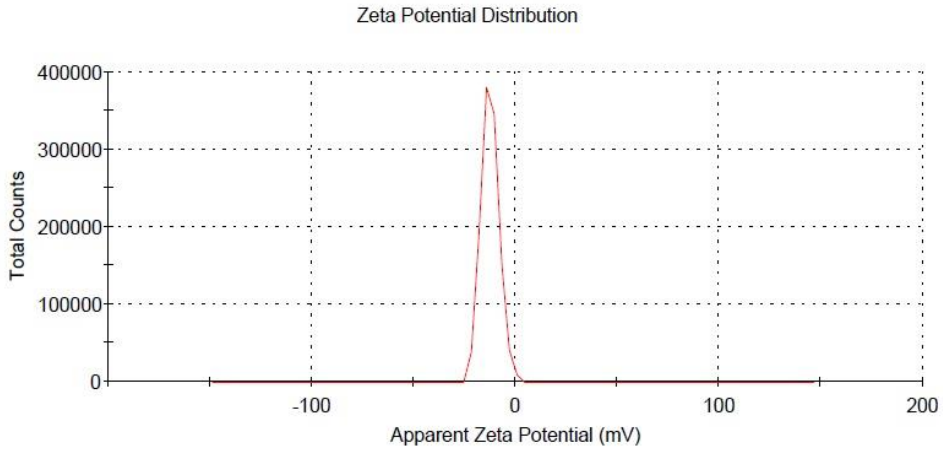

Fig 3.6.: Zeta Potential Distribution graph of Formulation FF4

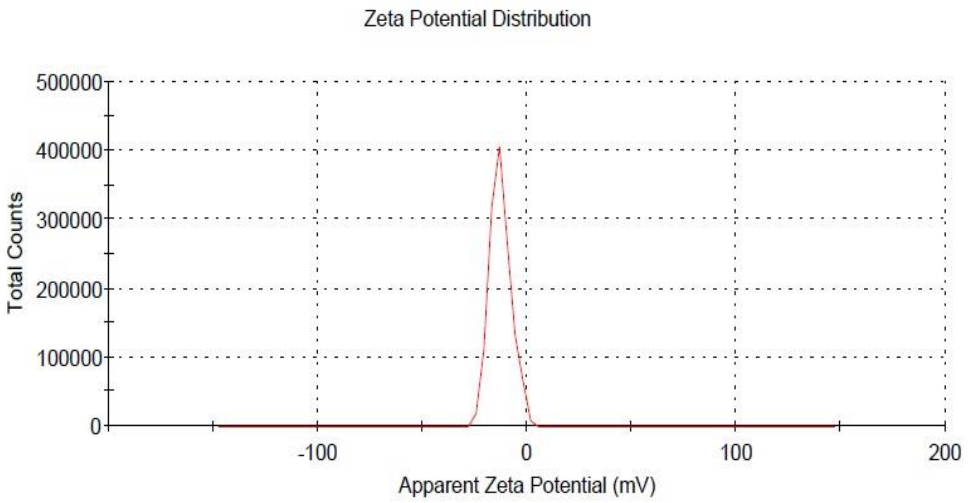

Fig 3.7.: Zeta Potential Distribution graph of Formulation FF5

From observed particle size, PdI and zeta potential values, it was clearly observed that formulation FF1, FF2 and FF3 (that is with 1.5% w/v surfactant) were not suitable for further study as they have large particle size and their PdI values are very high as compared to other formulations. Therefore, formulation from FF4 to FF10 (that is with 2.5% w/v surfactant) were selected for further evaluation.

3.1.2. Surface morphology studies

Surface morphology of formulation FF5 was shown in **Fig 3.8**. SEM analysis of formulation FF5 shows smooth surface of drug loaded SLN with a slight sphere-shaped.

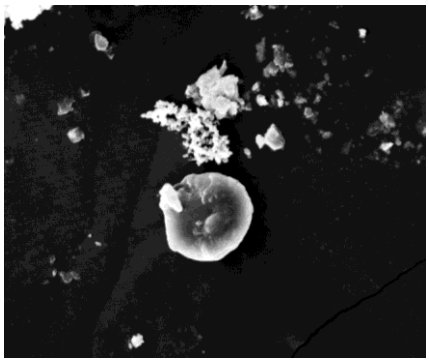

Fig 3.8. SEM image of formulation FF5

3.1.3. Surface entrapment and drug entrapment efficiency

Surface entrapment and drug entrapment values are reported in **Table No. 3.4.** and graphs shown in **Fig 3.9. and 3.10. respectively.** Surface entrapment (%) of prepared drug loaded SLNs was found in between 0.94% to 3.15% and drug entrapment (%) of prepared drug loaded SLNs was found in between 96.85 to 99.06%. From the calculated values of surface entrapment and drug entrapment, it was clearly observed that less amount of drug was present on the surface of drug loaded solid lipid nanoparticles and a higher amount of drug was found to be entrapped in drug loaded solid lipid nanoparticles. Therefore, it may be concluded that by increasing the amount of lipid during formulation, the drug entrapment increases and surface entrapment decreases.

Table No. 3.4. Surface entrapment and drug entrapment efficiency of Venlafaxine hydrochloride loaded solid lipid nanoparticles

S.No.	Formulation Code	Surface entrapment (%) ± SD	Drug entrapment (%) ± SD
1	FF4	3.15 ± 0.12	96.85 ± 0.25
2	FF5	2.36 ± 0.14	97.64 ± 0.26
3	FF6	2.27 ± 0.09	97.73 ± 0.25
4	FF7	1.85 ± 0.10	98.15 ± 0.35
5	FF8	1.15 ± 0.05	98.85 ± 0.33
6	FF9	1.56 ± 0.04	98.44 ± 0.14
7	FF10	0.94 ± 0.07	99.06 ± 0.24

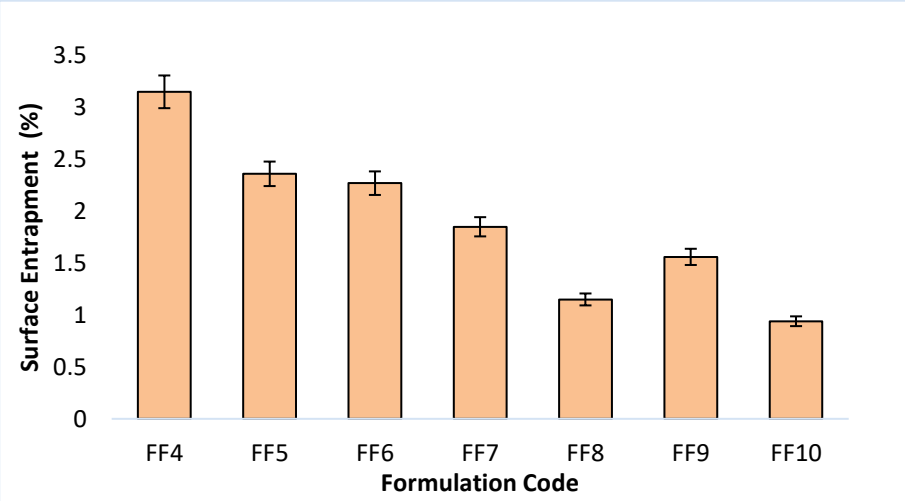

Fig 3.9. % Surface entrapment graph of Venlafaxine hydrochloride loaded solid lipid nanoparticles

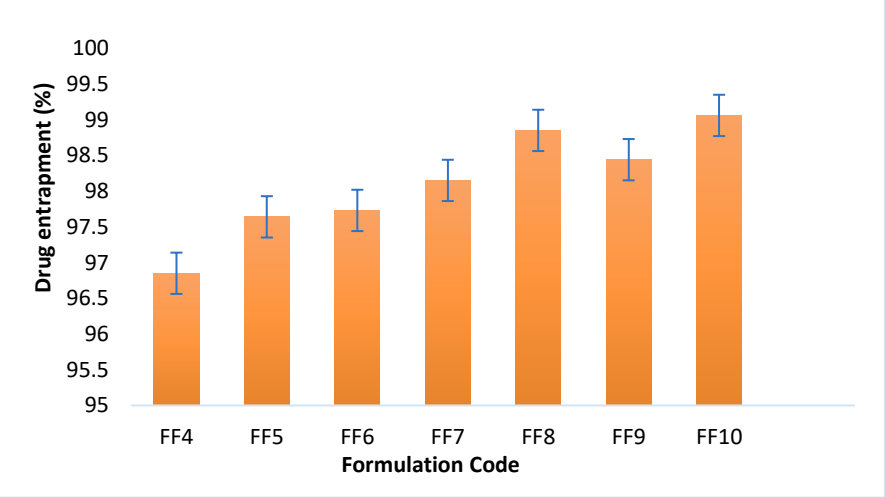

Fig 3.10. % Drug entrapment graph of Venlafaxine hydrochloride loaded solid lipid nanoparticles

3.2. Evaluation of venlafaxine HCl loaded solid lipid nanoparticulated gel

3.2.1. Viscosity

Viscosity of the venlafaxine HCl loaded solid lipid nanoparticulated gel was determined by Brookfield Viscometer **(Table No. 3.5)**. From the values observed, it was revealed that when rpm increases, the viscosity

of the gel decreases and % torque increases. Graph was plotted between rpm and torque which revealed the pseudoplastic flowing behaviour of the solid lipid nanoparticulated gel (**Fig 3.11)**.

Table No. 3.5. Viscosity of prepared venlafaxine HCl loaded solid lipid nanoparticulated gel

Spindle	RPM	% Torque	Viscosity (cps)	Average Viscosity (cps)
64	2	1.3	3900	1791
	4	1.7	2550	
	6	2	2000	
	10	2.8	1680	
	20	4.2	1260	
	30	5.4	1080	
	50	7.9	948	
	60	9.1	910	

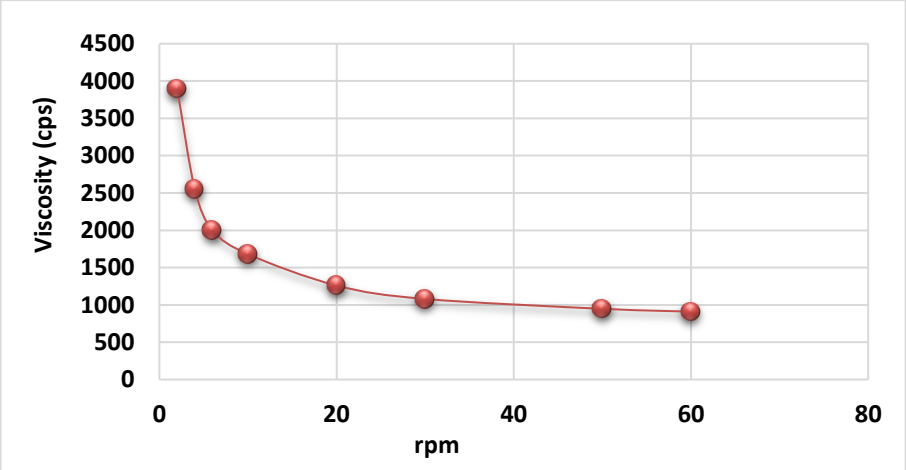

Fig 3.11. Viscosity of prepared venlafaxine HCl loaded solid lipid nanoparticulated gel against rpm

3.2.2. Measurement of pH and Spreadability

pH of the prepared solid lipid nanoparticulated gel was determined by using digital pH meter. From the obtained experimental values, it was observed that the pH of the solid lipid nanoparticulated gel was found to be **6.9 ± 0.081** which match with prescribed pH value of skin that is 6.8 that suggested no irritation on application.

Spreadability of the solid lipid nanoparticulated gel was calculated and found to be **17.63 cm^2 ± 2.24**. For better patient compliance, the gel should have excellent spreadability. The observed value suggested that the prepared gel has good spreadability which indicate that prepared drug loaded solid lipid nanoparticulated gel was easily spreaded over the skin and ease the application.

3.2.3. Drug content of prepared venlafaxine HCl loaded solid lipid nanoparticulated gel

Drug content of prepared venlafaxine HCl loaded solid lipid nanoparticulated gel was reported in **Table 3.6.** and graph was shown in **Fig 3.12**. Drug content of all the prepared solid lipid nanoparticulated gel was ranged from 71.94% to 88.95%. Therefore, it may be concluded that with increasing the amount of lipid, % drug content also increases.

Table No. 3.6. % Drug content table of prepared venlafaxine HCl loaded solid lipid nanoparticulated gel

S.No.	Formulation Code	Drug Content (%) ± SD
1	FF4	71.94 ± 0.83
2	FF5	73.54 ± 0.97
3	FF6	75.00 ± 0.45
4	FF7	79.42 ± 0.84
5	FF8	81.09 ± 0.64
6	FF9	83.37 ± 0.23
7	FF10	88.95 ± 0.34

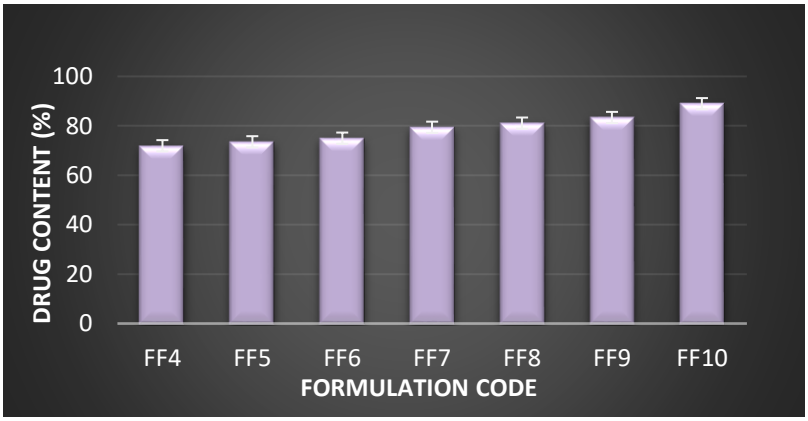

Fig 3.12. Drug content graph of prepared venlafaxine HCl loaded solid lipid nanoparticulated gel

3.3. *In vitro* diffusion study of venlafaxine hydrochloride loaded solid lipid nanoparticulated gel

In vitro diffusion study of venlafaxine hydrochloride loaded solid lipid nanoparticulated gel was performed by using Franz diffusion cell and the graph of formulation FF4 and FF5 was shown in **Fig 3.13 and Fig 3.14.**

In vitro diffusion results revealed that 64.05% - 90.25% of drug released from the formulations in 24 hrs study period.

During 24 hr study, formulation FF4, FF5, FF6, FF7, FF8, FF9 and FF10 releases 90.25, 87.55, 80.96, 77.30, 74.94, 67.77, and 64.05% respectively. From the observed values of % Cumulative drug release (%CR) of all the formulations, it was revealed that there is a direct relationship between amount of lipid used during the formulation and % Cumulative drug release because on increasing the amount of lipid, % CR decreases significantly.

t_{50} and t_{80} values reported in **Table No.3.7.** and graphs were shown in **Fig 3.15. and Fig 3.16.** From the observed values of t_{50}, it was observed that 50 % of drug was released in minimum 10.37 hrs and maximum 14.58 hrs from formulation FF5 and FF10 respectively.

Table No. 3.7. t_{50} and t_{80} values of formulations FF4 to FF10

S.no.	Formulation Code	Predicted time for drug release by model fitting	
		t_{50} (hrs)	t_{80} (hrs)
1.	FF4	10.86	17.38
2.	FF5	10.37	16.59
3.	FF6	11.74	18.78
4.	FF7	12.81	20.5
5.	FF8	12.75	20.4
6.	FF9	13.92	22.27
7.	FF10	14.58	23.32

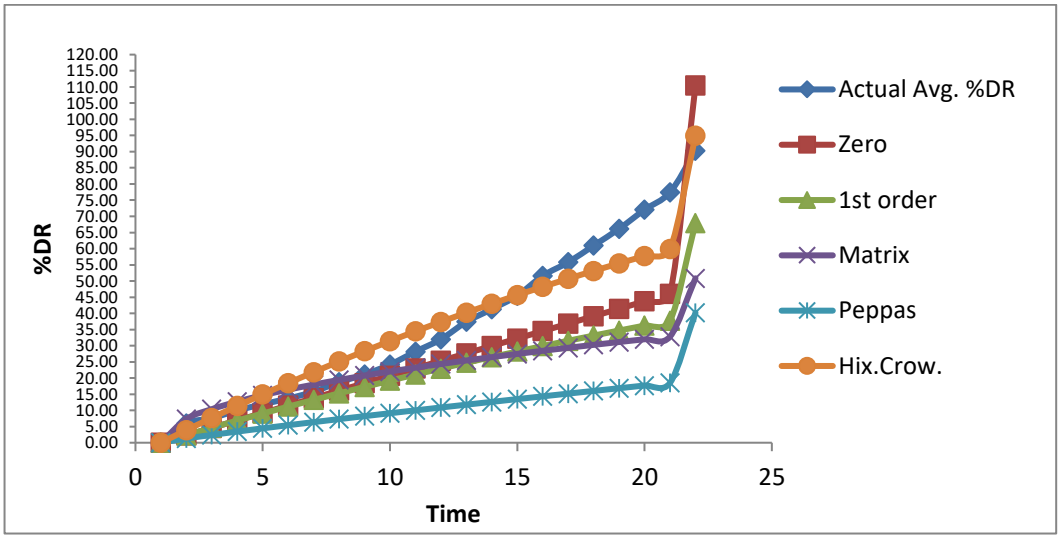

Fig 3.13. In-vitro diffusion study of Formulation FF4

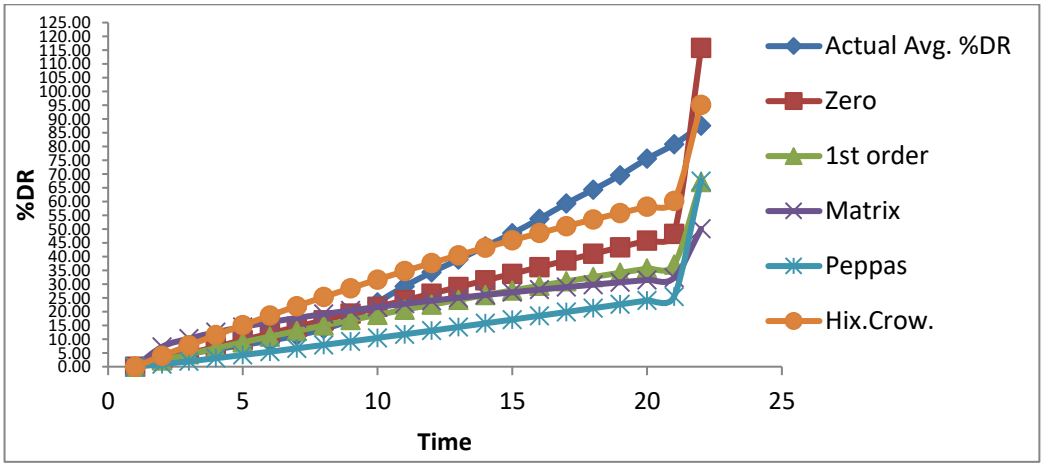

Fig 3.14. In-vitro diffusion study of Formulation FF5

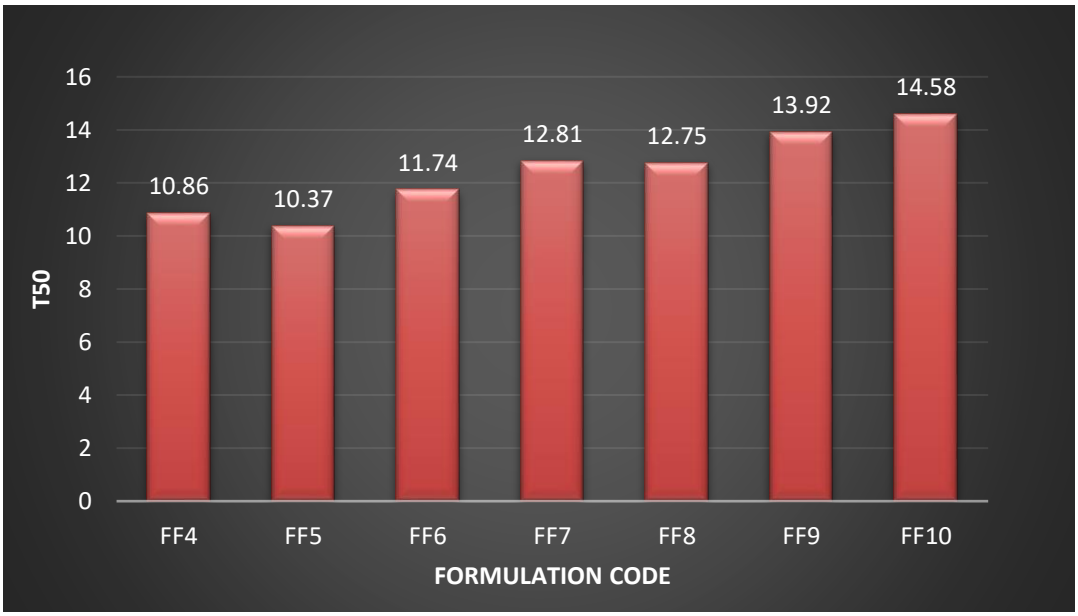

Fig 3.15. Comparative study of t_{50} value of different formulations FF4-FF10

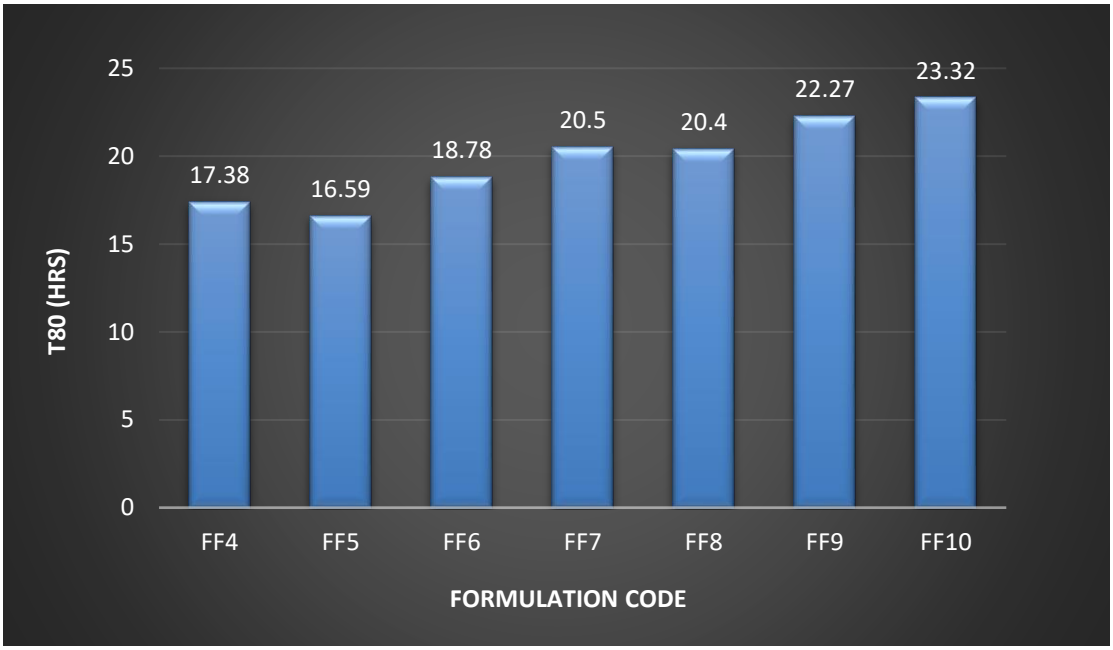

Fig 3.16. Comparative study of t_{80} value of different formulations FF4-FF10

From the observed values of t_{80}, it was observed that 80 % of drug was released in minimum 16.59 hrs and maximum 23.32 hrs from formulation FF5 and FF10 respectively. The reported t_{50} value for venlafaxine HCl is 5 hrs in conventional dosage form. Increased t_{50} in solid lipid nanoparticulated gel of Venlafaxine gives strong evidence of controlled release pattern of the formulation which is desirable for brain targeting to reduce the dose dumping.

3.4. *In-vitro* pharmacokinetic study

Pharmacokinetic models generally used to define the release of drug from immediate as well as modified release formulations. Different kinetic graphs was plotted like zero order, hixon crowell model, higuchi, first order and Korsmeyer – Peppas Model to calculate the value of coefficient of regression (R^2). The kinetic model having highest value of R^2 was declared to be best fitted for the particular formulation.

In order to predict the mechanism of release from the nanoparticulated gel, the following equation **$Mt/M\infty = kt^n$** was used. From the value of n of Korsmeyer – Peppas Model, the mechanism of release was predicted.

n=0.5 indicates Fickian diffusion

n= 0.5 to 1 indicates Non-Fickian diffusion or anomalous diffusion

n= more than 1 indicates Supercase II transport

Kinetic study of formulations FF4 to FF10 was reported in **Table No. 3.8**. From the R^2 values, it was observed that best fitted model for all the formulation was zero order. In formulation FF4 and FF7, by observing the value of n it was confirmed that the anomalous transport is dominant and in formulation FF5, FF6, FF8, FF9 and FF10, Supercase II Transport is dominant. Supercase II transport may be due to the erosion of hydrophilic polymer and anomalous transport may be due to the presence of hydrophilic polymer that tends to swell when comes in contact of water. The hydrophilic polymer then shows anomalous diffusion due to the rearrangement of polymeric macromolecular chains.

Table No. 3.8. *In-vitro* kinetic study of prepared formulations from FF4 to FF10

Formulation Code	R^2				n	Best fitted model	Mechanism of release
	Zero Order	First Order	Higuchi Matrix	Hixon Crowell			
FF4	0.9713	0.8870	0.9321	0.9226	0.9329	Zero order	Anomalous Transport
FF5	0.9675	0.8832	0.9443	0.9205	1.1995	Zero order	Supercase II Transport
FF6	0.9811	0.9219	0.9365	0.9469	1.1076	Zero order	Supercase II Transport
FF7	0.9871	0.9302	0.9263	0.9547	0.9610	Zero order	Anomalous Transport
FF8	0.9687	0.9111	0.9359	0.9339	1.1151	Zero order	Supercase II Transport
FF9	0.9887	0.9492	0.9319	0.9658	1.3494	Zero order	Supercase II Transport
FF10	0.9480	0.8939	0.9364	0.9144	1.2487	Zero order	Supercase II Transport

After performing all evaluation parameters and observing every experimental results, formulation **FF5 (with drug - lipid ratio of 1:2 and 2.5% w/v tween 80)** with particle size of 275.8 d.nm [with 100% intensity], Z average of 255.3 d.nm, PdI of 0.246, zeta potential value -12.8 mV, 2.36 % surface entrapment, 97.64 % drug entrapment, 87.55 % drug release during 24 hr study, t_{50} of 10.37 hrs , t_{80} of 16.59 hrs, zero order release and Supercase II transport was selected as optimized formulation.

CONCLUSION

The main aim of the study was to formulate and evaluate solid lipid nanoparticles of Venlafaxine hydrochloride for effective treatment of depression. In the present research, Venlafaxine hydrochloride loaded solid lipid nanoparticles were prepared by using modified solvent diffusion technique. For this, Monostearin was used as a lipid. Ten formulations were prepared from which three formulations contain 1.5% w/v tween 80 and rest of the formulations contain 2.5% w/v tween 80. Among these formulations, SLNs with 2.5% w/v tween 80 were selected for further study. After performing all the evaluation parameters, **formulation FF5** was selected as optimized formulation because of its small particle size (275.8d.nm with 100% intensity), Z average of 255.3 d.nm, mid ranged polydispersity (PdI of 0.246), with zeta potential value -12.8 mV which lies in the range of zeta potential (-15mV to +15mV) that is required for effective delivery of drug loaded solid lipid nanoformulation to brain, low surface entrapment value (2.36 %), high drug entrapment (97.64 %) indicating higher amount of drug was entrapped in drug loaded solid lipid nanoparticles, 87.55 % drug release during 24 hr study, t_{50} of 10.37 hrs indicating its controlled release pattern , t_{80} of 16.59 hrs, zero order release with Supercase II transport indicating release of drug due to erosion of hydrophilic polymer. So, it was confirmed that prepared formulation was able

to provide better management of depression and hence improve patient compliance.

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***Corresponding Author:**
Sayantan Mukhopadhyay*
Email: **sayantan.pharmaceutics@gmail.com**