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Significances of Ziprasidone Nanoparticles in Psychotic Disorders †

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Abstract: Nanotechnology is used today in a wide range of industries. Weakly water-soluble medications are better soluble and bioavailable when delivered by nano-specific drug delivery methods, such as nanocrystals. Another name for ziprasidone is (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one. A brand-new "atypical" or "second-generation" antipsychotic drug. Its multipotent G-protein-coupled (GPCR) receptor binding profile is distinctive. It is used to treat bipolar disorder-related acute manic or mixed episodes as well as schizophrenia. Schizophrenia is a serious mental condition in which a person experiences bizarre reality views. Ziprasidone is a highly lipophilic and unstable drug. Another incarnation of ziprasidone nanoparticles is used to treat diseases.When ziprasidone is present in the form of particles with an effective average crystal size of less than or equal to 100 nm, the term "nanoparticle" is frequently used to characterise them. A colloidal submicron dispersion of ziprasidone particles is what ziprasidone nanosuspension and nanoemulsion are made of. One formulation that makes use of solubilization technology is a nanosuspension of crystalline ziprasidone free base. In order to get around the drug's solubility issue and investigate its potential for nose to brain delivery, the buffered nanoemulsion of ziprasidone HCl has also been created. We discussed numerous ziprasidone nanoformulations used to treat psychotic illnesses in this review.

Keywords: ziprasidone; schizophrenia; colloidal dispersion; nanosuspension; Nanoemulsion

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1. Introduction

Today, nanotechnology is a crucial method for making poorly water-soluble pharmaceuticals more soluble. Because of the increase in surface area and saturation caused by the reduction of these medications' particle sizes to the nanometer range, they can dissolve more quickly and have greater bioavailability [1,2]. About 40% of recently developed medicines have poor water solubility [3]. Drugs' poor bioavailability is due to their poor water solubility [4]. To make weakly water-soluble medications more soluble, there are numerous methods. Using co-solvents, surfactants, and complexing are a few of these methods for preparing pharmaceuticals as salts [5]. Additionally, it has been claimed that particle size reduction medicines can make them more soluble [6]. Applications of nanotechnology for pharmacists include medications with active components that are nanoscale in size [7]. As a result of the smaller drug delivery systems, drugs can now be deposited in previously inaccessible body parts;relevance in the identification and treatment of specific illnesses like cancer.Target therapy and advancements in medical devices

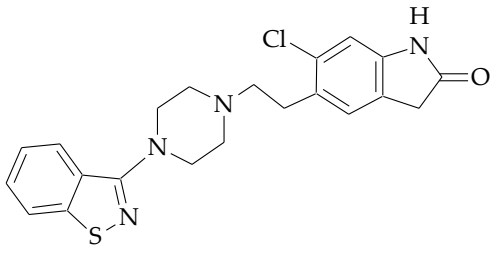
and diagnostic tests are new discoveries in medication delivery [8]. The science underlying nanotechnology is still in its infancy, which raises certain concerns about the advancement.

National Nanotechnology Initiative (NNI) defines nanotechnology as the study of all particles with a diameter of less than 100 nanometers. One nanometer equals one- sized in billionths of a meter [9]. Among the most crucial the ratio of the benefits of the smaller particle size to surface molecules or atoms as a percentage of all increases. They therefore have substantial surface areas which caused them to become more active on their surface and produce modifications to their biological and physical characteristics properties.

The benefits of nanoparticles can be summed up as follows: (i) Increased bioavailability, (ii) Less toxicity, (iii) Sustained and controlled release, (iv) Targetability are among the benefits, (v) Provide efficient intracellular and brain delivery compartment, (vi) Improved permeability, (vii) Faster, illness diagnosis that is more secure and accurate, (viii) More surgery that is accurate, less intrusive, (ix) Expensive and (x) Production on a large scale is doable, (xi) But smaller dosage, (xii) Stable dosage formulations, e.g., a smaller pill, (xiii) Greater speed of dissolving, particularly in internal aqueous fluid.In general, quicker disintegration results in larger bioavailability, lower dosages, and less toxicity. (xiv) Drugs' capacity to remain stable in biological fluids helps to avoid allergic reactions, discomfort following an injection, and/or drug precipitate due to its dilution in the environment blood [10,11].

2. Drug Profile

The IUPAC name of Ziprasidone is 5-{2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-1,3-dihydro-2H-indol-2-one.The molecular formula is $C_{21}H_{21}ClN_4OS$ and having molecular weight 412.94 g/mol. It is atypical antipsychotic drug and it is slightly soluble in DMSO and methanol. It's melting point is about 213–215 °C. The pKa value is 13.34 ± 0.20 (pe-redicted). It is brown to dark brown solid. The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown [12–14]. The Figure 1 shows structure of Ziprasidone.



Ziprasidone

Figure 1. Structure of Ziprasidone.

3. Various Nanoformulations of Ziprasidone

Nanoformulations are a novel method of drug administration because they are easy to manipulate, US FDA approved, non-toxic, and selectively and specifically degraded in the colon region. These qualities are promising materials for application in a colon specific drug delivery system. As drug particle size is lowered to the nanoscale, there is an improvement in dissolving properties and an increase in saturation solubility, which may be due to an increase in particle surface area. That result in the drug's saturation solubility significantly rises as particle size is reduced.Because of their numerous advantages, including their very small particle size, nanosuspensions and nanoemulsions have become

a viable method for the effective administration of hydrophobic medications. There are various nano formulations of ziprasidone such as nanosuspension and nanoemulsion.

3.1. Ziprasidone Nanosuspension

The term "nanosuspensions" refers to colloidal dispersions of pharmaceutical active component particles smaller than 1 micrometer in diameter in a liquid phase, being stabilised by without the need of any matrix material polymers and surfactants [15]. Nanosuspension can be produced by an appropriate size-reduction method and stabilized by a suitable stabilizer [16–18]. The Noyes-Whitney and Ostwald-Freundlich principles state that particles with a size in the nanometer range may have higher dissolution rates and saturation solubilities for a nanosuspension, which often comes with an enhancement of bioavailability [16,19,20]. Nanosuspensions differ from nanoparticles and solid lipid nanoparticles with respect to the fact that nanoparticles are polymeric colloidal carriers of drug while solid lipid nanoparticles are lipid carrier of drugs. More and more recently created medications have poor solubility; frequently, pharmaceuticals have poor solubility in both. Aside from the conventional media, aqueous and organic methods for resolving these solubility issues leading in issues with bioavailability. Producing drug nanoparticles (also known as nanosuspensions) is an alternate and promising strategy to combat various challenges. As a new technology, nanosuspensions promising approach to the effective delivery of due to their wide range of properties, hydrophobic medicines and distinctive advantages. The specific characteristics of nanosuspensions have made it possible for them to be used in a variety of dosage forms, including customised delivery systems such is hydrogels that adhere to mucous membranes. The important general benefits of this technique include simplicity and applicability to the majority of medications [21].

All medications that are insoluble in water can be prepared as nanosuspension, which is a straightforward process. Nanosuspensions are prepared by using wet mill, emulsion solvent, high pressure homogenizer, supercritical fluids, melt emulsification, and evaporation fluid methods. Delivery of nano-suspensions is possible through pulmonary, ocular, parenteral, and oral routes. When included in ocular inserts and mucoadhesive hydrogels, nanosuspensions can also be employed for targeted medication administration. At the moment, efforts are being specifically aimed towards expanding their uses in site-particular medication delivery. Rapid advancements have been made in the parenteral, preoral, ophthalmic, and pulmonary delivery of nanosuspensions. Strictly speaking, nanosuspension preparations are a less complex alternative to liposomes and other types of conventional colloidal drug carriers, however they are said to have more economically sensible. It is very beneficial for people who are struggling soluble medications and to provide a physiologically more stable product. For making nanosuspensions, there are two opposite approaches, "Top-down procedure technology" and "Bottom-up process technology" [22].

One formulation that makes use of solubilization technology is a nanosuspension of crystalline ziprasidone free base. Atypical antipsychotic drugs include ziprasidone hydrochloride. It is a white or slightly pink powder that is essentially insoluble in water but slightly soluble in the melting point of methylene chloride and methanol 300 °C. It is regarded as a BCS Class II medication due to its strong permeability and low solubility. Under fed conditions, the 20 mg dose's absolute bioavailability is about 60% was reported. Ziprasidone Hydrochloride is well absorbed from the gastrointestinal tract with peak plasma concentrations being reached 6 to 8 h after oral dose. Ziprasidone Hydrochloride is extensively metabolized by aldehyde oxidase (about 66% of a dose) and by the cytochrome P450 iso-enzyme CYP3A4. Less than 5% of a dosage is eliminated primarily as metabolites in the urine (20%) and faeces (about 66%) unchanging medicine. Drug binds to plasma proteins in 99% of cases. According to reports, terminal elimination occurs after 7 h, and the volume of distribution is 1.5 L/kg. Peak plasma levels of ziprasidone hydrochloride are about 2 to 3 h after an oral dose, 89ng/mL is reached [23–28].

3.1.1. Advantages

i. Most cost effective;
ii. Useful for poorly soluble drugs;
iii. Physically more stable than liposomes;
iv. Provide ease of manufacture and scale up for large scale production;
v. Rapid dissolution and tissue targeting;
vi. Reduction in tissue irritation;
vii. Higher bioavailability in ocular and inhalational drug delivery [29,30].

3.1.2. Disadvantages

i. Compaction, sedimentation, and physical stability can all be problematic;
ii. Because of its weight, extra caution must be used while handling and transporting;
iii. Unsuitable dosage [31].

3.2. Ziprasidone Nanoemulsion

Nanoemulsions/Sub-micron emulsions (SMEs)/Mini-emulsions are thermodynamically stable transparent or translucent dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a globule size of less than 100 nm. Nanoemulsions are now commonly employed to deliver vaccines, DNA-encoded drugs, antibiotics, and other medications, cosmetic and topical products are advertised via a variety of channels, including oral, pulmonary, transdermal, intranasal, and ocular etc. As a type of multi-phase colloidal dispersion, nanoemulsions are distinguished by their stability and clarity. The scattered generally contains tiny particles or droplets with very little oil/water interaction, strain on the face. Nanoemulsions can sometimes develop naturally without high-energy input and spontaneously and readily. There are several occurrences where a cosurfactant or cosolvent is utilised, the oil phase, in addition to the surfactant, and the water phase.

Three types of nanoemulsions are formed depending on the composition:

1. Oil in water (o/w):Nanoemulsions wherein oil droplets are dispersed in the continuous aqueous phase;
2. Water in oil (w/o):Nanoemulsions wherein water droplets are dispersed in the continuous oil phase;
3. Bi-continuous:Nanoemulsions wherein micro domains of oil and water are interspersed within the system.

An adequate mixture of surfactants and/or cosurfactants stabilises the interface in all three forms of Nanoemulsions. Emulsions and Nanoemulsions have a significant difference in that the former, while they may exhibit great stability of kinetic processes is thermodynamically unstable and likely to change over time separation. Emulsions and nanoemulsions both have distinct visual characteristics; emulsions are hazy, whereas nanoemulsions are transparent [32–36].

The goal is to develop a method that will effectively deliver the medicine to the target spot in the brain by avoiding first-pass metabolism while also increasing bioavailability by invasive procedure. Such strategies will not only decrease the dose while minimising ancillary side effects. Intranasal (i. n.) route has been shown in studies to be a useful, non-invasive, and alternate mechanism for quick medication delivery to the brain [37] and thus, for many medications and vaccines, nasal administration has been used as an alternative to oral delivery and injection [38]. The highly vascularised and immunogenic nasal mucosa offers potential advantages in terms of quick action, improved bioavailability and patient compliance [39]. According to reports, exogenous materials penetrate the blood-brain barrier (BBB) on their way directly from the nose to the brain via the olfactory and trigeminal nerve pathways [40–42]. In order to administer medications to central nervous system, the nasal cavity's olfactory area can be used as a conduit between the nose and the brain [43,44]. Based on these considerations, develop buffered nanoemulsion of ZP

HCl nanoemulsion to overcome its solubility limitation and to explore its potential for nose to brain delivery. As the target site of the ZP HCl for antipsychotic activity is the temporal and prefrontal area that constitutes the limbic system and meso-cardial area in the brain, intranasal route might be a better approach for rapid attainment of effective drug concentration in brain [45].

3.2.1. Advantages

i. Takes away variations in absorption;
ii. Increases the rate of absorption;
iii. Supports lipophilic drug solubilization;
iv. Offers aqueous dosage forms for medications that are not water soluble;
v. Enhances bioavailability;
vi. Several delivery methods, including topical, oral, intravenous route can be used to administerproduct;
vii. Effective and quick penetration of the drug substance's aids in flavors muffling;
viii. Offers defence against hydrolysis and drug oxidation in the oil phase in o/w emulsion;
ix. Less energy is necessary;
x. Liquid dose forms promote patient compliance;
xi. Nanoemulsions are thermally stable systems that are stable and that allow system's ability to self-emulsify characteristics do not rely on the process was used;
xii. Nanoemulsions transport both lipophilic and hydrophilic substances;
xiii. Use of Nanoemulsion as a Delivery System tems increases a drug's effectiveness, and reducing the overall dose to be decreased and hence reducing side [46].

3.2.2. Disadvantages

i. Use of a high concentration of cosurfactants and surfactants is required for stabilising nanodroplets;
ii. Low solubilizing ability for high melting substances;
iii. The surfactant must not be harmful to pharmaceutical uses;
iv. The following factors affect the stability of nanoemulsions: environmental aspects like temperature and pH. These specifications when a nanoemulsion is delivered, it transforms to patients [47].

4. Significances of Ziprasidone Nanoparticles

Another name for ziprasidone is (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one. A brand-new "atypical" or "second-generation" antipsychotic drug. Its multipotent G-protein-coupled (GPCR) receptor binding profile is distinctive. It is used to treat bipolar disorder-related acute manic or mixed episodes as well as schizophrenia. Schizophrenia is a serious mental condition in which a person experiences bizarre reality views. Ziprasidone is a highly lipophilic and unstable drug. Another incarnation of ziprasidone nanoparticles is used to treat diseases. When ziprasidone is present in the form of particles with an effective average crystal size of less than or equal to 100 nm, the term "nanoparticle" is frequently used to characterise them. Cognitive disorders include hallucinations, delirium, dementia, schizophrenia, and delusions are clinical manifestations of psychoses, which are brain illnesses. Significant side effects of antipsychotic medications include dystonia, tardive dyskinesia, uncontrollable muscular movement, and metabolic abnormalities. Moreover, due to the blood-brain barrier, the antipsychotics that are currently on the market have low bioavailability, drug-related side effects, poor therapeutic efficacy, and inadequate brain delivery. Traditional dose forms, which release the medications into the bloodstream, are ineffective at efficiently delivering the drugs to the brain. As a result, a logical strategy based on nanotherapeutics may be able to circumvent these restrictions; such strategies can be employed to

transport medication molecules to their intended spot. Nanotherapeutics are colloidal systems made up of particles in the nanosize range with special physicochemical characteristics, such as plasticity, biodegradability, and bioacceptability. They also have a variety of surface modification capabilities and can protect drug molecules from degradation. Various nanoformulations for delivery of antipsychotic drugs to the brain; these include nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsion, nanosuspensions. Also the ability of these formulations to improve drug bioavailability and targeting affinity, as well as their ability to circumvent the first-pass metabolism [48,49].

5. Conclusions

Nanotechnology for pharmacists include medications with active components that are nanoscale in size. The review focuses on Ziprasidone nanoparticles which is used in treatment of psychotic disorders. Ziprasidone Hydrochloride is atypical antipsychotic drug. Its multipotent G-protein-coupled (GPCR) receptor binding profile is distinctive. It is used to treat bipolar disorder-related acute manic or mixed episodes as well as schizophrenia. Ziprasidone nanosuspension and nanoemulsion are a submicron colloidal dispersion of Ziprasidone particles. A nanosuspension of crystalline ziprasidone free base is already a formulation utilizing solubilization technology. Also the buffered nanoemulsion of ziprasidone HCl has been developed to overcome its solubility limitation and to explore its potential for nose to brain delivery. These formulations have ability to improve drug bioavailability and targeting affinity.

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