IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION DEVOLOPMENT AND *IN VITRO* EVALUATION OF MIRTAZAPINE ENTRAPPED NANOSPONGES

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ABSTRACT:

Bioavailability can be enhanced , drug toxicity can be minimised, release of drug in a controlled manner can be achieved by preparing nanosponges. Nanosponges entrap both hydrophilic and lipophilic drug substances. Mirtazapine is an antidepressant drug. Mirtazapine entrapped nanosponges are prepared by Emulsion solvent diffusion method using Eudragit E-100 , PVA as polymers and dichloromethane as a solvent. The prepared nanosponges were evaluated for percentage yield, entrapment efficiency, particle size, drug polymer compatibility, scanning electron microscopy and invitro drug release. SEM studies confirmed their porous structure. The FTIR spectra showed compatibility of Mirtazapine with polymers and revealed the absence of drug polymer interactions. The particle size ranged from 83.8 to 189.7 nm, PDI ranged from 0.384 to 0.508, zeta potential from - 29.3 to -38.5 mV and entrapment efficiency was ranged from 68.15 to 82.64%. The cumulative percentage drug release from nanosponges for 6 hours varied from 56.81 to 92.71% .

KEY WORDS:

Mirtazapine, PVA, Depression ,hydrophobicity, entrapment.

INTRODUCTION :

Nanosponges is a novel drug delivery system made of tiny particles measures in nanometers with narrow cavities. Both hydrophilic and lipophilic drugs can be entrapped in these narrow cavities [1]. Release the drug at specific target site instead of circulate through the body it will more effective [2, 3]. The development of nanosponges has become significant step towards overcoming the demerits associated with conventional dosage forms. The tiny size and porous nature of nanosponges are able to entrap drugs with poor solubility to .enhance their solubility and bioavailability [4]. Nanosponges prepared by using suitable cross-linking agent with suitable organic and inorganic substances [5]. The characteristic features of nanosponges includes, stability in a wide range of pH in GI fluids and at different temperatures up to 130 °C , also they are

compatible with most vehicles and chemical substances. When compared with the conventional drug delivery system dosing frequency can be reduced and thereby patient compliance and comfort can be increased, adverse effects can be minimised, elegant products can be prepared. [6]. The challenging task in the drug development is to enhance the solubility of poorly soluble drug substances but the formulation of nanosponges shows promising results in improving the dissolution ,bioavailability of poorly soluble drug substances. The nanosponges can overcome some of the demerits of the conventional dosage forms.

Depression is a state of low mood and aversion to activity that can have a negative effect on a person's thoughts, behaviour, feelings, world view and physical well-being. Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Moreover, depression often comes with symptoms of anxiety. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide.[8]

Antidepressants are the drugs used to treat depression. By balancing the neurotransmitters in the brain which are responsible for change in mood and behaviour of the individual. Different class of antidepressants balances the neurotransmitters like norepinephrine, serotonin, and dopamine etc. While selecting the antidepressants side effects and drug interactions are to be considered. Antidepressants are of different types:[9]

- Selective serotonin reuptake inhibitors(SSRIs)
- Serotonin-norepinephrine reuptake inhibitors(SNRIs)
- Tricyclic antidepressants(TCAs)

Mirtazapine(MTZ), is an safe and versatile antidepressant belongs to BCS class II, insoluble in water,dissolves in ethanol

[±]-2-methyl-1,2,3,4,10,14 b-hexahydropyrazino [2,1-a] pyrido[2,3-e] benzazepine,its molecular weight is 265.36,belongs to BCS class II and is considered to be a safe and versatile antidepressant, MTZ is insoluble in water, with a logarithm partition coefficient (octanol–water) of 2.9. This indicates a high hydrophobicity, but it does dissolve in ethanol and an acidic condition. The MTZ has a low bioavailability (50%), high protein-binding (85%), and a long half-life (20–40 h). [10]

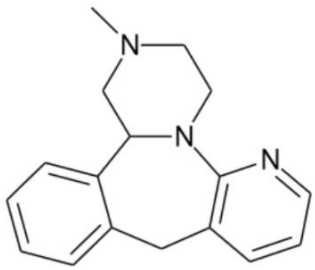

Fig 1.Chemical structure of Mirtazapine.

Mirtazapine is an antidepressant and is used primarily for the treatment of a major depressive disorder, for treating moderate and severe depression. The drug has sedative, antiemetic, anxiolytic, and appetite stimulant effects, insomnia, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, generalized anxiety disorder, social anxiety disorder, headaches, and migraines. Clinicians usually prescribe mirtazapine for major depressive disorder. Mirtazapine is used predominantly in depressed patients with insomnia and/or underweight individuals.[10]

Mirtazapine is a tetracyclic antidepressant drug (TCA). Mirtazapine inhibits the central presynaptic alpha-2-adrenergic receptors, which causes an increased release of serotonin and norepinephrine. Mirtazapine is also sometimes called a noradrenergic and specific serotonergic antidepressant (NaSSA). Noradrenaline is known to have an activating effect on the sympathetic nervous system, explaining the general increase in activity and increased metabolism seen with mirtazapine. It also acts as a potent antagonist of H1 histamine receptors (producing a sedating, calming effect) and 5-HT2A, 5-HT2C, and 5-HT3 serotonin receptors.[10]

MATERIALS AND METHOD:

Materials:

Mirtazapine(MTZ),PVA was purchased from Balaji Chemicals, Bangalore. Eudragit E-100 from Research lab fine chem industries, all the reagents were of analytical grade.

Method:

Mirtazapine nanosponges were prepared by emulsion solvent diffusion method. In this method, two phases used are aqueous and organic. Aqueous phase consists of polyvinyl alcohol and organic phase include drug and Eudragit E-100. After dissolving drug and Eudragit E100 to suitable organic solvent. This phase added slowly to the aqueous phase and stirred for two or more hours and then nanosponges are collected by filtration, washed, and then dried in air at room temperature or in hot air oven .[11]

Table No 1: Composition of different formulation of Mirtazapine nanosponges.

Formulations	Drug (mg)	EudragitE-100 (mg)	PVA %w/v	Dichloromethane (ml)	Distilled Water (ml)
F1	7.5	15	0.5	20	100
F2	7.5	30	0.5	20	100
F3	7.5	45	0.5	20	100
F4	7.5	60	0.5	20	100
F5	7.5	75	0.5	20	100

Calibration curve Determination of calibration curve in phosphate buffer of pH 6.8

λ max of mirtazapine was found at 289 nm in phosphate buffer pH 6.8 using UV Visible spectrophotometer. Absorbance of both the sample and standard solution was measured spectrophotometrically at 316 nm using 0.1N HCl as blank. The drug content in percentage was calculated. Dilute solution of (7.53µg/ml, 15.06µg/ml, 22.59µg/ml, 30.12µg/ml, and 37.65 µg/ml) mirtazapine were prepared in phosphate buffer of pH 6.8 for mirtazapine USP reference standard (RS). The absorbance of the individual solution was observed at 289 nm in a UV-visible spectrophotometer (Shimadzu 1800). A caliberation curve is plotted by taking absorbance versus concentration.The linear regression equation obtained for the mirtazapine calibration curve in phosphate buffer of pH 6.8 at 289nm was - 0.008 with the regression coefficient of 0.998 which indicates good correlation among the measured values.[11]

Table No 2: Absorbance of Mirtazapine in phosphate buffer of pH 6.8 at 289nm.

Sl no	Concentration (µg/ml)	Absorbance @ 289nm
1	7.5	0.18
2	15	0.37
3	22.5	0.56
4	30	0.77
5	37.5	0.94

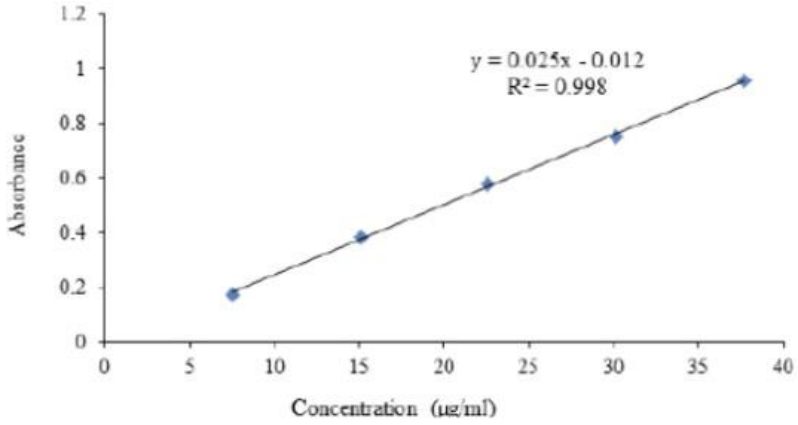

Fig 2.Calibration curve of Mirtazapine in phosphate buffer pH 6.8

EVALUATION OF NANOSPONGES:

Particle size analysis

The particle size was determined by using a Malvern system, with vertically polarized light supplied by an argon-ion laser (Cyonics) operated at 40 mW. The technique of laser diffraction is based around the principle that particles passing through a laser beam will scatter light at an angle that is directly related to their size. As the particle size decreases, the observed scattering angle increases logarithmically The observed scattering intensity is also dependent on particle sizes and diminishes, to a good approximation, in relation to the particle's cross-sectional area. Large particles therefore scatter light at narrow angles with high intensity, whereas small particles scatter at wider angles but with low intensity. [12]

Zeta potential

The stability of a nanosponge can be determined by the result of zeta potential. It is a measure of effect of electrostatic charges. A basic force that causes the repulsion between adjacent particles. Net results are attraction or repulsion depends upon the magnitude of both forces. The thumb rule describes the relation between zeta potential determination responses of the Nano-particles.[12]

Scanning electron microscopy

For the evaluation of the surface morphology of nanosponges, the sample was analyzed in a scanning electron microscope after preparing the sample by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum. The stub containing the coated sample was placed in a scanning electron microscope. The samples were then randomly scanned and photomicrographs were taken at the acceleration voltage of 20 kV. From the resulting image, average particle size was determined. [13]

Drug Content

An accurately weighed amount of 20mg of nanosponges were added to 20ml of ethanol and placed in a thermo-shaker, operated at 100rpm at 25^0 C for 45minutes followed by vortexing for 10min. the solution was filtered through a 45µm membrane filter. Filtrate is observed under UV spectrophotometry.[13]

$$\%\ \boldsymbol{Drugcontent} = \frac{\boldsymbol{Practical\ amount\ of\ the\ drug\ obtained}}{\textbf{Theroretical amount of drug added}} \boldsymbol{X100}$$

***In vitro* Drug Release Study**

In vitro drug release studies were carried out in *Franz* diffusion cell. 20mg of nanosponges dispersed in 2ml of Simulated saliva buffer. The dispersion was used for diffusion study. Nanosponges containing drug were placed in donor compartment while the receiver compartment consists of 22 ml of diffusion medium Simulated saliva buffer pH 6.8 is maintained at room temperature in Franz diffusion cell. The rpm of the magnetic bead was maintained at 50 rpm. 1 ml of the aliquot was withdrawn at predetermined intervals. The samples were analysed for the drug content by UV spectrophotometer at 289 nm. Equal volume of the diffusion medium was replaced in the vessel after each withdrawal to maintain sink condition. Three trails were carried out for all formulation. From the data obtained the percentage drug release was calculated and plotted against function of time to study the pattern of drug release.[13]

RESULTS AND DISCUSSION:

Drugs-polymer interaction study by FT-IR spectrophotometer

The drug and excipient compatibility studies were carried out by Fourier transform-infrared spectroscopy (FT-IR).

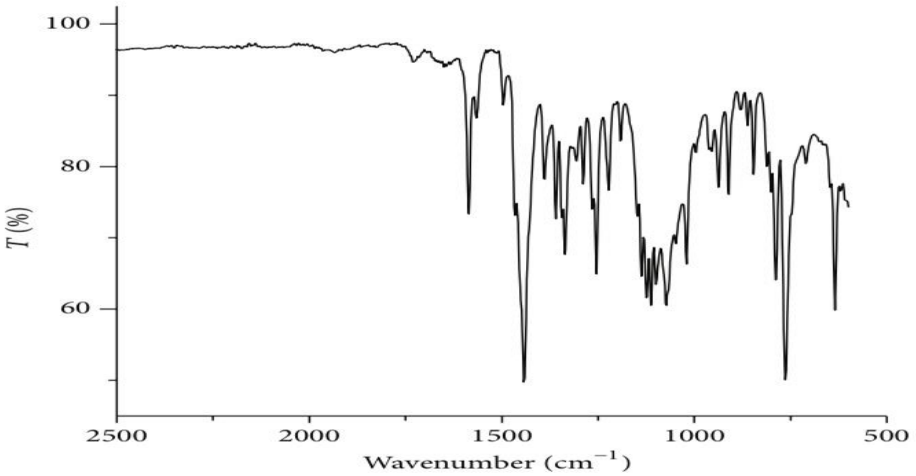

FIG 3.FT-IR spectrum of pure Mirtazapine

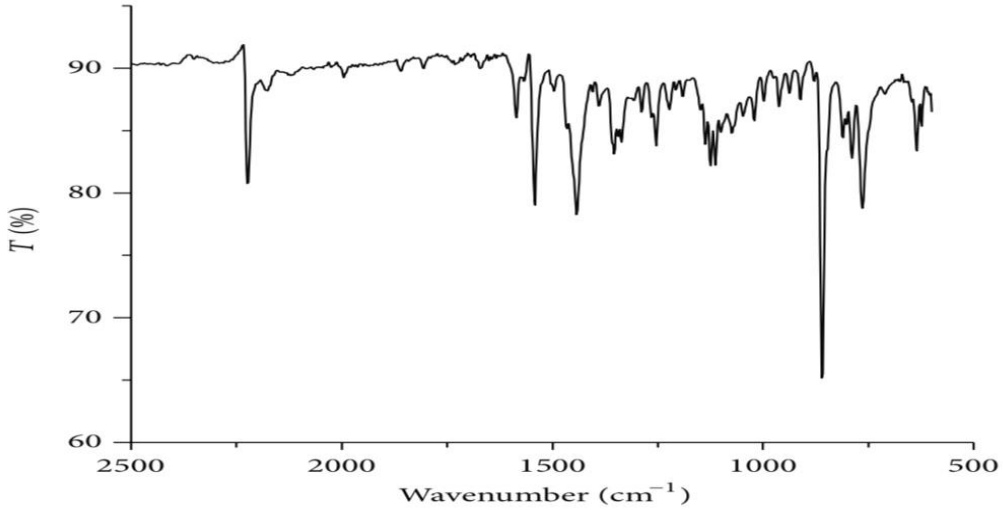

Fig 4. FT-IR spectrum of pure mirtazapine with Eudragit E-100

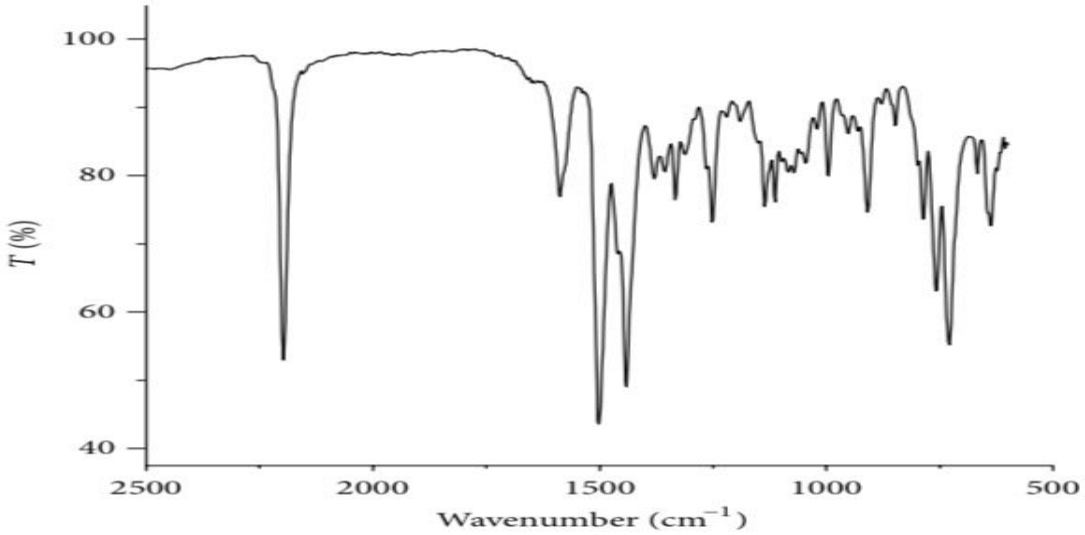

Fig 5.FT-IR spectrum of pure mirtazapine with Eudragit E-100 and PVA

OPTIMIZATION OF NANOSPONGES:

Particle size, zeta potential and PDI

Report of size, PDI and zeta potential obtained from the zeta sizer, shown in the Table no.2 The particle size ranged from 83.8 to 189.7 nm, PDI ranged from 0.384 to 0.508, zeta potential from -29.3 to -38.3 mV.

Table No 3: The particle size, PDI and zeta potential of Mirtazapine nanosponges prepared using Eudragit E-100 , PVA and dichloromethane.

Sl no	Formulations	Particle size (nm)	Zeta potential (mV)	PDI
1	F1	189.7	-38.5	0.384
2	F2	83.8	-34.2	0.432
3	F3	104.1	-33.7	0.487
4	F4	110.9	-29.3	0.508
5	F5	136.3	-34.5	0.409

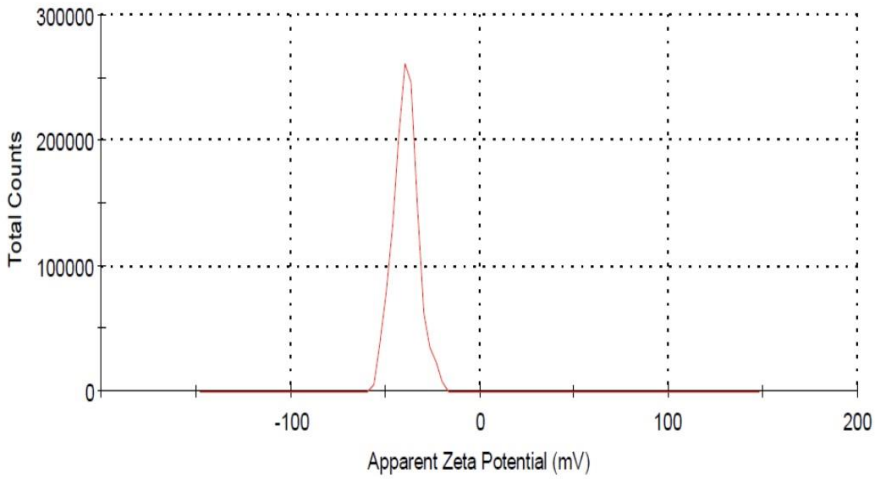

Fig 6.Zeta potential profile of Mirtazapine nanosponges

Scanning Electron Microscopy

SEM analysis of the formulated Mirtazapine loaded nanosponges were performed to evaluate the surface morphology of Nanosponges. The SEM images of Optimised formulation is shown in below.

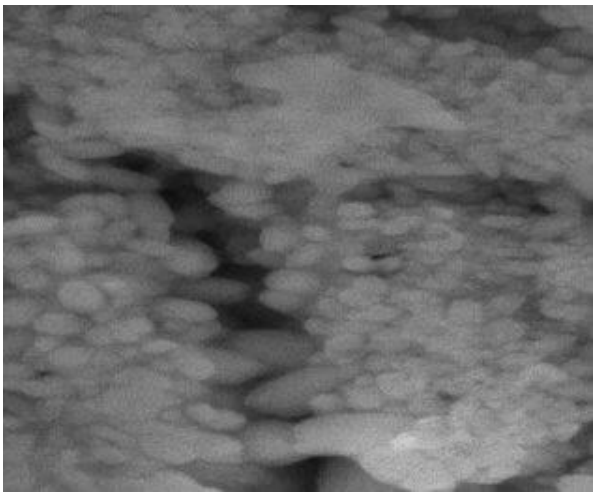

Fig7.SEM image of Mirtazapine nanosponges

Drug content and Entrapment Efficiency:

The drug content and the entrapment efficiency results are shown in the below Table.The drug content results of nanosponges were obtained in the range from 92.87 to 96.98%. Entrapment efficiency of nanosponges were obtained in the range from 69.23 to 82.64%.

Table No 4: The Drug content, Entrapment efficiency of Mirtazapine nanosponges prepared using Eudragit E-100 , PVA and dichloromethane.

Sl no	**Formulations**	**Drug content (%)**	**Entrapment efficiency(%)**
1	F1	92.87	69.23
2	F2	93.24	72.45
3	F3	94.61	68.15
4	F4	95.47	78.91
5	F5	96.98	82.64

Release studies

The drug release from the Nanosponges were studied by *Franz* diffusion method. The cumulative drug release percentage shown in Table No.5

Table No.5: Percentage drug release from different formulations (F1-F5) during 6 Hours.

Time (Hours)	F1	F2	F3	F4	F5
0.5	10.74	12.14	15.02	22.76	26.32
1	13.38	19.58	23.67	27.32	37.51
2	18.01	27.98	34.02	35.17	49.65
3	22.32	36.14	43.45	48.12	55.12
4	39.86	42.76	52.94	57.89	68.41
5	48.15	51.08	61.04	68.61	80.11
6	56.81	60.51	70.65	79.01	92.17

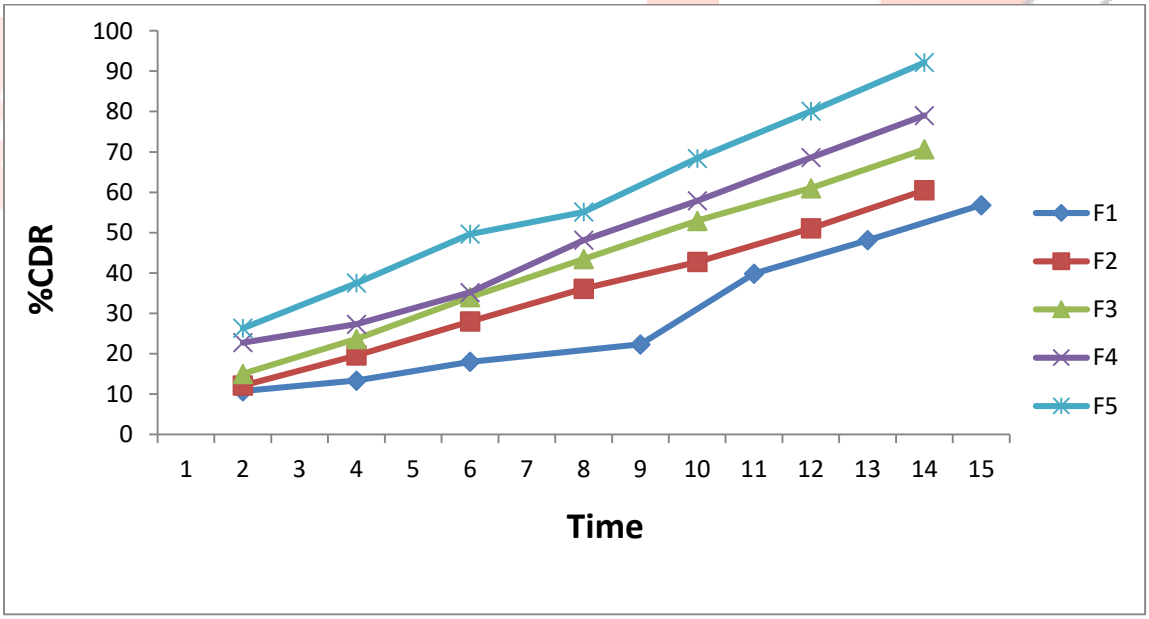

Fig 8.Cumulative drug release from Mirtazapine nanosponges.

CONCLUSION:

The aim of the study is to develop Nanosponge delivery system for Mirtazapine using Eudragit E-100, PVA as polymers, and dichloromethane as a solvent. Mirtazapine is a antidepressant and is used primarily for the treatment of a major depressive disorder,it is insoluble in water and belongs to BCS class II. Mirtazapine Nanosponges prepared by emulsion solvent diffusion method shows improved dissolution and bioavailability profile of drug, good entrapment efficiency ranged between 68.15 to 82.64% , particle size of nanosponges varies from 83.8 to 189.7 mm ,zeta potential ranges from -29.3 to 38.5mV and drug release is 56.81 to 92.71% . The compatibility of drug and polymers determined by FT-IR. The outcome of the study concludes that nanosponges are able to encapsulate various types of drug molecules and enhance the dissolution and bioavailability.

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