Comparing and Contrasting the Use of Nanoparticle-assisted Drug-delivery of Antidepressants to that of the Gold Standard

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ABSTRACT

Nanoparticles (NP) are small-scale particles of elements at a scale that ranges between 1 to 100 nanometers. NP can be used to benefit drug delivery to the brain due to its ability to efficiently cross the blood-brain barrier (BBB). Depression is a widespread neuropsychiatric disorder with treatments that embody numerous flaws and shortcomings. A potential solution to this lack of treatment was pondered. NPs' ability to be implemented within antidepressants through encapsulation methods was investigated and the effects of NPs on the efficacy of the antidepressants were analyzed. Connections between the formulations of multiple NPs were made. Previous experiments and research regarding numerous NPs and how they were used to aid numerous types of antidepressants to treat various mental ailments were selected and analyzed thoroughly. From these findings, it was shown that various NP encapsulation and assistance methods can increase the efficacy of antidepressants.

Introduction

The current worldwide mental health crisis is causing detriment to the majority of the population. Globally, suicide acts as the second most cause of death among people from ages 15-29 (who). Approximately 20% of the youth worldwide suffer from a mental illness (who), and over 50% of those are left untreated (NAMI, 2019). One of the most prevalent mental illnesses is depression, which saw an increase of over 25% from years 2019 to 2022. The total number of adults experiencing depressive states increased to 20.2% - 31.1% (APA, 2021). Depression, schizophrenia, bipolar disorder, anxiety disorder, and other mental illnesses rose and rates of suicide followed (Lake, 2017). Despite being the most preventable cause of death, suicide rates increased and continue to increase as 10 to 20 million people attempt suicide each year. Contributing to this upcoming global issue, psychiatrists exemplified a new and urgent demand for modified and more efficient treatments. A large number of psychiatrists were overwhelmed by the amount of referrals received (APA, 2021). 72% of psychologists treating depression reported an increase in depression referrals, and as a result of this, 41% of psychologists disclosed their inability to keep up with the increasing demand. Responsible for over ⅓ of the adult disability globally, mental health treatment was left in a state of dire need (Lake, 2017). This new demand has become a necessity. The pandemic of mental illness has become a global emergency, and research of both biomedical therapy and psychotherapy with increased efficacy is of utmost importance. Depression consists of serotonin imbalances inducing severe negative feelings. Depression alters the way one views their surroundings and their own personal worth, often contributing to a change in behavior and thought process. For the last fifty years, research of neurobiology and processes regarding depression within the brain have been heavily based on what is known as the "monoamine deficiency theory" (Yale Med). The "monoamine deficiency theory" otherwise known as the monoamine deficiency hypothesis, is the conjecture that depression is caused by a significant imbalance or deficit of monoamine neurotransmitters (MB, 3). Monoamine neurotransmitters remove monoamines such as serotonin, dopamine, and norepinephrine from the brain, resulting in the influx of varying emotions (Mayo, 2019). Dopamine, serotonin, and nore-

pinephrine are neurotransmitters utilized within the central nervous system and result in the modulation of neurological processes including emotions, impulses, and desires (Pitt). Within depression research, serotonin and norepinephrine have been a primary scapegoat within the causes for depression. Abnormalities within these two neurotransmitters have been recognized as the most likely conviction for depression due to their ability to alter mood and motivation when imbalanced. (Yale Med). This discovery fifty years ago led to the modernization of biomedical treatment for depression and other mental illnesses. Using the foundation of knowledge presented by the monoamine deficiency theory, antidepressants were cultivated and quickly produced for clinical prescription. Antidepressants were constructed to balance the abnormalities in serotonin and norepinephrine neurotransmitters and limit the dispirited feelings accompanying the lower levels of the chemicals. These antidepressants rely on monoaminergic systems and induced serotonin and norepinephrine to combat depressive emotions and normalize levels of neurotransmitters within the brain. This process, entirely based on the monoamine deficiency theory, has become a crucial aspect of antidepressants and the advancement of treatment for mental illness.

Current Medication Flaws

From recent concerns regarding the efficacy of biomedical therapeutics and pharmaceuticals, numerous studies have been conducted and reviewed to work towards re-revolutionizing the treatments for mental illness. Studies and trials used to determine the effectiveness of antidepressants are commonly based on randomized trials and recordings of group data. Due to their inconsistency, these studies become “susceptible to biases” (Saha 2021). The studies themselves vary due to a variety of factors regarding the patients themselves. Genetic indifferences as well as situational experiences and other subjectivities limit the research’s accuracy. Significant flaws and inconsistencies have been discovered in these studies, furthering the contemplation of the validity and efficiency of present-day antidepressants. These inconsistencies reveal the gap within biomedical treatment for mental illness, portraying the need for improved methods of treatment. In addition to the lack of function outside of placebo, antidepressants also cause unfavorable side effects in patients. Numerous antidepressants cause damage to patients' health after extensive use. Selective Serotonin Reuptake inhibitors (SSRIs) are antidepressants commonly prescribed due to their ability to reduce symptoms of depression. SSRIs affect behavioral patterns by obstructing the reuptake of serotonin into neurons, enhancing neurotransmission by making more serotonin available (Mayo). Because of this regulation of serotonin, many other bodily functions and habits are altered such as sleep, sexual functionality, appetite, and pains (Saha, 2021). The FDA-approved SSRIs, Citalopram, Escitalopram, Fluoxetine, Paroxetine, and Sertraline, accompany versatile side effects that vary from person to person. Sertraline, for example, has proven to have the biggest detriment on the body's ability to be able to determine the right times to sleep or wake (Sasha, 2021). This differs from Fluoxetine commonly caused issues with eating and anxiety, or Duloxetine issuance of pain (Sasha, 2021). In summation, antidepressant effectiveness and side effects vary depending on specific factors of the person prescribed, contributing to the need for a more generalized and efficient treatment.

Solution

NP can be used in brain drug delivery to aid a wide variety of medicines pass the BBB and enhance their proficiency within the brain. Specifically, NP can be used in the drug delivery of antidepressants and other psychiatric medications to better the balance of neurotransmitters involved with mood. NP-assisted delivery of antidepressants can be used to heighten the effects and efficacy of the drugs, eliminate side effects, and regulate the number of doses needed through prolonged release. This discovery will help to decrease the widespread stigma around mental illness and antidepressants, as many people have developed new disorders or seen their symptoms worsen from clinical use. The de-stigmatization of antidepressants will indefinitely fruit a valuable provocation to receive medical treatments for those affected.

Expanding further, the implementation of this method into clinical use will lead to further advancement in the medical field. NPs and nanotechnology have concurrently inspired numerous studies and research-based on their implementation in a multitude of fields. Its use in clinical and medical studies will naturally be an incentive to further adaptation.

Blood-brain barrier

A crucial factor contributing to the abilities of this discovery is the blood-brain barrier (BBB). The BBB is a system of capillaries (blood vessels) and tissue forming a deterrent between the brain's blood vessels and neurological biopsy. The BBB is the depiction of the functions carried out by the microvasculature network for the central nervous system (CNS) (Richard & Prat, 2015). It protects the brain from toxins and invading pathogens by only allowing small molecules and some gaseous substances to pass through. This function is caused by the endothelial cells that line the walls in the blood vessels forming tight junctions due to them being closely compacted. The BBB is highly restrictive, aiding the safety of neurological processes and homeostasis (Daneman & Prat, 2015). Because of this restrictive nature, the BBB has acted as a major hindrance in the medical field due to its obstruction of direct drug delivery to the brain. The BBB prevents a majority of drugs from entering the brain through the blood, as only 98% of small molecules lack the chemical structure to pass the barrier, the BBB has halted advancements in eliminating the treatment of neurological diseases and disorders (Pardridge, 2012). Consequently, numerous studies have been enacted to establish modifications to current medicines to manipulate them to be able to pass the BBB and to procure entirely new medications and derivatives. Many trials and methods have been tested and studied to bypass the BBB. Many studies surround the manipulation of drugs to intercept the BBB and the manipulation of the BBB itself through external methods such as ultrasound. These methods aim to disrupt the BBB and exploit its functions to allow specific molecules to pass. Additionally, many studies have tried and tested the implementation of antibodies to target specific receptors in the BBB that control and regulate movement across the barrier (Khawli and Prabhu 2013). NP carriers have shown to be prevalent in successful methods of drug transport across the BBB. This is due to the minuscule size of the drugs and their ability to cross the molecular size threshold of the BBB (Padridge, 2012). Neutrally charged surfaces of NPs or altered surfaces of the NPs through the use of polysorbates, allows them to safely pass through the BBB. In their success, these NPs have been able to not only deliver the medicine but also increase the concentration of the drug. Many NPs have also shown increased efficiency and enhancement of current neurological and psychiatric medications.

Review of past studies

Study 1:

Shadabul Haque et al. investigated the possible outcomes of the integration of Venlafaxine (VLF) into alginate NPs (AG-NP) through intranasal transport to treat depression (Haque, 2010). VLF is a dual-action reuptake SNRI commonly used to treat MDD (Major Depressive Disorder), anxiety disorders, and other panic disorders. As an SNRI, VLF acts as an agent to rebalance levels of serotonin and norepinephrine within the brain. VLF is heavily reliant on its ability to maintain occupancy in the site of action, meaning it is extremely important that VLF can be safely transported and conserved (Sarei, 2013). AG-NP are hydrophilic mucoadhesive polymers used to exploit their favorable adjuvant properties (Sarei, 2013). In this study, AG-NP was used to cultivate a transnasal passage to the brain to better exhibit VLF's properties and reduce the necessary dosage requirements.

Methods

The alginate NPs were cultivated inside of a sodium alginate solution with the implementation of calcium chloride (CaCl2) and poly-L-lysine (Rajaonarivony, 2016). This method, based on the ionotropic pre-gelification, and the cross-linking process allowed for the preparation of the AG-NPs (to make them small?). Mucoadhesive systems were then cultivated between the AG-NPs and the VLF through a strenuous procedure. The process resulted in a VLF ratio of 0.75:1 in the loaded AG-NPs. The VLF-loaded NPs were finalized and induced within a nasal saline solution for further use. Wistar rats were selected for this experiment to be ethically used as test subjects. The dosages of the nasal medication were calculated through a conversion factor of 0.018 and the bioavailability of VLF (45%) to scale the human dosage of 75mg/day to the rat dosage of 0.6075mg/day. The drug was administered to five groups of three separate Wistar rats at different rates. Group 1 consisted of untreated and non-depressed rats, Group 2 was used as the control group and stayed both untreated and depressed in the experiment and was administered 50 µL of saline solution in each nostril for 15 days, Group 3 was given standard VLF tablets in a regular dosage each day, Group 4 was treated with concentrated VLF solution at the calculated dose for 15 days, and Group 5 was administered the calculated dose of VLF AG-NPS at 0.6075mg/day transnasally through 100 µL of saline solution for 15 days. It is important to note the use of multiple placebo rat groups to ensure accurate and explainable results. Groups 1 and 2 were compared individually, while the other groups were each compared to the control Group 2. At the end of the 15 days, all of the rats were humanely sacrificed and dissected. The brains were individually harvested and the blood was extracted from the rats to analyze the results of the experiment.

Results

As a result of this experiment, many factors contributing to the increased efficacy of the VLF AG NPs were recorded. Firstly, the AG NPs were able to control the release of VLF beyond 24 hours, differentiating significantly from the basis of the antidepressant. The Cumulative amount of drug permeated (CADP)was also significantly amplified by the VLF AG NPs. The pure VLF CADP was recorded at 142.67 mg/cm2 while the altered VLF AG NPs were recorded at 397.58 mg/cm2. This increased absorption of the drug plays a significant role in the efficacy of the drug. This increased efficacy can be seen in the Forced Swimming Test results of the experiment. The Forced Swimming Test (FST) is a method to test the proficiency of antidepressants by testing them in rats and making comparisons to the efficacy of human dosages. The process involves the placement of rats inside of water to necessitate behavioral responses. From the results of the FST, VLF AG NPs resulted in large increases in efficacy not only in the depressed control group (Group 2) but in the pure VLF oral and VLF solution groups as well (Groups 3 and 4). VLF AG-NPs in group 5 showed an immobility time of 6.1 seconds compared to the control result of 2.28. This decreased immobility time was a result of the increased swimming and climbing time of Group 5. The results of Group 5 also surpassed those of Groups 3 and 4, the pure VLF solution and tablet-treated rats. Group 5 results were recorded at 1.99 while Group 4 and 3 Swimming: 2.08 and 1.59 respectively. The VLF AG NPs proved a tremendous increase in efficacy than their pure VLF counterparts. The VLF AG NPs had the greatest effect on the normalization of values in naive, undepressed, and untreated rats. The results of this experiment prove the increased efficacy of NP-assisted antidepressants. The alginate NPs not only increased the efficiency of drug delivery to the brain but also increased the capabilities of the antidepressants themselves. Lastly, an analysis of the brains and blood of the rats was conducted to determine levels of plasma and concentration of drugs. The results showed significantly lower amounts of plasma and drug concentration in the rats treated with pure VLF concentration than with the VLF AG NPs. The brain/blood ratio was also calculated indicating an impactful ascendancy of the VLF AG NPs' ability to cross the BBB. The brain concentration of each drug was also significantly higher in VLF AG Nps at specific time points. From this analysis, VLF AG NPs were proven to have a higher percentage of drugs directly transported to the brain.

Significance

This study proved the increased efficiency of NP-assisted drugs for the increased effectiveness of antidepressants' ability to normalize neurotransmission levels, as well as prove the heightened ability to cross the BBB and transport drugs directly to the brain using NPs. The results of this experiment prove NPs to be an efficient method of neural drug delivery, and enhancement of effectiveness through increased concentration and drug permeations. This study influences and questions the concurrent treatments for mental illness. The increased efficacy further contributes to the solution for VLF's issue of inconsistency and demand for extreme amounts of dosages. The NP-assisted antidepressants contained prolonged drug release, eliminating the need for excessive dosage.

Study 2:

Another experiment was conducted by Parva Jani et al. testing the use of polymeric NPs loaded with agomelatine for the increased efficacy of the antidepressant and its delivery to the brain (Jani, 2019). Agomelatine is an antidepressant commonly used to treat major depressive disorder (MDD) and other mental illnesses. Agomelatine is unique from other antidepressants as it is not an SSRI or an SNRI. It is an agonist to the melatonin receptors MT1 and MT2 and acts as an antagonist to the serotonin receptors 5HT2B and 5HT2C. Agomelatine is particularly effective in its resistance to unfavorable side effects of more common SSRIs and SNRI antidepressants. With the positive effects of agomelatine on the circadian rhythm, common side effects are significantly reduced. This is due to the lack of increase in the amino levels in plasma that cause adverse effects in other antidepressants leading to unfavorable side effects (Kasper 1). The polymeric NP used in this experiment was poly-lactic-co-glycolic acid (PLGA). PLGAs are biodegradable polymers commonly used in drug delivery. Its effectiveness derives from its biocompatibility and favorable kinetic attributes (Daniel 1).

Methods

Using nanoprecipitation, the Agomelatine-loaded PLGA particles were formulated at a 50:50 ratio. The particles were then added to a solution with an addition of acetone, where they were dissolved and then rapidly redeveloped through the addition of the NPs in their organic phase, to the solution. This led to the formation of NPs that could be identified within the solution. Adult rats and mice were used ethically in three groups. Group 1 was the control group receiving no treatment. Group 2 was the intranasally tested group using the solution of Agomelatine-loaded PLGA NPs. Group 3 was treated using pure agomelatine tablets orally. The rats were then placed in a swimming tank approximately one hour after the administration for 5 minutes. The rats were forced to swim each day for a week. (need help with this)

Results

Group 2 resulted in significant decreases in immobility times compared to Group 3. The PLGA Agomelatine formulation proved to be efficient in transport to the brain and antidepressant activity. The results were significantly higher than Group 3 which was treated with agomelatine alone, meaning NP-assisted drug delivery showed higher utility in treatments. The sizes of NPs used were also analyzed and concluded that smaller NPs are more likely to reach the target site. PLGA NPs also showed a controlled drug release for a total of 96 hours, proving to be significantly more efficient than unassisted agomelatine.

Significance

This study proved the increased efficiency of NP-assisted drug delivery to the brain through the use of Agomelatine-loaded polymeric NPs. This study furthered the discovery of the uses of polymeric NPs to treat diseases involving neurotransmission imbalances in the brain. This study proves the increased efficacy of antidepressants when assisted by NPs, and provides examples of how this type of advancement could be cultivated and used clinically.

Study 3:

Another study was conducted by Xiaoli He et al. to assess the benefactors of using curcumin and HU-211 encapsulated lipid NPs for drug delivery to treat major depression (He, 2016). Curcumin is a hydrophobic postulate of turmeric with significant pharmaceutical advantages and antidepressant effects. This effect has been traced to Cur's ability to control the release of dopamine, noradrenaline, and 5-hydroxyindoleacetic acid. Curcumin can rebalance these neurotransmitters, acting as a treatment for depressive disorders and other causes of neurotransmitter imbalances. In this study, Cur was paired with dexanabinol (HU-211), an artificially synthesized derivative cannabinoid with a lack of cannabimimetic effects. HU-211 was implemented for antioxidant properties as well as its ability to maintain the integrity of the BBB within its delivery through its anti-inflammatory attributes. This tested antidepressant combination could not efficiently be delivered to the brain across the BB, so solid lipid NPs (SLNs) were used to encapsulate the mixture. SLNs have a major ability to deliver drugs across the BBB and to the brain. They were specifically chosen over other NPs due to their heightened effects of controlled drug release and bioavailability.

Methods

The Cur/SLNs-HU-211 were procured using emulsification and low-temperature solidification methods as shown in Figure 1. The lipids were dissolved in an organic solvent, and an NP dispersion was formed after the evaporation of the solvent. The dispersion was formed as the result of lipid precipitation in the solution. The NPs were then added into a solution of Cur, stearic acid, lecithin, and HU-211 through a vigorous stirring and adding process. The Cur/SLNs-HU-211 were then dried for 24 hours. Control SLNs were also procured using the same method subtracting the use of Cur and HU-211 from the equation. Lastly, a mixture of Cur and SLN was also created with the same procedure. Corticosterone (CORT) was used to establish major depression in animal models. PC12 cells are catecholamine cells that store and release norepinephrine and dopamine, neurotransmitters affected by depression. These cells were induced with CORT to activate major depression within the animal models (in this case mice). CORT was incubated with PC12 cells at different concentrations for 24 hours. The mice were injected with CORT repeatedly for 21 days. The mice were divided into seven groups: Cort plus PBS, nontreated control, CORT plus Fluoxetine, HU-211, Cur, Cur/SLNs, and Cur/SLNs-HU-211. Treatments were performed 24 hours after the PC12 cells were seeded, and all groups were treated preemptively before the addition of CORT. The absorbance of the drug was analyzed through the use of a microplate reader. Additionally, Dopamine (DA) release from PC12 cells was measured. The DA releases were determined from the concentration levels for each treatment using the HPLC method to separate each compound and identify the amounts of specific components of the cells.

Results

It was found that Cur/SLNs-HU-211 proved to be efficient in its ability to cross the BBB. Cur/SLNs-HU-211 and Cur/SLNs caused significant increases in DA release within the depression models, meaning they were more efficient in treating the depression established in the PC12 cells of the mice. Compared to the other groups and antidepressant formulations, Cur/SLNs-HU-211 had the largest antidepressant effect. Additionally, an FST was enacted showing the

most significantly increased mobility rates from the Cur/SLNs-HU-211. Cur/SLNs-HU-211 also had the greatest sustained release out of all the tested groups, further proving it to be the most efficient.

Significance

From this study, it was concluded that SLNs can assist in drug delivery to efficiently pass the BBB and sustain the controlled release of the drug for prolonged periods. This study proved the betterment of antidepressants through NPs. Additionally, Curcumin was proven efficient as an antidepressant.

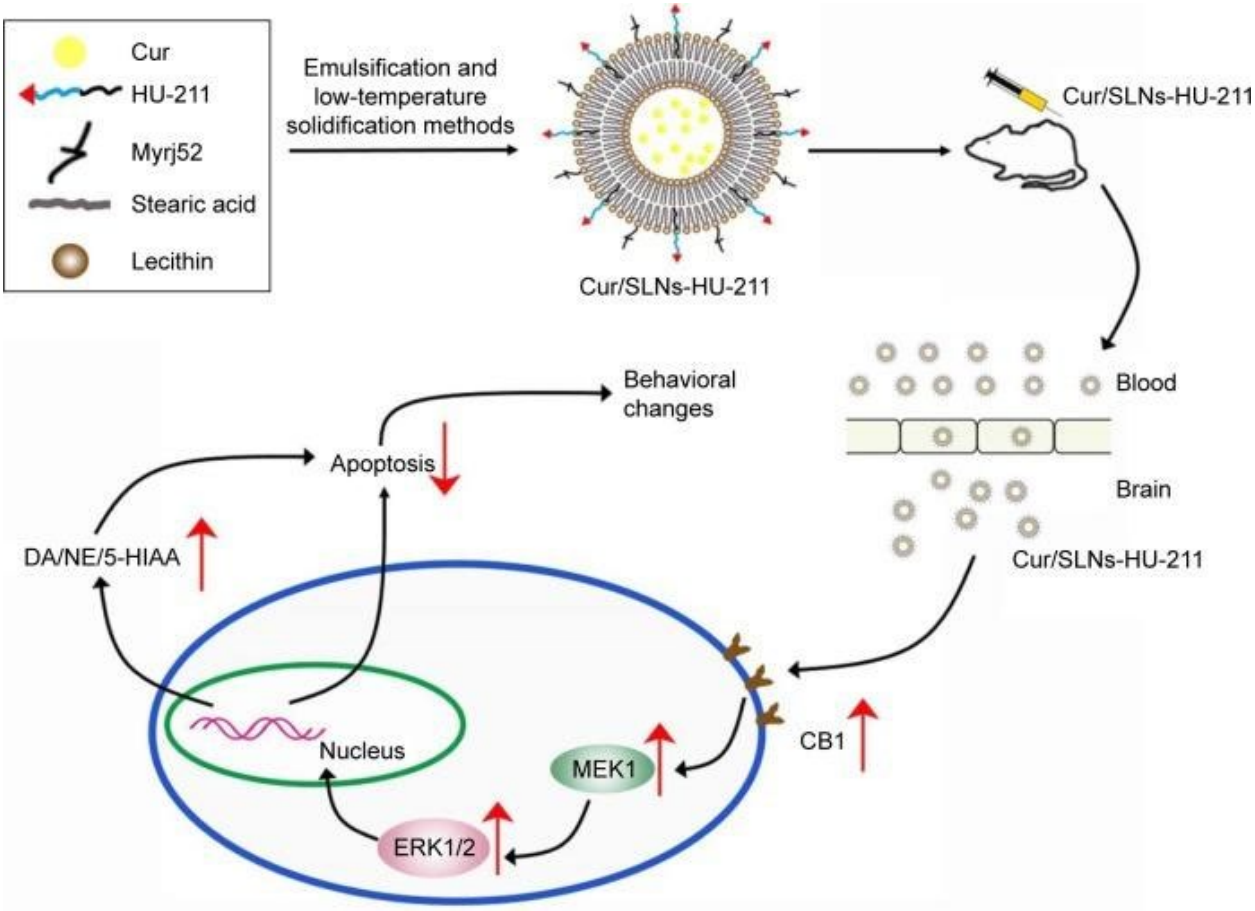

Figure 1. Schematic showing lipid nanoparticle formation from He et. al. 2020

Discussion

From the provided analyses, numerous comparisons can be deduced based on the unique attributes and enhancements of each NP. The formulations of each NP and their implementations into the antidepressant solutions conclude with varying results and conclusions. From each of these studies, clear comparisons and significant differences can be extrapolated to establish valuable conclusions. The purpose of the analysis of the capabilities of NP in the mental health field is to further previously conducted research, better the reputation of NP, and invoke new hypotheses in the field. Each of the formulations of medicine showed drastic benefits in dosages based on their ability to sustain intensive prolonged release within the brain as opposed to the gold-standard antidepressants. The method formulations of each encapsulated antidepressant contribute to their efficacy in vivo experiments. The AG-NPs from Study 1 were

formulated through the encapsulation of venlafaxine within alginate nanoparticles. The AG-NPs were formed through ionic interactions by crosslinking negatively charged alginate and positively charged calcium and spinning CaCl2 at 800 rpm with droplets collected in AG solution. The procedure used different concentrations of Alginate, calcium, and glutamate (CS), implemented these mixtures into the drug, and then tested it. Alginate nanoparticles are hydrophilic, leading to the modified drug sustaining bulk release within the body. Due to the capsulation's hydrophilic nature, water can enter the formation of the drug and obtain the VLF at a sustainable rate. This hydrophilic shell prevents the immediate release of the antidepressant, causing a sustained release in the form of bursts. Conversely, the PLGA NP used in Study 2 is hydrophobic, leading to unfavorable burst releases due to the surface concentrations of the encapsulated drugs (Myat 1). Because of this factor, PLGA is often modified to increase sustainability in drug release. In Study 2, an altered nanoprecipitation method was used to formulate the PLGA nanoparticles as carriers. Agomelatine and PLGA were vortexed until a clear solution with an addition of acetone until fully dissolved. The solution was then evaporated after it was stirred at 2100 rpm for 4 hours. Nanoparticles then formed within the solution and were used to encapsulate the agomelatine. PLGA nanoparticles can carry both hydrophobic and hydrophilic drugs, contributing to their efficiency and adaptability as a carrier. In this experiment, PLGA increased the bioavailability of agomelatine in the brain, increasing the prolonged release and uptake of the drug within the brain. In Study 3, lipid nanoparticles were used to encapsulate Curcumin and HU-211 antidepressants. Lipid nanoparticles can be used to dissolve hydrophobic material and deliver in a hydrophilic environment. They can encapsulate drugs within either a lipid bilayer or micell, creating a shell around the drug. In this study, an emulsification and low-temperature solidification method was used to form the nanoparticles. A lipid material was dissolved in an organic solvent and nanoparticle dispersion was formed as a result of the dissolution. The Cur and HU-211 were then added to the solution and stirred rapidly at 1200 rpm for 1 hour. The solution was then diluted and stirred again for 2 hours and centrifuged for 2 hours at 20,000 rpm until SLNs were formed and encapsulated the drugs. SLNs are extremely effective at targeting specific areas within the body, making them an effective NP for this study. The composition of each encapsulated drug heavily influences its ability to contribute to efficient targeted delivery and prolonged release of antidepressants. Each of the different encapsulation methods listed affects the way the drugs react within the body. Alginate nanoparticles contribute bulk release and hydrophobic properties, while PLGA nanoparticles are more efficient in surface release and adaptability in carrying methods. SLNs have increased efficiency in the targeting of locations within the body. These differences establish reliance on modification and drugs used. The antidepressant used in each study acts as the determining factor for which nanoparticle is used, as some are more suitable than others in specific situations. Despite their difference, each nanoparticle contributed to the prolonged release of antidepressants within the brain. As opposed to the direct clearance of the drug within gold standard antidepressants, the nanoparticle-assisted formulations sustain prolonged release of the drug, limiting dosages and high-concentration side effects. The NPs used also displayed differences in the ability to sufficiently pass the BBB. The findings of the drug concentrations of the drugs in the brain after each experiment showed significant increases compared to generic antidepressants. Additionally, the efficacy of each drug formulation to combat depressive activity also displays increased efficiency to pass the BBB. In Study 1, pharmacokinetic analysis was completed to analyze the concentrations of drugs within the brain. This was done through the analysis of plasma concentration-time profiles of VLF within different parts of the body and blood. The brain concentration of VLF after the administration of VLF AG-NPs proved to be higher than the gold-standard VLF solution. VLF AG NPs had a brain concentration over two times higher than the concentration of mice treated with lone VLF. The bioavailability of VLF AG NPs was 28.6% higher than that of VLF. The results of this analysis prove the higher efficiency of NP-assisted drug delivery in passing the BBB. A general attribute aiding to NPs' increased ability to cross the BBB is their minuscule size. In Study 2, the particle size of the PLGA-encapsulated agomelatine was less than 200 nm. This particle size was a leading benefactor in the drug's ability to cross the BBB through the nasal route in the experiment. The nanoparticle delivery to the brain and past the BBB was confirmed by the increase in bioavailability and uptake of agomelatine within the brain. In Study 3, SLNs were analyzed for their ability to cross the BBB. SLNs are small and of a lipid nature, which increases their contact with the BBB for the production of a concentration gradient across the BBB. In the study, it was found that the Cur/SLNs-HU-211s were

successful in crossing the BBB from their electron microscopic image data and zeta potential distribution. The analysis of the biodistribution of Cur concluded that an increase in Cur accumulation in the brain site. The concentration of Cur in the SLNs carried solution was significantly higher than that of the gold-standard Cur solution. Each formulation resulted in higher mobility rates in depressed mice after treatment than their gold-standard counterparts. The formulations showed increased efficacy in the treatment of depression through its display of the altering of behavioral patterns. Mobility rates are generally lesser within depressed subjects and show an increase in antidepressant effectiveness. This allows for the measuring of effectiveness and antidepressant activity within test subjects. In Study 1, the FST data concluded that VLF AG-NPs were more effective than the gold standard in inducing antidepressant activity. The swimming and climbing times were significantly higher with VLF AG-NP treated mice as opposed to the VLF tablet and VLF solution groups. The VLF AG-NPs returned the climbing and swimming time of the mice to normal levels, proving the efficacy of the formulation. The maximum locomotor counts were also analyzed for each group, showing that VLF AG-NPs were superior to the gold standard. Similarly, Study 2's formulation resulted in a significant reduction of immobility time in comparison to the untreated group. This proves that the AG PLGA NPs were able to reach the targeted site and induce antidepressant activity. In Study 3, Cur/SLNs-HU-211 was effective at reducing immobility rates and increasing concentrations of dopamine within the brain. The NP formulation was more effective than both Cur and HU-211, providing the most abundant antidepressant activity. All of the formulations showed significant antidepressant effects superior to the gold-standard antidepressants. The efficacy of nanoparticle-assisted drugs was proven to be highly favorable.

Conclusion

NP-assisted treatment of mental illness was analyzed within this study, providing evidence for the increased efficiency of the investigated treatments. The treatments were successful in reaching the brain and inducing antidepressant activity for prolonged periods. NP treatments showed superior antidepressant activity than gold-standard antidepressants. The efficacy of these treatments was shown to be higher than those of the gold standard in their ability to cross the BBB, prolong sustained release, and aid neurotransmitter imbalances. This study also demonstrates future applications of nanoparticles in the medical field through their usage to increase the efficacy of medicines and treatments for neurological health issues. In sum, NP-assisted drug delivery for the treatment of depression was shown to be more effective than generic antidepressants in many aspects.

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