Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 11 [4] March 2022 : 264-273

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

A Simplified Review on Mirtazapine Nanocapsules , Their Various Method's and Different Applications

Rutuja Gaikwad,* Nitin Devhadrao, Shubhrajit Mantry , Ganesh Dama
Sharadchandra Pawar College of Pharmacy, Dumbarwadi, Otur, Maharashtra 410504, India.
Correspondence Email: rutujaga04@gmail.com

ABSTRACT
Mirtazapine is an antidepressant drug. Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.The new antidepressant drugs with less adverse effects than imipramine derivatives, have been developed ; they are selectively block both the serotonin transporter and the nor adrenaline (NA) transporter, that is mixed serotonin or nor adrenaline reuptake inhibitors, SNRIs, NaSSA e.g. Mirtazapine. Pharmacological profile of mirtazapine is characterized by potent presynaptic two adrenergic antagonistic activity.
Keywords: *Nanocapsules, antidepressant, nanocarriers, polymeric nanocapsules*

Received 24.12.2021 Revised 16.01.2022 Accepted 17.02.2022

INTRODUCTION

Nanoparticles are defined as particulate dissipations with a size in the range of 10-1000nm. Nanocapsules are systems in which the medicine is confined to a depression girdled by a unique polymer membrane, while nanospheres are matrix systems in which the medicine is physically and slightly dispersed. The major pretensions in designing nanoparticles as a delivery system are to control flyspeck size, face parcels and release of pharmacologically active agents in order to achieve the point-specific action of the medicine at the therapeutically optimal rate and cure regimen1 Polymers used in medication of nanoparticles The polymers should be compatible with the body in the terms of rigidity (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatible [1].

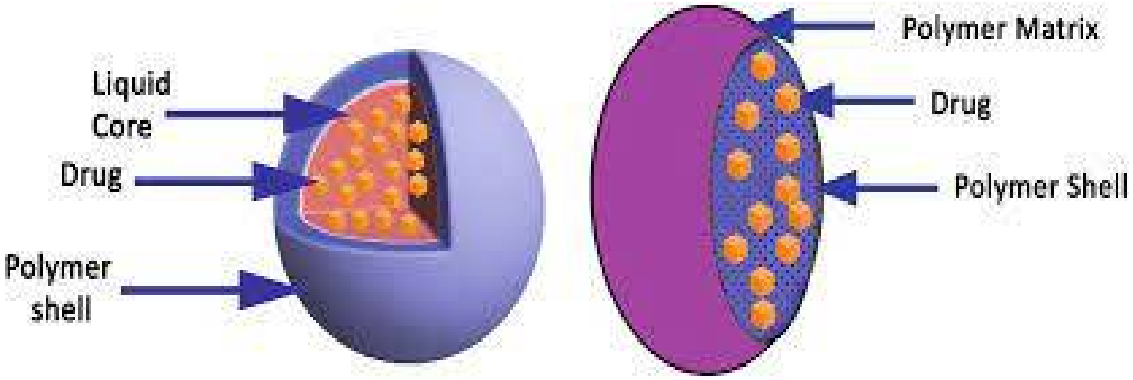

Fig. 1 Structure of Nanocapsule

Depression is regarded a psychiatric or mental illness with a high rate of human development reaching 21% of the world's population. It is well known that depression pathophysiology includes the dysfunction of monoamine neurotransmitter circuits in the central nervous system; therefore, monoamines, their receptors and transporters are the targets of the suggested depression therapies. In that respect are different classes of synthetic drugs available for depression treatment. Nevertheless, the latest synthetic antidepressants have various side effects that affect the patients ' quality of life and, subsequently, their clinical use by causing the therapy to relapse and the symptoms to recur. In addition, about 30% of patients do not have remission under treatment with these medicines, which leads to the combination of more than one class of antidepressants as atypical antipsychotics beyond other groups of medicines. All

these combinations of pharmacology predispose the patient to serious side effects. The low bioavailability and therapeutic efficacy of TQ in its indigenous form may however decrease and improve its use[2-5].

Advantages: -

- Higher dose loading.
- Increase bioavailability of drug.
- Control and sustain release of the drug at site of localization.
- Improve patient compliance.
- Site specific action.
- Reduced irritation of drug at site of administration.
- The system can be used for various routes of administration including oral, nasal, parenteral, intra – ocular, etc [3].

Disadvantages:-

- Limited targeting abilities.
- Discontinuation of therapy is not possible.
- Pulmonary inflammation and pulmonary carcinogenicity [4].

Properties:-

1. Polymeric Nano capsules can be made in the specific sizes, shapes, and in reasonable quantities.
2. Nano capsules can be made to function in different ways.
3. They can be produced like monodisperse particles with exactly defined biochemical, electrical, optical, and magnetic properties.
4.They can be tailored to suit the complexity of whatever application they are intended for, such causing the release of the contents in response to the particular bimolecular triggering mechanism in targeted drug-delivery systems [5].

- **Polymers used in nanocapsules :-**

There are two types of polymers used in the preparation of nanocapsules.

a) Natural polymers
b) Synthetic polymers

Natural polymers :- Natural polymers used as effective in formulating the various variety's of the pharmaceutical product.

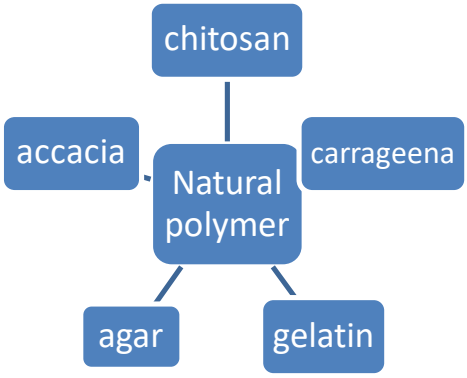

Fig. 2 Types of Natural polymers

Synthetic polymers :- Synthetic polymers are the human made polymers.
They are classified into 4 classes. They are follows as :-

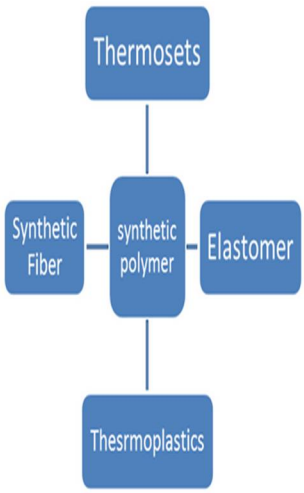

Fig. 3 Types of Synthetic polymers

Method of Preparation of Nano capsules :-

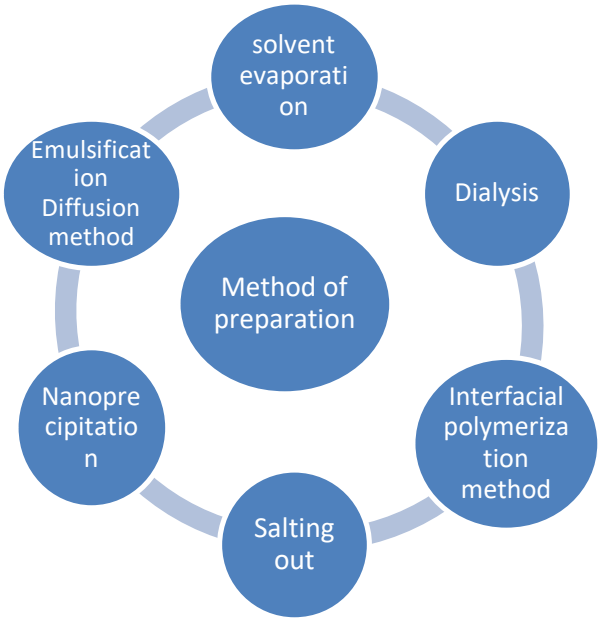

Fig. 4 Method of Preparation of Nanocapsules [4]

1) Solvent Evaporation:-

Solvent evaporation was the first method that developed for the preparation of nanoparticles, in this technique the polymer solutions were prepared in the volatile solvents and emulsions were formulated by employing dichloromethane and chloroform, but now it is replaced with ethyl acetate that is shows a much better toxicological profile to obtain polymeric particles less than 500 nm in size. During the preparation, emulsion is converted into the nanoparticle suspension on evaporation of the solvent, after that the solution is allowed to diffuse through the continuous phase of the emulsion to carry out conventional mode of methods i.e. single emulsions e.g., oil-in-water (o/w) and double emulsions e.g., (water-in-oil)-in-water, (w/o)/w. Such type of methods utilize high-speed homogenization or ultrasonication, followed by the evaporation of solvent either by continuous magnetic stirring at room temperature or under reduced pressure resulting in the formation of solidified Nanosized particle collected by ultracentrifugation followed by washing to remove surfactants and at last the product is lyophilized [7-8].

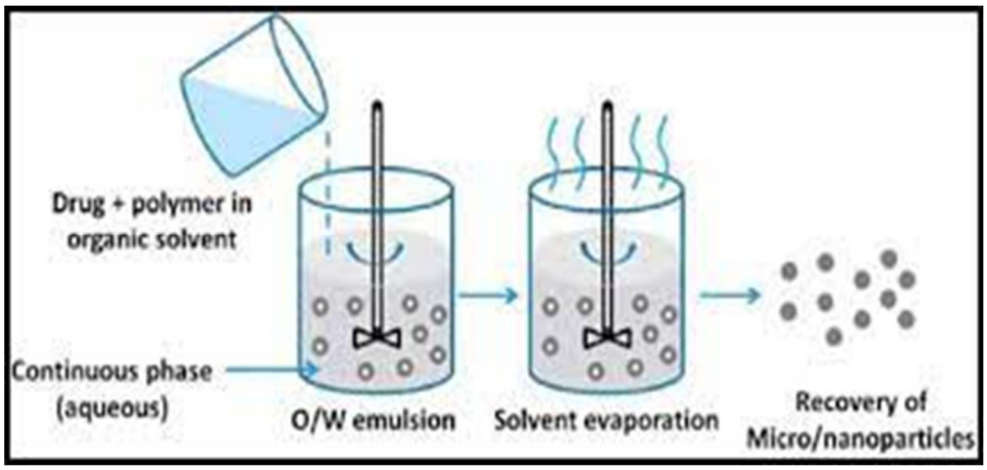

Fig.5 Solvent Evaporation Method

2) Nanoprecipitation Method / Solvent displacement method :-

In this method solvent displacement involves the precipitation of preformed polymer from an organic solution and diffusion of the organic solvent in the aqueous medium in the presence or absence of surfactant. Polymer is dissolved in water-miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. Phase is injected into stirred aqueous solution containing stabilizer as a surfactant. Polymer diposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent , leads to the instantaneous formation of colloidal suspension[5-9].

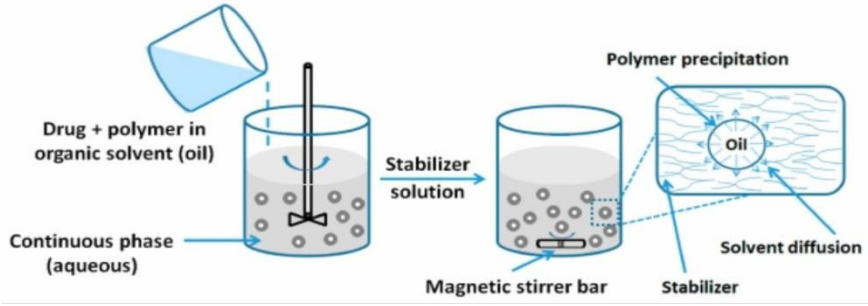

Fig. 6 Nanoprecipitation Method

3) Emulsification diffusion method:-

Emulsification or solvent diffusion technique is the modification of solvent evaporation method which utilizes water miscible solvent and a small amount of water immiscible organic solvent due to the spontaneous diffusion of immiscible solvents that generate turbulence between the two phases result the formation of nanosized particles. The formation of nanoparticles depends only on the diffusion of the solvent of the dispersed phase and the formation of nanospheres or nanocapsules, according to the oil to polymer ratio in which an aqueous solution containing stabilizer successfully leads to solvent diffusion to the external phase of the solution for the formation of nanoparticles [9].

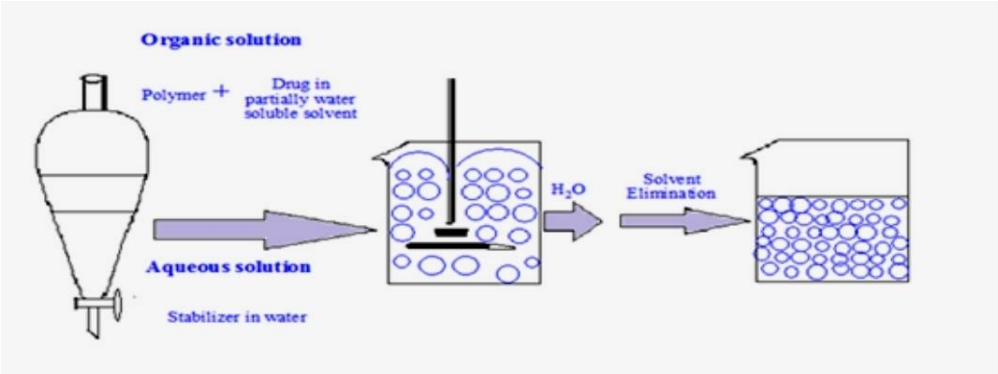

Fig. 7 Emulsification Diffusion Method

4) Dialysis method:-

Dialysis is a simple and effective method for the preparation of small, narrow - distributed nanoparticles synthesis in which polymer is dissolved in an organic solvent and placed inside a dialysis tube with

proper molecular weight cut off and the displacement of solvent inside the membrane is followed by the progressive aggregation of polymer due to loss of solubility and the formation of homogeneous suspensions, of the nanoparticles.

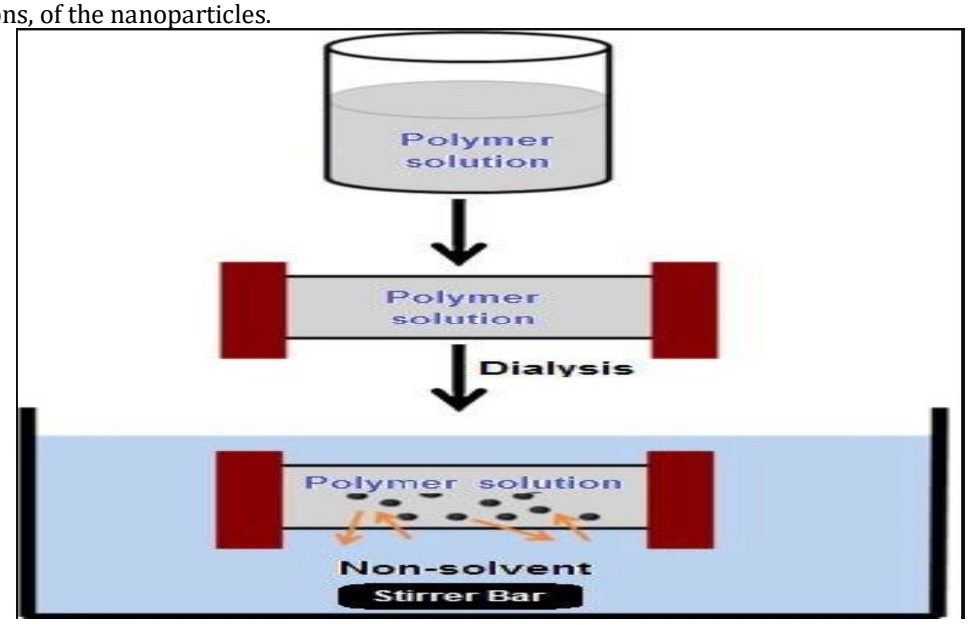

Fig. 8 Dialysis Method

5) Salting out method :-

The salting out is modification of the emulsification solvent diffusion technique in which water miscible solvent is separated from aqueous solutions through salting out process where, initially polymer and drug are dissolved in a solvent such as acetone , then it emulsifies into an aqueous gel consisting a salting out agent in it as electrolytes such as magnesium acetate, or non - electrolytes such as sucrose. Importance of technique depends upon the type of salting out agent used , as it play an important property of encapsulating efficiency of the drugs because the solvent and the salting out agent are then eliminated by cross - flow filtration [10,11].

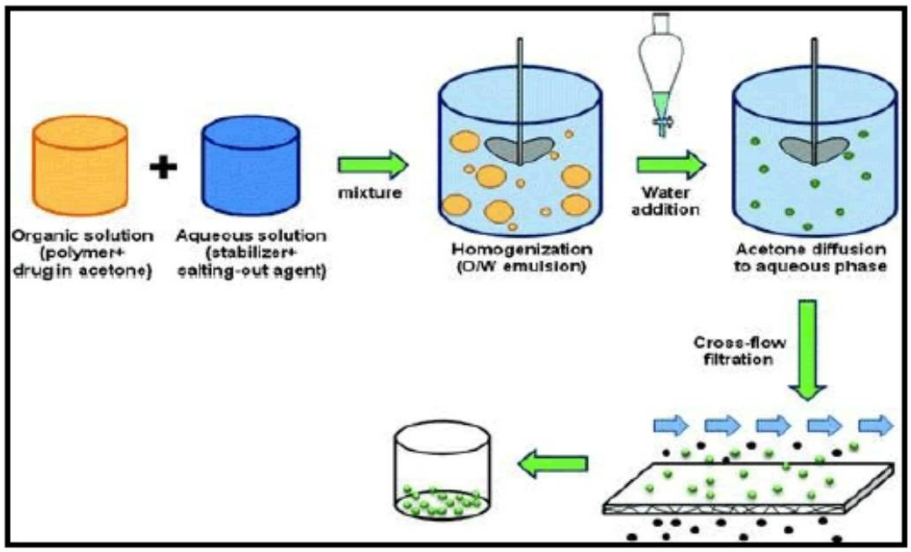

Fig. 9 Salting Out Method

6) Interfacial polymerization method:-

Interfacial polymerization is an alternative to bulk polymerization of condensation polymers, which would require high temperatures. It comprises of two immiscible solvents, in which monomer in one solvent instantaneously reacting with monomer of the other solvent or it may depend on the time scale. Higher molecular weights of monomers are obtained since it is more likely to stumble upon a growing chain than the opposing monomer. For instance, the nanocapsules can be formulated by using the aqueous core containing oligonucleotides of isobutyl cyanoacrylate in a W/O emulsion. The resultant nanocapsules are then purified by ultracentrifugation followed by re suspending in water to yield a dispersion of aqueous core nanocapsules [12].

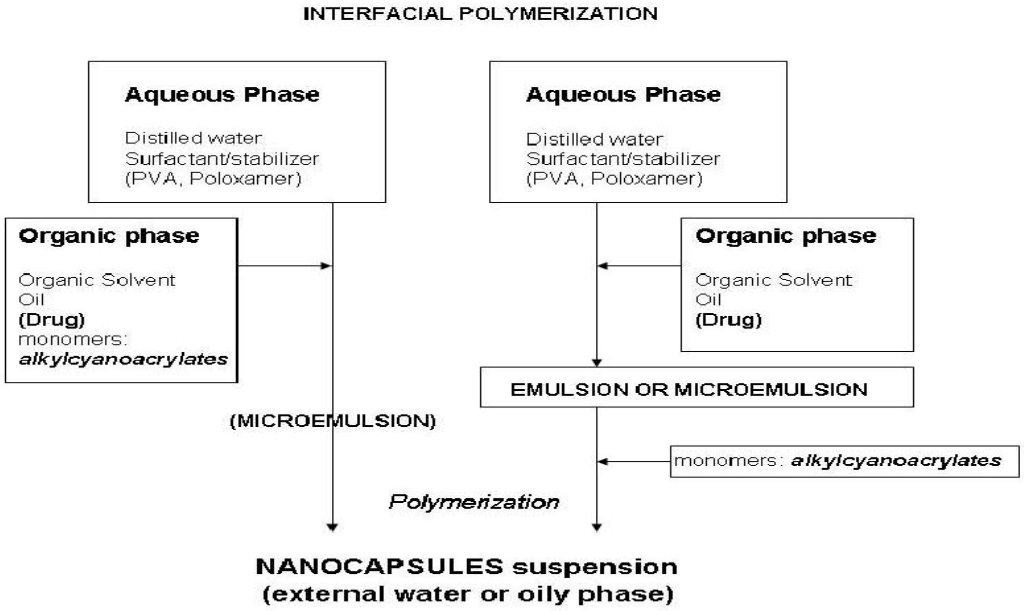

Fig. 10 Interfacial Polymerization Method

EVALUATIONS :-

1) Morphological characteristics :-

The colour, odour and taste of the drug were characterized and recorded.

2) Solubility Study:-

The solubility study was done to select a suitable solvent system to dissolve the drug as well as various excipients used for the formulation and also to test drugs solubility in the dissolution medium.

3) Melting point determination: -

Melting point of Mirtazapine was determined by using capillary method. The fine powder of the Mirtazapine is filled in capillary tube (previously sealed at one end). The capillary tube is inserted in the sample holder of the melting point apparatus and the thermometer is also placed in the apparatus. The temperature at which powder melted was noticed.

4) Measurement of Zeta potential:-

The measurement of Zeta potential is by using the Malvern Zetasizer .

5) Drug excipients compatibility study:-

The drug - excipients compatibility study was carried out by using FT - IR infrared spectrum of the pure drug was seen and the study was carried out on individual pure drug and it's Physical mixture with the excipients used in the study.

6) UV calibration :-

a) Determination of the λ max of Mirtazapine :-

From the standard stock solution 10 µg /ml was scanned under the spectrum mode for 200 – 400 nm wavelength range a sharp peak was obtained at 232 nm.

c) Calibration curve of Mirtazapine :-

Preparation of standard stock solution :-

Mirtazapine (10 mg) was accurately weighed and transferred to a to a 100 ml volumetric flask and it was dissolved in 25 ml of phosphate buffer (pH 6.8) and the mixture was sonicated for about10 – 15 min. The finally made upto the volume with the phosphate buffer (pH 6.8) (100 µg / ml).

Preparation of calibration curve -

From the above standard stock solution fresh aliquots were pipetted out and suitably diluted with the phosphate buffer (pH 6.8) to get the final concentration in the range of 5 - 30 µG / ml. the solutions were scanned under spectrum mode for 200 - 400 nm wavelength range and a sharp peak was obtained at 232 nm .

Therapeutic Applications :-

Depressive disorders :-

As an antidepressant, mirtazapine has validated to be similarly as powerful because the tricyclic antidepressants and trazodone in sufferers with moderate-to-extreme despair in each inpatient and ambulatory settings. Mirtazapine become discovered to be as powerful as amitriptyline, however it reasons fewer and much less extreme anticholinergic and cardiovascular aspect results. When as

compared with the ssris fluoxetine, citalopram, sertraline, four and paroxetine, in addition to the serotonin-norepinephrine reuptake inhibitor venlafaxine, mirtazapine become proven to be similarly powerful however with a considerably in advance onset of action, with results visible as early as 1 and a couple of weeks after remedy initiation. as compared to contributors taking ssris, the ones taking mirtazapine had a 74% extra probability of attaining remission at some point of the primary 2 weeks of therapy. this early development seems to be a particular antidepressant impact this is unbiased of mirtazapine's sleep-enhancing properties, and it's been recognized as a enormously touchy predictor of later solid reaction or solid remission. early development become additionally referred to withinside the number one care placing in depressed sufferers dealt with with mirtazapine. similarly, in number one care, mirtazapine (30–forty five mg/d) confirmed a statistically sizable early development over paroxetine (20–30 mg/d), even though each have been discovered to be efficacious [13,14].

Depression and Comorbid Medical Conditions

a) Post–myocardial infarction depression:-

Depression after myocardial infarction is associated with increased cardiac morbidity and mortality, while antidepressant treatment in cases with cardiac complaint and depression may affect in significant remedial benefit. also, there's substantiation that nonresponse to treatment of post – myocardial infarction depression may be associated with further cardiac events.

b) Post stroke depression:-

Niedermaier *et al* start that precautionary treatment with mirtazapine (30 mg) begun 1 day post stroke significantly reduced the rate of developing post stroke depression, with 5.7 (2/35) of treated cases getting depressed compared to 40 (14/35) of non-treated cases. Mirtazapine was also shown to be effective in treating post stroke depression in the non-treated cases who developed depression in the first phase of the study.

c) Temporal lobe epilepsy and comorbid depression:-

Mirtazapine, citalopram, and reboxetine were each evaluated for the treatment of patients with temporal lobe epilepsy and depression in an inpatient setting. treatment was efficacious with all 3 antidepressants. No serious adverse events, drug interactions, or increase in frequency or severity of seizures occurred. However, the endpoint dropout rate for patients treated with mirtazapine was significantly higher than for those treated with either citalopram or reboxetine [15].

d) Substance dependence and comorbid depression :-

In a study of patients with alcohol dependence and comorbid depressive disorder, Altintoprak *et al* demonstrated significant improvement in depression and alcohol craving scores with both mirtazapine and amitriptyline, although mirtazapine was better tolerated. Another study looked at treating depressed cocaine-dependent subjects with either mirtazapine (45 mg daily) or placebo for 12 weeks. Urine concentrations of benzoylecgonine (the main cocaine metabolite) and self-reports did not show mirtazapine to be more effective than a placebo in reducing cocaine use or improving symptoms of depression.

e) Geriatric depression:-

A 10-week, open-label trial of mirtazapine in 16 elderly patients with depression and 1 or more serious comorbid medical illnesses found that mirtazapine improves depression, insomnia, anxiety, somatic symptoms, and certain quality-of-life measures. A 12-week open-label trial suggested that mirtazapine orally disintegrating tablets were effective and well tolerated in depressed nursing home residents aged 85 years or older. A comparison study of depressed subjects aged 65 years or older found both mirtazapine and paroxetine to be effective during acute (8 weeks) and extension (16 weeks) phases of the trial. However, mirtazapine demonstrated a faster median response time of 26 days compared to 40 days for paroxetine and was associated with greater reduction in anxiety/somatization and sleep disturbance scores. Additionally, mirtazapine (15–45 mg) was found to be similar in efficacy and safety when compared to amitriptyline (30–90 mg) in the treatment of depressed patients aged 60–85 years [16].

Movement disorders

The use of mirtazapine in treating tremors started with the description by Pact and Giduz77 of the reduction or elimination of parkinsonian tremor, action tremor, and levodopa-induced dyskinesias in 5 patients taking mirtazapine (30 mg). Tremor and dyskinesias reemerged on discontinuation of mirtazapine in 2 patients and once again abated when mirtazapine was restarted. A double-blind, placebo-controlled, cross-over pilot study of mirtazapine as an add-on therapy in reducing essential tremor in patients, of whom were already treated with other anti-tremor medications, showed global improvement in 3 patients but no significant improvement compared to baseline. Uccellini et al conducted an open-label observer-blind study of 30 patients with untreated essential tremor and found that 85% of those who remained on mirtazapine treatment therapy after 1 month demonstrated good

control of essential tremor. After 1 year of treatment, 55% of patients continued to show benefit, which is comparable to the estimated 50% improvement rate seen with propranolol and primidone [17-22].

a) Tension-type headache:-

A randomized, double-blind, placebo-controlled, crossover trial in 24 patients with chronic tension-type headache found mirtazapine to be effective in reducing headache severity81 at a rate comparable to treatment with amitriptylineIn a follow-up double-blind, placebo-controlled, parallel trial of mirtazapine, ibuprofen, or the combination of both in 93 patients with chronic tension-type headache, low-dose mirtazapine alone was found to reduce headache severity by 20%, with a noted dose-response effect on efficacy and tolerance [23].

Other Possible Therapeutic Benefits

a) Pain in advanced cancer:-

Interest in the use of mirtazapine as an adjuvant treatment in the palliation of advanced cancer was originally spurred by the hope that it could offer an alternative to tricyclic antidepressants in pain management. In fact, a double-blind cross-over trial demonstrated that a single dose of mirtazapine could significantly increase the pain threshold of healthy participants. A pilot open-label trial, which targeted advanced cancer patients who were experiencing moderate-to-severe residual pain despite opioid maintenance, identified only a small insignificant improvement in pain and pain relief scores with mirtazapine, although there were significant dose-independent improvements in self-rated depression and functional assessment measures [17].

b) Fibromyalgia:-

In a 6-week open-label trial of mirtazapine, 54% of the 26 fibromyalgia patients who completed the study demonstrated a clinically significant reduction in pain intensity and in mean weekly dosage of acetaminophen. Additionally, there was a significant improvement in sleep quality and somatic symptoms, including cold extremities, dry mouth, sweating, dizziness, and headache. Of note, the magnitude of reduction in major fibromyalgia symptoms was significantly correlated with the magnitude of reduction in depression [18].

c) Insomnia:-

The high incidence of somnolence, 53.3% reported across US trials of mirtazapine, spurred an interest in leveraging this side effect for the treatment of insomnia. A 2-week parallel trial of 15 mg versus 30 mg daily mirtazapine in 130 depressed patients with insomnia found persistent improvement in sleep quality and quantity, ease of getting to sleep, and daytime alertness with both doses. The initial 10% incidence of somnolence decreased as the trial progressed, suggesting rapid development of tolerance to the sleep induction effect of H1 antagonism. In a double-blind placebo-controlled study of 20 young healthy volunteers given 1 dose of 30 mg of mirtazapine, confirmed the findings of increased sleep continuity and efficiency in the acute setting while reporting additional benefit of prolonged slow-wave sleep attributed to 5-HT2A/C antagonism. Of note, 5-HT2A/C antagonism has not been implicated in unwanted sedation or tolerance. A double-blind study of 19 depressed patients with insomnia compared mirtazapine versus fluoxetine over an 8-week period and found that the mirtazapine group alone demonstrated significant improvements in total sleep time and sleep latency without the unwanted rapid eye movement suppression that is seen with many antidepressants, including fluoxetine [19].

d) Obstructive sleep apnea:-

Although a manufacturer-sponsored, double-blind, 3-arm, crossover trial of placebo versus mirtazapine in 12 newly diagnosed patients with uncomplicated obstructive sleep apnea showed significant reduction of apnea-hypopnea index, randomized, double-blind, placebo-controlled trials of mirtazapine in patients with obstructive sleep apnea found no measurement of sleep apnea improved with mirtazapine.

I. Substance use disorders

a) Alcohol dependence:-

Liappas et al demonstrated that mirtazapine significantly improved the effects of cognitive-behavioral therapy on social anxiety symptoms in patients with alcohol dependence after a detoxification protocol. Mirtazapine also reduced anxiety and depressive symptoms more quickly when administered in combination with psychotherapy during the post withdrawal phase. Compared to venlafaxine, mirtazapine significantly improved anxiety and depression scores in patients undergoing detoxification from alcohol [20].

b) Methamphetamine use disorders:-

A randomized controlled trial found that treatment with mirtazapine in actively using methamphetamine-dependent men who have sex with men resulted in decreased methamphetamine use and decreased sexual risk behaviors despite low-to-moderate medication adherence. In a double-blind, randomized, placebo-controlled trial of withdrawal treatment in 31 participants ,mirtazapine was not associated with a significant difference in participant retention or symptom reduction. In another study of withdrawal

treatment, mirtazapine was associated with a less severe withdrawal than pericyazine, although modafinil resulted in the mildest withdrawal [21-23].

CONCLUSION

Nanocapsules are a contribution to the methodological development formulation by the various methods , interfacial polymerization and nanoprecipitation method. They are also be release as the monodispersed particle's with well defined biochemical, electrical , optical as well as magnetic properties. Nanocapsules have efficient application in the different fields like agrochemicals, cosmetic products, genetic engineering techniques, waste water treatment, and cleaning products. Nanocapsules can be used as smart drug.

REFERENCES

1. Nilewar, G., Mute, P. B., Talhan, P. P., & Thakre, S. (2017). Nanocapsules: Nano novel drug delivery system. *PharmaTutor*, *5*(6), 14-16.
2. Alam, A., Voronovich, Z., & Carley, J. A. (2013). A review of therapeutic uses of mirtazapine in psychiatric and medical conditions. *The primary care companion for CNS disorders*, *15*(5), 27255.
3. Midha, K (2019). An Overview of the Nanoparticles in CNS Targeted Drug Delivery: An Emerging Trend. Curr Trends Pharma Clinical Trials. 2 (2), 180018.
4. Erdoğar, N., Akkın, S., & Bilensoy, E. (2018). Nanocapsules for drug delivery: an updated review of the last decade. *Recent Patents on Drug Delivery & Formulation*, *12*(4), 252-266.
5. Choudhary, R., Goswami, L., & Kothiyal, P. (2013). Preparation of nanoparticles loaded nasal gel of mirtazapine for treatment of depression. *Journal of Advanced Pharmaceutical Sciences*, *3*(2), 511-520.
6. Yıldız, S., Aytekin, E., Yavuz, B., Bozdağ Pehlivan, S., Vural, İ., & Ünlü, N. (2018). Development and evaluation of orally disintegrating tablets comprising taste-masked mirtazapine granules. *Pharmaceutical Development and Technology*, *23*(5), 488-495.
7. Koushik, O., Rao, Y., Kumar, P., & Karthikeyan, R. (2016). Nano drug delivery systems to overcome cancer drug resistance—a review. *J Nanomed Nanotechnol*, *7*(378), 2.
8. Nielloud, F., & Marti-Mestres, G. (Eds.). (2000). *Pharmaceutical emulsions and suspensions* (Vol. 105). Marcel Dekker, Incorporated.
9. Alivisatos, P. (2004). The use of nanocrystals in biological detection. *Nature biotechnology*, *22*(1), 47-52.
10. Lone, B. (2016). Adsorption of cytosineon single-walled carbon nanotubes. *J Nanomed Nanotechnol*, *7*(354), 2.
11. Sindhwani, S., Syed, A. M., Wilhelm, S., Glancy, D. R., Chen, Y. Y., Dobosz, M., & Chan, W. C. (2016). Three-dimensional optical mapping of nanoparticle distribution in intact tissues. *ACS nano*, *10*(5), 5468-5478.
12. Lambert, G., Fattal, E., Pinto-Alphandary, H., Gulik, A., & Couvreur, P. (2000). Polyisobutylcyanoacrylate nanocapsules containing an aqueous core as a novel colloidal carrier for the delivery of oligonucleotides. *Pharmaceutical research*, *17*, 707-714.
13. Bremner, J. D. (1995). A double-blind comparison or Org 3770, amitriptyline, and placebo in major depression. *The Journal of clinical psychiatry*.
14. Wheatley, D. P., Van Moffaert, M., Timmerman, L., & Kremer, C. M. (1998). Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. *Journal of Clinical Psychiatry*, *59*(6), 306-312.
15. Kühn, K. U., Quednow, B. B., Thiel, M., Falkai, P., Maier, W., & Elger, C. E. (2003). Antidepressive treatment in patients with temporal lobe epilepsy and major depression: a prospective study with three different antidepressants. *Epilepsy & Behavior*, *4*(6), 674-679.
16. Hsyøerg, O. J., Maragakis, B., Mullin, J., Norum, D., Stordall, E., Ekdahl, P., ... & Sennef, C. (1996). A double-blind multicentre comparison of mirtazapine and amitriptyline in elderly depressed patients. *Acta Psychiatrica Scandinavica*, *93*(3), 184-190.
17. Arnold, P., Vuadens, P., Kuntzer, T., Gobelet, C., & Deriaz, O. (2008). Mirtazapine decreases the pain feeling in healthy participants. *The Clinical journal of pain*, *24*(2), 116-119.
18. Samborski, W., Lezanska-Szpera, M., & Rybakowski, J. K. (2004). Open trial of mirtazapine in patients with fibromyalgia. *Pharmacopsychiatry*, *37*(04), 168-170.

19. Aslan, S., Isik, E., & Cosar, B. (2002). The effects of mirtazapine on sleep: a placebo controlled, double-blind study in young healthy volunteers. *Sleep*, *25*(6), 666-668.
20. Liappas, J., Paparrigopoulos, T., Tzavellas, E., & Rabavilas, A. (2005). Mirtazapine and venlafaxine in the management of collateral psychopathology during alcohol detoxification. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(1), 55-60.
21. McGregor, C., Srisurapanont, M., Mitchell, A., Wickes, W., & White, J. M. (2008). Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: a comparison of mirtazapine and modafinil with treatment as usual. *Journal of substance abuse treatment*, *35*(3), 334-342.
22. Fenelon, G. (2015). Antidepressants and movement disorders. *Medication-Induced Movement Disorders (Ed J Friedman)*, 141-9.
23. Bobes, J., Garcia-Portilla, P., Saiz, P. A., Bascaran, T., & Bousono, M. (2005). Quality of life measures in schizophrenia. *European Psychiatry*, *20*(S3), S313-S317.

CITATION OF THIS ARTICLE

Rutuja Gaikwad, Nitin Devhadrao, Shubhrajit Mantry , Ganesh Dama. A Simplified Review on Mirtazapine Nanocapsules , Their Various Method's and Different Applications. Bull. Env. Pharmacol. Life Sci., Vol 11[4] March 2022 : 264-273.