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Formulation and Invitro Characterization of Fluvoxamine Loaded Nanoparticles

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Abstract

Fluvoxamine is an antidepressant that functions pharmacologically as a selective serotonin reuptake inhibitor. Though it is in the same class as other SSRI drugs, it is most often used to treat obsessive-compulsive disorder. As the biological half-life of the drug is 15.6 hrs and belongs to BCS class II. To overcome these problems, Nanoparticles of Fluvoxamine were formulated by using Ethyl Cellulose, Eudragit RS 100 & Eudragit Rl 100 as a polymer by emulsification method. Among all the 9 formulations F6 formulation is optimized, as it shows maximum drug release at the end of 12hrs which suits the controlled release drug delivery system criteria as per our studies, having acceptable particle size, SEM, and Zeta potential value. From the drug release kinetics of the F8 formulation of Losartan Nanoparticles dispersion, it was concluded that the F8 formulation follows Zero-order drug release with super case II transport mechanism.

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Introduction

Poorly soluble drugs are very often a challenging problem in drug formulation, especially when the drugs are poorly soluble simultaneously in aqueous and non-aqueous media. This leads in most cases to poor bioavailability or poor erratic absorption of these drugs [1, 2]. Many attempts have been made to increase the saturation solubility of poorly soluble drugs [3, 4]. Ophthalmic drug delivery, more than any other route of administration, may benefit to a full extent from the characteristics of Nano-sized drug particles. Nanosystems are an emerging part of this strategy. Investigating the ocular biodistribution of nanoparticles can provide insights into the bioavailability, cellular uptake, duration of drug action, and toxicity. Many factors such as particle size, composition, surface charge and mode of administration influence the biodistribution in the retinal structures and also their drainage from the ocular tissues [8]. Nanosuspensions are sub-micron colloidal dispersions of pure drug particles in an outer liquid phase [5]. Nanosuspension has advantages in various aspects of dosing. Small particle size and large surface area can improve the dissolution, saturation solubility and bioavailability of

the drug [21]. The use of nanosuspension in the central nervous system can reduce not only systemic toxicity but also increase the concentrations of poorly water-soluble drugs in the brain [6, 7]. The Nano-size represents a state of matter characterized by higher solubility [9-11], the higher surface area available for dissolution [12, 13], higher dissolution rate [15], higher bio adhesion [16, 17] and corneal penetration. It has been recommended that particles be less than 10 μmto minimize particle irritation to the eye, decrease tearing and drainage of instilled dose and therefore increase the efficacy of an ocular treatment. Many published articles have indicated the importance of particle size in ophthalmic bioavailability [17, 18] most of these articles prove that decreasing the particle size increases the ophthalmic bioavailability. Selective serotonin reuptake inhibitors (SSRIs) are antidepressant drugs that increase serotoninergic neurotransmission via the selective inhibition of neuronal reuptake of serotonin. SSRIs are substituting the older tricyclic antidepressants (TCAs). Because of the Selective serotonin reuptake inhibitors (SSRIs) does not show significantly variation in the efficacy relative to the TCAs and the SSRIs do not show very important extrapyramidal side-effects, they are increasingly becoming the drugs of choice in depression remedy. In addition to the antidepressant properties of fluvoxamine, fluvoxamine is used for the treatment of generalized anxiety disorder, obsessive-compulsive disorder, eating disorders, social phobia, and anxiety disorders such as post-traumatic stress disorder and panic disorder [19]. Fluvoxamine is an antidepressant which functions pharmacologically as a selective serotonin reuptake inhibitor. Though it is in the same class as other SSRI drugs, it is most often used to treat obsessive-compulsive disorder. Is chemically called as (E)-(2-aminoethoxy)({5-methoxy-1-[4-(trifluoromethyl) phenyl] pentylidene}) amine. It blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on $5HT_{1A}$ autoreceptors.

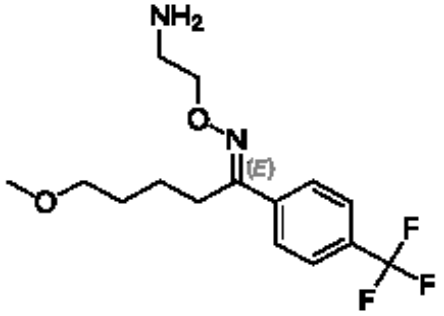


Fig 01: chemical structure of Fluvoxamine

Experimental work

Materials

Fluvoxamine from Spectrum labs, Ethyl cellulose from Signet Chemical Corp., Mumbai , Eudragit RS 100 , Eudragit RL 100 from sigma Aldrich Mumbai

Instruments

Digital balance form Essae-Teraoka ltd, DS-852j, UV Spectrophotometer from PG Instruments ,T60 , FTIR Spectrophotometer from Shimadzu -8400 S and pH meter from Hanna Instruments, Italy.

Methodology :

Pre-formulation studies [20-25]

Prior to the development of dosage form, it is essential that certain fundamental physical and chemical properties of the drug molecule alone and when combined with excipients are determined. This first learning phase is known as pre-formulation. The overall objective of the pre-formulation is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced. The goals of pre-formulation studies are:

- To evaluate the drug substance analytically and determine its necessary characteristics
- To establish its compatibility with different excipients.

Spectroscopic study

Identification of pure drug

Solubility studies

Solubilityof Fluvoxaminewas carriedoutin different solvents –like 0.1N HCL, 6.8pH buffer and 7.4 pH buffer. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48 hr. at25°C under constant vibration. Filtered samples (1ml) were determined spectrophotometrically at 250 nm.

Drug-Excipient Interactions Studies

There is always possibility of drug- excipient interaction in any formulation due to their intimate contact. The technique employed in this study is IR spectroscopy. IR spectroscopy is one of the most powerful analytical technique, which offers possibility of chemical identification. The IR spectra was obtained by KBr pellet method. (Perkin-Elmer series 1615 FTIR Spectrometer).

Determination of UV spectrum of Fluvoxamine

10mg of Fluvoxamine was dissolved in 2-3ml of 7.4pH buffer then makeupto10ml with 7.4 pH buffer so as to get a stock solution of 1000 μg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 7.4 pH buffer to get the concentration of 100μg/ml concentration. From

this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 7.4 pH buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of Calibration Curve of Fluvoxamine

Standard calibration curve of Fluvoxamine using 7.4 pH buffer

Method

10 mg drug was taken accurately in 10ml volumetric flask. It was dissolved in few ml of methanol and make up the volume upto the mark with 7.4 pH buffer to gives 1000 µg /ml. The standard stock solution was then serially diluted with 7.4 pH buffer to get 2 to 12µg/ml of Fluvoxamine. The absorbance was measured against 7.4 pH buffer as blank at 232 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Method of Preparation of Nanoparticles [26]

Fluvoxamine Nanoparticles were prepared by emulsification method.In this method Polymer was dissolved in organic solvent (methanol). Drug is dispersed in this solution. Then this mixuture emulsified in an aqueous phase containing surfactant (polyvinyl alcohol) make an oil in water emulsion by using mechanical stirring, or sonication. After formation of emulsion the organic solvent evaporate by increased the temperature and reduced pressure with continuous stirring.

Table 01: Formulation of Nanoparticles Fluvoxamine

Formulation code	Drug:polymer	Ratios	Concentartion of PVA (%w/v)
F1	Drug : Ethyl cellulose	1:1	2
F2	Drug : Ethyl cellulose	1:2	2
F3	Drug : Ethyl cellulose	1:3	2
F4	Drug : Eudragit RS 100	1:1	2
F5	Drug : Eudragit RS 100	1:2	2
F6	Drug : Eudragit RS 100	1:3	2
F7	Drug : Eudragit RL 100	1:1	2
F8	Drug : Eudragit RL 100	1:2	2
F9	Drug : Eudragit RL 100	1:3	2

Evaluation parameters of Nanoparticles Fluvoxamine [27]

The Nanoparticles was evaluated for various parameters

1. Entrapmentefficiency
2. Particlessizeanalysis
3. Zeta potential
4. In-vitrodrugreleasestudies
5. Scanning electron microscopy

Entrapment efficacy

The freshly prepared Nanoparticles was centrifuged at 10,000 rpm for 20 min using ultracentrifuge. The amount of unincorporated drug was measured by taking the absorbance of the appropriately diluted 5 ml of supernatant solution at 250nm using UV spectrophotometer against blank/control Nanoparticless. DEE was calculated by subtracting the amount of free drug in the supernatant from the initial amount of drug taken.

The entrapment efficiency (EE %) could be achieved by the following equation

%Entrapment efficiency= Drug content *100/Drug added in each formulation

Scanning electron microscopy

The morphological features of Fluvoxamine Nanoparticles are observed by scanning electron microscopy at different magnifications.

Particle size and shape

Average particle size and shape of the formulated Nanoparticless was determined by using Malvern Zetasizer ZS using water as dispersions medium. The sample was scanned 100 times for determination of particle size.

***In vitro* drug release study**

In vitro Release studies Drug release from nanoparticles in-vitro was carried out by dialysis method (Dialysis membrane-60 HI MEDIA, Mumbai). The donor chamber filled with 5ml of nanoparticles suspension, whereas reservoir chamber containing the phosphate buffer pH 7.4. This total setup was placed on a rotary shaker rotating at 50 rpm at 37°C ± 0.5°C. In pre determined

time intervals the content of receiver chamber was withdrawn and replaced with equal volume of fresh phosphate buffer, the amount of Fluvoxamine that diffused into the receiver chamber was quantified by UV- spectrophotometer at 232 nm. The results of invitro release profiles obtained for the NDDS formulations were fitted into Fourmodels of data treatment as follows:28-29. Different release kinetic equations (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r_2) was calculated [30-38].

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be representedby the equation

$$Qt = Q0 + K0t$$

Where Qt is the amount of drug dissolved in time *t*, Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and K0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtainedfrom*in vitro* drug release studies were plotted as cumulative amount of drug released versustime.

Application

It is used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as tablets with low soluble drugs in coated forms, osmotic systems, etc.

First Order Model

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order equation:

$$Log\ C = Log\ Co - kt/2.303$$

Where C is the amount of drug dissolved at time t,

Co is the amount of drug dissolved at t=0 and

k is the first order rate constant.

A graph of log cumulative of % drug remaining vs time yields a straight line

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

The first example of a mathematical model aimed to describe drug release from a system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then sustained to different geometrics and porous systems. This model is based on the hypothesis that

- initial drug concentration in the is much higher than drug solubility;
- drug diffusion takes place only in one dimension (edge effect must be negligible);
- drug particles are much smaller than system thickness;
- swelling and dissolution are negligible;
- drug diffusivity is constant; and
- Perfect sink conditions are always attained in the release environment.

In a general way the Higuchi model is simply expressed by following equation

$$Q = KH - t1/2$$

Where, KH is the Higuchi dissolution constant.

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Application

This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and tablets with water soluble drugs.

Korsmeyer-Peppasmodel

Korsmeyer*et al.*(1983) derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model,

$$Mt / M\infty = Ktn$$

where Mt / M∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. In this model, the value of *n* characterizes the release mechanism of drug as described in the following table.

Table 02: Drug transport mechanisms suggested based on 'n' value

S. No	Release exponent	Drug transport mechanism	Rate as a function of time

1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

To find out the exponent of *n* the portion of the release curve, where Mt / M∞ < 0.6 should only be used. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release *versus* log time.

Zetapotential

There are three ways by which a solid particle (colloid) dispersed in a liquid mediacan acquire a surface charge. First, by the adsorption of ions present in the solution. Second, by the ionization of functional groups on the particle's surface. Third, due to the difference in dielectric constant between the particle and the medium. Attention should be paid to the formation ofelectric double layer at the solid-liquid interface. The zeta Potential is defined as the difference in potential between the surface of the tightly bound layer (shearplane) and the electro-neutral region of the solution.

The potential gradually decreasesas the distance from the surfaceincreases. As the concentration of electrolyte increasesin the medium, the zeta potential falls off rapidly due to the screening effect of the counter ions (Fig 02).The zeta potential cannot be measured directly; however, it can be calculated using theoretical models and from experimentally determined electrophoretic mobility data. The theory is based on electrophoresis and can be expressed as:

$$\mu = \zeta\varepsilon/\eta$$

Where (μ) is the electro phoretic mobility,(ε) is the electric permittivity of the liquid,(η) Is the viscosity and (ζ) is the zetapotential

Results and discussion

Preformulation studies

Solubility studies

Saturation solubility was carried out at 25^{0}C using 0.1N HCL, 6.8 and 7.4 phosphate buffer, ethanol, and methanol.

Table 03: Solubility Studies Data of Fluvoxamine

Solvent	Solubility (μg/ml)
Methanol	2.25
Ethanol	1.45
1.2 pH buffer	0.676
7.4 pH buffer	0.652
6.8 pH buffer	0.737

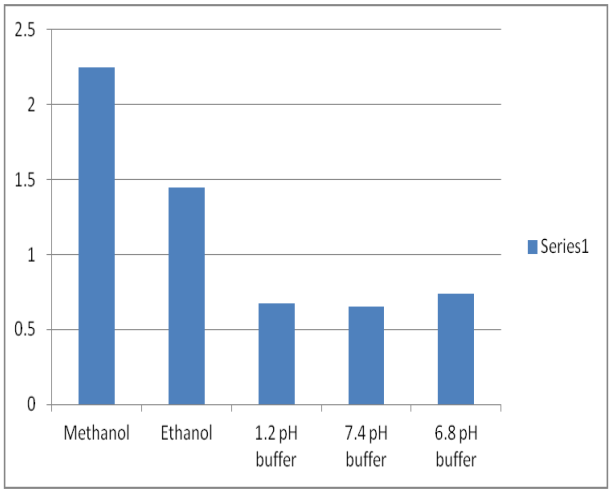


Fig 02: solubility chart in various solvents

From the above conducted solubility studies in various solvents we can say that methanol shows highest solubility than other solvents.

Determination of absorption maximum (λmax)

Determination of Fluvoxamine λ-max was done in pH 7.4 buffer medium for accurate quantitative assessment of drug dissolution rate.

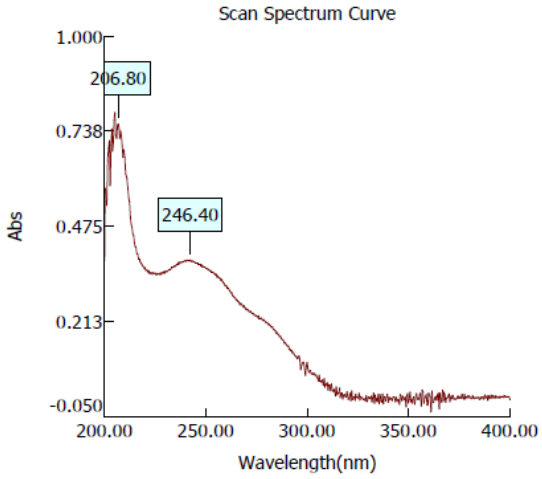


Fig 03: UV Spectrum of Fluvoxamine

Discussion

UV Spectra of Fluvoxamine at 10µg/ml concentration. Wavelength of maximum absorption in 7.4pH buffer was found to be 245nm

Standard Calibration curve of fluvoxamine

Table 04: Calibration curve of fluvoxamine in 7.4 pH buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.108
4	0.214
6	0.325
8	0.433
10	0.535
12	0.634

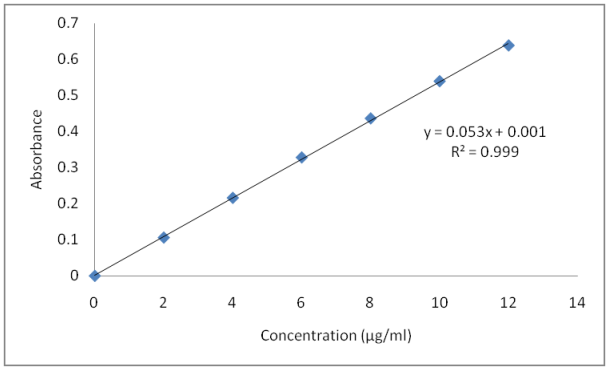


Fig 04: Calibration curve of fluvoxamine in 7.4 pH buffer

The linearity was found to be in the range of 2-12 µg/ml in pH 7.4 buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

Drug and Excipients compactability studies

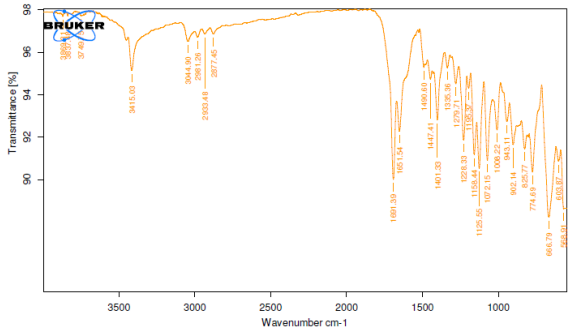


Fig 05: FTIR of Pure Drug

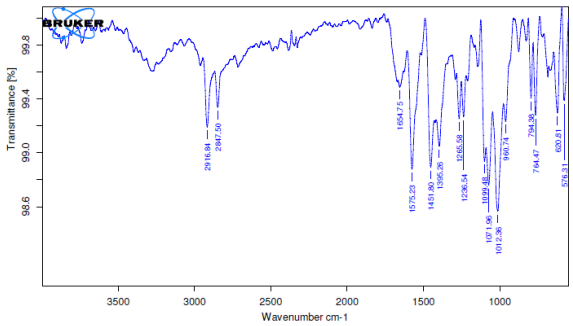


Fig 06: FTIR of Drug + Excipients

From the compatibility studies it was concluded that the functional groups that were presented in the pure drug were present in the optimized formulation with very minute changes, from this we can concluded that the drug and excipients have no interactions.

Drug entrapment efficacy

Table 05: Drug entrapment efficacy

Formulation code	%EE
F1	95.31
F2	96.47
F3	97.23
F4	98.43
F5	96.43
F6	95.08
F7	96.43
F8	95.36
F9	98.13

Discussion

The percentage of drug entrapment efficiency of formulation F1 was found to be 95.31%formulation F2 was found to be 92.47%formulation F3 was found to be 98.23%, formulation F4 was found to be 97.43%, formulation F5 was found to be 96.43%, formulation F6 was found to be 95.08%, formulation F7 was found to be 97.43%, formulation F8 was found to be 92.36%, formulation F9 was found to be 98.13%.

Scanning electron microscopy

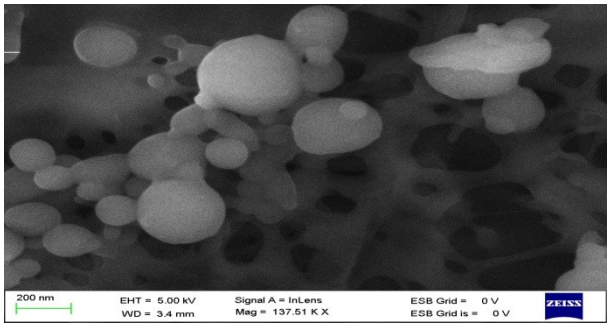
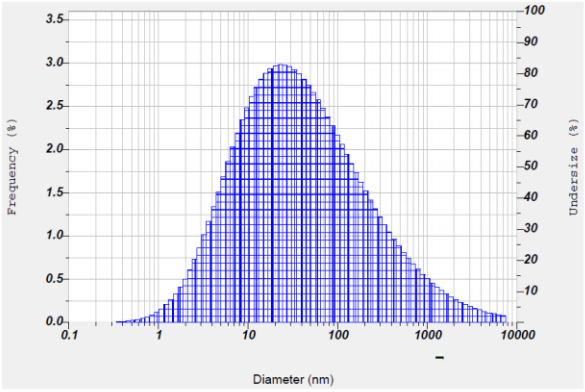


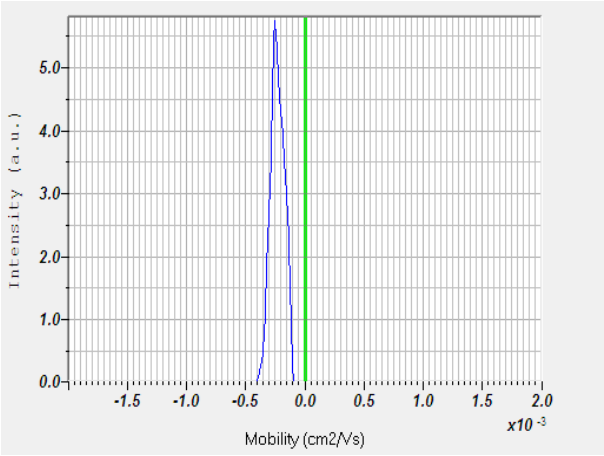
Fig 07: SEM Image of Optimized Nanoparticle formulation

Particle size analysis



Zeta Potential

The measurement itself is a particle electrophoresis, the particle velocity is determined via the doppler shift of the laser light scattered by the moving particles. The field strength applied was 20 V/cm. The electrophoretic mobility was converted to the zeta potential in mV using the Helmholtz-Smoluchowski equation. At standard measuring conditions (room temperature of 25 °C, water) this equation can be simplified to the multiplication of the measured electrophoretic mobility (µm/cm per V/cm) by a factor of 12.8, yielding the ZP in mV.



Invitro diffusion studies of fluvoxamine nano particles

Table 06: Invitro diffusion studies of fluvoxamine nano particles

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	36.15	40.18	45.46	39.42	34.15	40.81	27.31	22.63	28.49
2	53.16	50.45	57.71	46.98	42.87	46.97	39.52	37.49	36.05
3	67.49	58.08	66.18	58.05	54.98	50.18	51.18	50.02	48.18
4	80.52	70.98	72.31	70.46	66.52	58.51	65.08	62.31	59.17
6	95.75	81.08	85.18	79.32	77.42	65.19	75.98	75.53	65.79
8		97.35	92.21	91.05	83.16	73.94	94.75	91.49	72.43
10			98.42		95.21	82.05		98.61	85.19
12						98.05			96.19

All the 9 formulations of fluvoxamine nanoparticle dispersion were subjected to drug release studies. Formulations F1, F2, F3 containing the ethyl cellulose as polymer.F1 shows 95.75% drug release at the end of 6hrs. Where as F2 formulation shows 97.35% drug release at the end of 8hrs. While the F3 formulation shows 98.42% drug release at the end of 10hrs. As the concentration of polymer increasing drug release time is increased. So further trails were performed using Eudragit RS 100 with same proportions. Formulations F4, F5, F6 containing the Eudragit RS 100, F6 formulation shows maximum drug release at the end of 12hrs. while Formulation F7, F8, F9 containing Eudragit RL 100, in which F7 formulation shows 94.75% drug release at the end of 8th hour and F8, F9 shows 98.61% , 96.19% drug release at the end of 10, 12hrs. Among all the 9 formulations F6 formulation is optimized, as it shows maximum drug release at the end of 12hrs which suits the controlled release drug delivery system criteria as per our studies. Further drug release kinetics were performed to F6 formulation.

Drug Release Kinetics (F6)

Zero Order

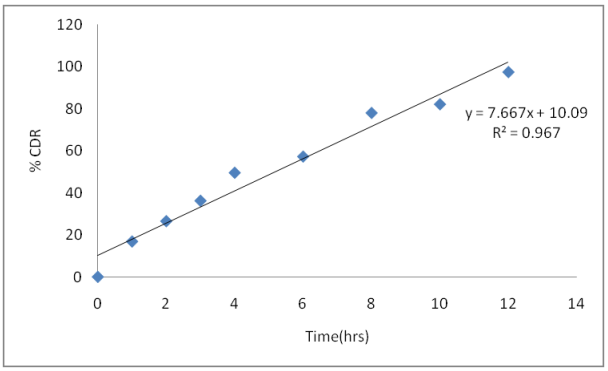


Fig 08: zero oder of optimized formulation (f6)

First order

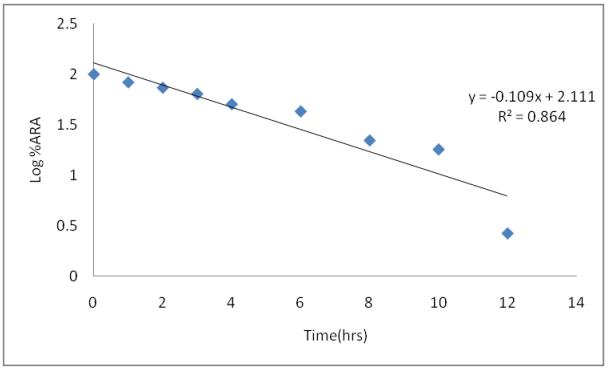


Fig 09: first oder of optimized formulation (f6)

Higuchi Plot

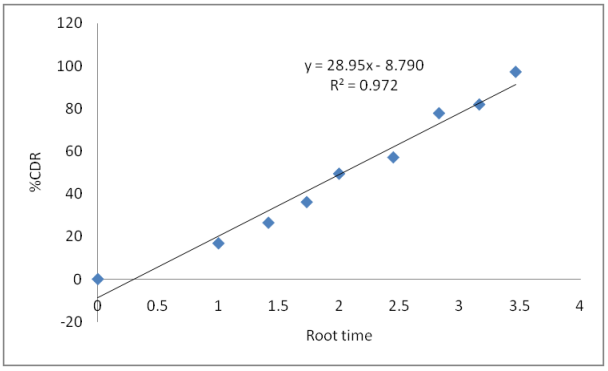


Fig 10: higuchi plot of optimized formulation (f6)

Peppas plot

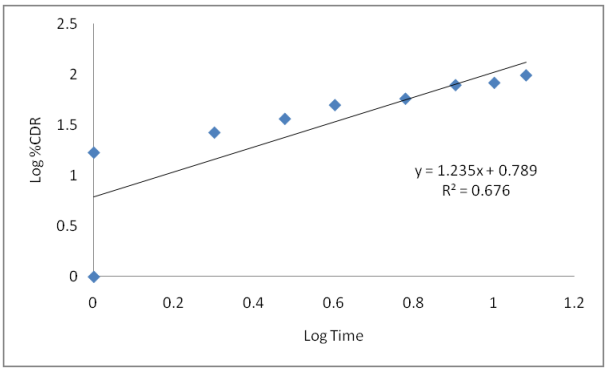


Fig 11: peppas plot of optimized formulation (f6)

Table 07: *in-vitro* drugrelease mechanism of best formulation

Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	R^2	R^2	R^2	R^2	n
F6	0.967	0.864	0.972	0.676	1.235

From the drug release kinetics of nanoparticles dispersion,it was concluded that the formulation F6shows 97.365 of drug release at the end of 12th hour. It follows zero order release and follows super case II transport mechanism.

Summary and Conclusion

Nanoparticulate carriers may provide a better therapeutic output by targeting drugs specifically to their site of action and by improving the pharmacokinetic profile of effective drugslow bioavailability and low halflife. In present investigation Nano particleswere prepared by emulsification method. New Nano particulate drug carrier that combines the benefits of polymeric nanoparticles to enhance the bioavailability of drugs, retain the drug in the absorption site more than the half life of the drug, reduce dose frequency, toxicity and patient compliance. Total nine nanoparticles formulations was formulated using Ethyl cellulose, Eudragit RS 100 & Eudragit RL 100. Estimation of Fluvoxamine was carried out spectrophotometrically at 245nm. The Nanoparticles were evaluated for parameters such as drug content uniformity, scanning electron microscopy,particle size analysis, zeta potential, in-vitro release, Drug release kinetics. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Fluvoxamine) and optimized formulation (Fluvoxamine+ excipients) which indicates there are no physical changes. Zeta potential value for the optimized formulation (F6) was found to be within the acceptable limits. Average particle size of Nanoparticles of optimized formulations (F6) was found to be 180 nm. From the invitro studies we can say that formulation F6 shows best drug release of 98.05% within 12 hrs to release the drug. The drug release from the Nanoparticles was explained by the using mathematical model equations such as zero order, first order, and equation methods.

Based on the regression values it was concluded that the optimized formulation F6 follows Zero order drug release with super case II transport mechanism.

Author Contribution

All authors Contributed Equally

Funding

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Conflict of Intrest

Authors Declare the no conflict of Intrest

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