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Development of Nanoformulation for Injectable Delivery of Sertraline: Enhancing Efficacy and Patient Compliance in Depression Treatment

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ABSTRACT
Injectable long-acting dosage forms are a highly preferred option in numerous treatment modalities, such as cancer, diabetes, and bacterial infections. This approach can produce better patient compliance and minimize the problems related to improved therapeutic efficacy, toxicity, affordability, and bioavailability. Depression is the most prevalent psychological disorder, and it is considered to be the second leading cause of disabilities. However, breakthrough innovations are desperately needed in contemporary medication due to increasingly painful and embarrassing dosing regimens. When patients adhere to their drug dosage, health benefits are enhanced. Nonetheless, depressive patients are more likely to experience treatment failure. If the rate of compliance could be increased, the benefits of depression treatment could also be improved. Conventional pharmacological dosage forms of sertraline face challenges such as poor solubility, limited ability in target localization, and dose-dependent adverse reactions. Researchers are currently fascinated by the prospective applications of nanotechnology in this field. Nanotechnology, particularly for drug delivery applications, could resolve many obstacles. Nanoparticles are particularly attractive carriers for use with injectable antidepressants to effectively deliver them to the brain. This manuscript illustrates that a suitable nanoformulation strategy for the injectable distribution of sertraline, one of the leading antidepressants, can significantly increase effective use and subsequently patient compliance.

Keywords: Nanoparticles, injectable, nanoformulation, sertraline.

Background And Rationale
Depression doubles the likelihood of the development of heart diseases. It is projected to become the leading cause of disability worldwide by 2030, surpassing infectious, nutritional, and maternal diseases(1). Although several treatment modalities are recommended for the management of depressive disorders, individuals overcoming such health problems often encounter challenges associated with existing approaches. Given these facts, the need for a more effective, patient-friendly formulation is therefore warranted. Nanoformulation for a wide variety of drug molecules facilitates their conversion into a suitable injectable form to enhance a quicker onset of action and minimize the frequency of drug administration(2). Sertraline is widely used in the treatment of depressive disorder and its long-term management. Patients are generally non-compliant with conventional oral therapy (3). The long-term use of immediate-release sertraline is associated with differential fluctuations in the blood level of the drug that may lead to the development of tolerance by the patient. The weekly sertraline therapy requires an initial titration period of 4 to 9 weeks to have the desired clinical effect (4). Therefore, a single injectable dose is preferred for ease of patient compliance.Injectable drug delivery systems impart rapid onset or management of any drug action due to better drug solubility and bioavailability,Nanotechnology is proposed to enhance the solubility of poorly water-soluble drug molecules to provide bioavailability(5). Nanotechnology is the science, engineering, and technology related to materials, structures, and systems on the nanoscale. Manipulation of materials at the nanoscale leads to unique properties and promising results at the therapeutic level in terms of biodegradability and toxicity of the drug moiety(6). Ultra-filtration and homogenization methods form nanosuspension. The conversion of nanosuspension into solid nanosized material provides nanocrystals. Lipid nanoformulation mainly includes nanoemulsion and liposome. Among lipid

carriers, solid lipid nanoparticles provide an advantage of better drug loading, modulation of release profile, and improved physical stability [7].

Mechanism of Action and Clinical Significance of Sertraline

Sertraline is a selective inhibitor of serotonin reuptake, and it is commonly prescribed for its once-daily oral dose and low potential for drug interaction. Serotonin is a neurotransmitter known for its role in mood regulation[8]. This molecule is released into the synaptic cleft to elicit neurotransmission, but it is taken back into the presynaptic neuron once the signal is completed to regulate available serotonin levels[9]. Sertraline, an SSRI, selectively inhibits this reuptake, thereby increasing serotonin levels in the synaptic cleft and elevating mood. For these reasons, serotonin reuptake inhibition accounts for the initial uplift effect of an SSRI in depression. The effectiveness of this type of drug in the treatment of major depressive disorder or depression is related to these pharmacokinetic and pharmacodynamic properties, which include a half-life that ranges from 18 to 24 hours as well as a time to response and time to remission [10].

Challenges in Current Sertraline Delivery Methods

Despite sertraline recovering more than US$ 1.5 billion in the market, limitations such as slow onset of action and frequent dose titrations are major patient compliance-related issues [11]. Additionally, this drug has a poor oral bioavailability of approximately 44% in the gastrointestinal system, with variable blood concentration levels leading to inadequate efficacy due to significant inter-individual pharmacokinetic variations [12]. The volume distribution varies by weight, genetic polymorphisms, concomitant drugs, liver capacity, disease, and other physiologic and metabolic mechanisms, including gender differences [13]. Moreover, gastrointestinal absorption varies depending on whether it is administered with food, and the first-pass effect is responsible for the blood eliminations, leading to a high oral first-pass metabolism. This necessitates higher amounts of the drug to maintain efficacy, which increases drug exposure and drug delivery-related potential adverse effects monitored throughout chronic use. Dosage titration-related side effects, such as insomnia, palpitations, and indigestion, may also lead to discontinuation[14].Improving the bioavailability of sertraline is expected to enhance the drug delivery system for potential payment. Alternative routes, such as transdermal, mouth-dissolving, and injectable formulations, have been explored as cost-effective therapies to improve drug efficacy by increasing the optimal concentration of the drug in the brain and subsequently the whole body[15].

Nanotechnology In Drug Delivery

In the last few years, nanotechnology has contributed innovative changes in developing drug delivery systems. The current advances in nanotechnology-based drug delivery systems have brought new tools in various therapeutics ranging from cancer to immunotherapy [16]. Nanoparticles offer various advantages in comparison to classical drug carriers; due to their small size, they offer high surface area, easy permeation through membranes, additional functionality, and limitless areas to customize[17]. Nanoparticles can enhance the solubility, stability, target tissue distribution, and bioavailability of the encapsulated drug and, therefore, reduce the elimination and reduce dosing intervals. The nanoparticles are known as hard-grade carriers because of their good stability and rapid bioavailability of the drugs[18]. Currently, various types of nanoparticles are being used as alternative carriers, including liposomes, niosomes, solid lipid nanoparticles, nanoemulsions, transferosomes, ethosomes, polymeric nanoparticles, and many more [19].

Nanoformulation Strategies for Injectable Delivery of Sertraline

Nanoformulation strategies for injectable delivery of sertraline are of significant importance to improve the therapeutic efficacy of sertraline with enhanced patient compliancedifferent strategies were implemented to develop and optimize a suitable nanoformulation of sertraline with favorable properties such as solubility enhancement, improved release profile, extended half-life, and minimal side effects [20]. The approaches were considered from a practical perspective, focusing on the patient's convenience and the positive interplay between the nanoformulation's properties, increased therapeutic efficacy, and sertraline release profile and safety. The injectable nanoformulation characteristic has attracted a great deal of interest for a relatively quick therapeutic effect without first-pass metabolism and has several advantages in terms of improved patient compliance due to the reduced frequency of sertraline administration,For the injectable formulation development, its stability, solubility, compatibility, and ease of administration have been thoroughly researched [21].

Characterization Techniques for Nanoformulations

- **Size, Shape, and Morphology Evaluation of Nanoparticles and Nanoformulation:** Differential interference contrast and phase contrast microscopy: Shape and dendricity. Dynamic light scattering and laser diffraction analysis: Hydrodynamic size in solution. Nanoparticle tracking analysis: Particle concentration in solution/elucidation of agglomeration. Flow cytometry: Detection of particles in cell systems. Multiple angle and single angle light scattering: Molecular mass and size. Scanning electron

microscopy and field emission scanning electron microscopy: Size, shape, surface pores. Transmission electron microscopy: Size, shape, and morphology. Atomic force microscopy: Surface analysis. Confocal light scanning microscopy: Spatial arrangement and three-dimensional analysis of surface. Size, Surface Charge, and Polydispersity Index (PDI): An essential physicochemical characteristic that gives information about the respective drug delivery systems. They can be elucidated from the hydrodynamic size [(22)].

- **Physicochemical Properties:** Zeta potential or electrokinetic potential: It provides information about the surface charge of nanoparticles, and thus, it also provides a good indication of the free energy of settled nanoparticles. These values often affect the uptake of nanoparticles and the interactions between particles to be taken up. Porosity or BET analysis: It evaluates the average pore size, specific surface area, adsorption potential, and total internal pore volume. Moreover, it also provides information regarding the size of the cross-section of the channels [(23)].
- **Stability Parameters:** Centrifugation: Centrifuge methodology has been widely used for determining the centrifugal parameters to observe the effect of modifications of the formulation and surface on the aggregation or flocculation of nanoparticles after different time intervals. The stability of nanoformulations with respect to the changes in pH, temperature, and time could also be determined to assay the compatibility of the developed system. Preferential aggregation and sedimentation phenomena should be studied to understand the formulation fibered. The stability of nanoformulations under physiological environment and toxicological studies should be performed to facilitate human translation [(24)].
- **Drug Loading Efficiency and EE%:** Drug loading efficiency (LE%) and encapsulation efficiency (EE%) are vital parameters that indicate drug loading and are highly relevant to nanoformulation design. Salting-out induced precipitation may also play a role in such a loading process. At this step, assaying of drug by validated analytical methods is relevant[(25)].
- **In Vitro Drug Release:** Drug release methodology is equally important to identify the drug released from nanoformulation that is adsorbed or entrapped at the surface. Many efflux mechanisms and pathways opt for nanoformulated drug in comparison to conventional drug formulations. Therefore, the release kinetics play an important role in identifying such phenomena. There are other conventional methods available for daily dose determination. Therefore, drug release in non-physiological (release at fixed time) and physiological conditions (sink condition) could be measured in a more reasonable way. All these procedures can, therefore, be used to gather information about the most suitable release lots to be used for the in vivo experiments[(26)].
- **Compliance with Regulatory Guidelines:** Intravenous administration of nano-carriers, depending on the country, is still considered a pharmaceutical product, and hence different regulatory guidelines and documentation apply to these formulations. Ideal test strategies in the development of nanoformulations focus on the use of suitable in vitro, in vivo, and ex vivo methods to predict in vivo behavior. These techniques can also be used to support and justify the pharmaceutical imprints implemented in the concentration of active liposomes or similar colloidal dosage forms[(27)].

Enhanced Efficacy OfNanoformulated Sertraline

The enhanced efficacy observed upon nanoforming sertraline is believed to stem from at least three principal mechanisms. Firstly, nanoformulation can optimize the release kinetics of the drug, resulting in more consistent and prolonged plasma levels, less subsensitivity of the receptors responsible for the therapeutic effect, and fewer fluctuations around the effective plasma levels. A sustained release of sertraline from nanoparticles could lead to a weekly dosing regimen providing similar therapeutic effects to those achieved with the oral daily standard dosing [(28)]. Secondly, drug uptake into cells can be facilitated by targeted delivery mechanisms taking advantage of organic anion transporting polypeptides or other absorption-enhancing transporters[(29)]. For sertraline, the localized attachment of the tropane unit to the polymer requires detaching it and restoring the free amine functions prior to its transformation into the active drug at the gastrointestinal stage. The enhanced uptake and utilization of sertraline in biological systems may provide the therapeutic effect at lower dosages. Thirdly, modifications to the formulation could potentially reduce adverse effects of sertraline. By increasing the overall permeability and absorption of the nanoparticles, sertraline will be degraded and metabolized at a lower rate, thus reducing the first pass and enhancing the absorption of the drug [(30)].The mechanisms of action guiding the enhanced efficacy of nanoformulated sertraline require further investigation at the molecular level, including an evaluation of the ability of the nanoparticles to enhance the binding properties of serotonin receptors. Reasons for specific formulations resulting in enhanced efficacy include investigations on cellular uptake of the formulations, a comparison of the bioavailability and plasma levels of sertraline over several days upon dosing of traditional and optimized formulations in healthy subjects, and are further detailed herein[(31)].

Improving Patient Compliance Through Nanoformulation

Sertraline is used in the treatment of depression, and the currently available formulations are meant for oral administration. As injectable dosage formulations can be administered using alternate routes, the new formulations were expected to improve patient compliance, especially for those having difficulty swallowing the

tablet[32]. Many depressed patients take drugs intermittently because of their unwillingness to take the medication orally, and such patients can particularly benefit from the new formulations. In addition, since the required frequency of administration of injectable dosage forms is reduced, the likelihood of patient compliance increases, even for those willing to take the medication orally [33].Some patients are not willing to take the medication into their own hands and prefer the medication to be given entirely by the healthcare provider[34]. Despite the above limitations, anecdotal evidence suggests that patients find it "easier" to take the medication weekly by the healthcare provider (mentally and emotionally, even though their potential place and time were restricted) as compared to their being given the responsibility to take it daily on their own. This will hopefully offset some of the non-compliance of patients taking sertraline in their regular range. Understanding that patients' responses and adherence to nanoformulations will be variable is also important[35]. The healthcare businesses have detailed resources for this purpose. When deciding which patients might not benefit from this technology, the healthcare provider should take into consideration that patients fall on a spectrum of care. However, these concepts may need to be generally integrated into patient and provider training when this technology becomes more widely available[36].

Regulatory Considerations ForNanoformulated Sertraline

The development of nanoformulated sertraline has several unique regulatory challenges. Different regulatory agencies have outlined guidelines for the development of nanomedicines. In both cases, it is shown that nanoparticles that are in the approved ranges are mostly considered as a reformulation. The state of the art, the potential advantages, and patient risk are the basis of the approval pathway[37]. In most of these cases, the pharmacokinetics and toxicity profile evaluated on the nanoformulation is to be discussed. In addition to considerations concerning the pharmacokinetics, toxicity, and possible off-target effects, as well as a lack of parallelism between drug and nanoformulation, the development and manufacturing of nanomedicines can face specific problems related to the properties unique to nanoparticles. Stability of colloidal systems in long-term storage conditions and scalability can be challenging due to fabricated particle size[38]. Manufacturing and scalability of nanoparticle fabrication, handling, and packaging, along with a comprehensive study on industrial hygiene, cytotoxicity, and environmental risk, must be adequately addressed during the production, industrial, and transport activities. During the past decade, the requests of industries, authorities, and stakeholders for new products and technologies based on nanoscale science and technology have markedly increased. In addition, it is now recognized that nanotechnologies have an important impact on pharmaceutical processes[39]. The present regulatory framework was not intended to address such unique properties. It is reported that pharmaceutical regulation has a mandate to ensure the quality, safety, and efficacy of medicinal products. A more rigorous preclinical and regulatory evaluation, in combination with post-marketing surveillance, is required to ensure the safe and efficient use of these novel formulations[40].

Future Directions and Emerging Trends in Nanoformulation Research

This review article highlights the impact of nanoformulation research on the capability of therapeutic deliveries of sertraline. The substantial discussion shows the untapped potential of innovative nanomaterials and strategies in nanoformulation to improve pharmaceuticals . Substantial efforts have been made to explore next-generation nanocarriers in nanoformulation research, such as carbon dots, dendrimers, and polymer-drug conjugates[41]. Engineering drug delivery systems for increasing drug stability and/or improving patient compliance in the treatment of depression is a growing area of interest in nanoformulation[42]. Personalized nanomedicines that contain patient-specific concentrations, dosage, and dosage schedule favor the development areas of personalized medicine. Nanoformulation research is in line with the trending practice of personalized/precision medicine[43]. Technology may also play an important role in the development of nanocarriers, assisting researchers in developing smart nanocarriers. Smart nanoformulations are other kinds of nanoformulation that the scientific community has recently started exploring.The future theragnostic perspective of sertraline in nanoformulation could lead to novel formulations. The environment surrounding nanoparticles is also an area where significant research is being conducted[44].The ethical aspects of nanoformulation research are also elaborated in the field of artificial intelligence. Artificial intelligence, with its sprawling connections, could ease multidisciplinary collaborations and pave the way for nanoformulation designs compatible with research objectives[45]. To explore novel strategies and nanoformulations, the future should hold exploratory activities including the development of newer fields of research, computational modeling in the engineering of nanoformulations, process development and quality assessment, the availability of in-silico studies, and more. It is hoped that ethics will continue to function as a guide when developing advanced technology and possible concerns with nanoformulation. It is crucial to remember that the development of novel approaches, particularly for psychiatry treatment, will never end[46].

CONCLUSION

Nanoformulation that would facilitate sertraline drug delivery upon injection, bypassing many of the hurdles associated with PEGylation and other conventional drug delivery methods like oral tablets. The challenges associated with the aforementioned methods, including low bioavailability, delayed onset of action, low compliance and adherence, low efficacy, and lack of remission, are key drivers for the development of this new formulation. It is known that by incorporating nanotechnology, nanosized delivery systems may offer many therapeutic advantages that include(high distribution rates in brain tissues upon systemic intravenous administration, ,amelioration of compliance by simplification of drug administration, reduced ethanol consumption due to a faster onset of action,higher bioavailability, increased release of bioactive drug when dissolved drug is limited or ineffective,increased neuronal survival and neuroprotective effect, and improved remission rates in patients and effectiveness of treatment with the potential onset of action similar to that observed in ECT treatment.

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