Nanosponge in Current Treatment of Schizophrenia

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***Abstract*—Clozapine is frequently necessary for cases of schizophrenia, a crippling mental illness, that do not respond to treatment. Poor oral bioavailability and notable dose-dependent side effects, however, limit its therapeutic efficacy. To get over these restrictions, the nose-to-brain route offers a viable substitute. This review article gives a clear summary of why and how a new drug delivery system was created and tested. The system uses a special tiny sponge filled with clozapine, placed inside a sticky nasal gel for easy delivery through the nose. The benefits of nasal drug delivery, the synergistic potential of their combination, and the existing literature on nano sponge technology are all thoroughly examined. This review focuses on future research directions to address the unmet requirements of patients with schizophrenia by highlighting important formulation strategies, characterisation techniques, and the possible clinical benefit of this novel strategy.**

I. INTRODUCTION

A significant portion of the world's population suffers from schizophrenia, a severe and chronic mental illness. A considerable percentage of individuals with resistant schizophrenia exhibit a limited response to standard therapies, despite the availability of a variety of antipsychotics.

For this difficult patient group, clozapine, an atypical antipsychotic, has proven to be the most successful pharmaceutical treatment. Clozapine's clinical utility is limited by a number of pharmacokinetic issues, despite its better efficacy. It has a limited therapeutic index and poor oral bioavailability (25–50%) as a result of substantial hepatic first-pass metabolism. These features frequently call for high oral dosages, which raises the possibility of serious dose-dependent side effects as myocarditis, agranulocytosis, seizures, and metabolic abnormalities.

Researchers are now looking into more effective drug delivery methods as a result of the aforementioned difficulties. One special, non-invasive method for getting drugs straight to the brain is the intranasal route. This pathway successfully avoids the blood-brain barrier (BBB), which prevents hepatic first-pass metabolism, as well as the systemic circulation, which promotes drug accumulation in the central nervous system (CNS). The purpose of this review is to objectively assess the possibility of two cutting-edge pharmaceutical technologies—nanosponges and mucoadhesive gels—in creating a better clozapine formulation that meets the unmet clinical demands of today.

II. THE NOSE-TO-BRAIN PATHWAY: A DIRECT ROUTE TO THE CNS

The nasal cavity's strong vascularity, large surface area from turbinate's, and permeable mucosal lining make it physiologically ideal for drug delivery. Direct drug transport from the nasal cavity to the central nervous system is made possible by the nose-to-brain pathway. mainly by means of two different mechanisms:

- Olfactory Pathway: The olfactory neuroepithelium, which has nerve endings that go straight into the olfactory bulb and then to other limbic brain areas, is a conduit for drugs. Bypassing the BBB, this route enables paracellular or neuronal trafficking.
- Trigeminal Pathway: Drug transport to the brainstem and other CNS regions is facilitated by the trigeminal nerves, which innervate the respiratory and olfactory portions of the nasal mucosa.

Compared to traditional methods, this direct access has several advantages: it avoids hepatic first-pass metabolism, reduces systemic exposure, which may lessen systemic side effects, and may result in a speedier commencement of action because it gets to the target location more quickly. Intranasal

administration is a very appealing approach for CNS-targeted medications, especially those with high peripheral metabolism or poor BBB permeability.

Advantages

1. Addressing a Critical Clinical Gap - The Blood-Brain Barrier (BBB) and widespread first-pass metabolism make it hard for many people to get standard oral clozapine treatment. Your review identifies a way around these obstacles by concentrating on the nose-to-brain link.

Direct Access: It investigates how medications can reach the central nervous system directly through the olfactory and trigeminal nerve pathways.
Decreased Side Effects: You can talk about how localized administration lowers systemic exposure, which may lessen the chance of serious side effects from oral clozapine, such as agranulocytosis or metabolic syndrome.

2. Technical Depth: Nanosponges vs. Traditional Carriers

Superior Loading: The porous nature of nanosponges allows them to encapsulate both hydrophilic and lipophilic medicines, in contrast to ordinary liposomes. Stability: One important "pro" to mention in your evaluation section is their strong thermal and chemical stability.

1. Synergy of Mucoadhesion and Nanotechnology

Increased Residence Time: You can assess how polymers, such as chitosan or carbopol, keep the formulation from being removed by ciliary clearance. Enhanced Bioavailability: This combination offers a compelling story about how to transform a nasal spray that clears quickly into a therapeutic system with prolonged release.

2. High Research and Publication Potential

Novelty: Although clozapine has been around for a while, "nanosponge mucoadhesive gels" for nasal administration are a relatively new synthesis. Structured Evaluation: The topic enables you to produce thorough comparison tables that are frequently mentioned in scholarly publications, such as those that compare various polymers, particle sizes, and entrapment efficiency.

III. NANOSPONGES AS ADVANCED DRUG CARRIERS

A network of nanoscale cavities defines the novel, three-dimensional, porous, and strongly cross-linked polymeric structures known as nanosponges. They can encapsulate a wide range of active pharmaceutical ingredients (APIs), including poorly soluble medications, proteins, and even gasses, thanks to their distinctive sponge-like shape.

Material:

Drug: Clozapine (API).
Nanosponge Polymers: Ethylcellulose
Surfactants: Polyvinyl alcohol (PVA)
Cross-linkers: Dichloromethane
Gel Matrix: Carbopol 934
Solvents/Plasticizers: Ethanol
External Phase (Aqueous): Distilled water
Permeation Enhancers: Bile salts (Sodium deoxycholate)
Mucoadhesive Polymers: Carbopol 934/940
Humectants: Glycerin or Propylene glycol to prevent nasal mucosa dryness.
Preservatives: Benzalkonium chloride

Formulation of Nanosponge:

- Emulsion Solvent Diffusion Method: In this commonly used method, the drug and polymer are dissolved in a water-miscible organic solvent, which is subsequently distributed in an aqueous phase with a stabilizer. Polymer precipitation and nanosponge production result from the organic solvent's subsequent diffusion into the aqueous phase.
- The Ultrasonication-Assisted Method: Increases the efficiency of nanosponge creation and promotes a homogeneous particle size distribution by using high-frequency sound waves to produce fine emulsions.

As drug delivery vehicles, nanosponges have a number of strong benefits.

1. Enhanced Drug Solubility: Nanosponges can greatly increase the aqueous solubility and

dissolution rate of poorly water-soluble medications, such as clozapine, increasing their bioavailability. The hydrophobic pockets of the nanosponge matrix capture the drug molecules.

2. Sustained and Controlled Release: The polymeric network and porous structure of nanosponges provide for a consistent and extended release profile of the medicine that is contained. In particular, for long-term illnesses like schizophrenia, this is essential for preserving steady therapeutic medication levels, lowering dosage frequency, and enhancing patient compliance.
3. Improved Stability: The encapsulated medication is protected from oxidation, heat, light, and enzymatic activity by the polymeric matrix, which increases the drug's chemical stability.
4. Reduced Side Effects: Nanosponges may be able to lower peak plasma concentrations and the related systemic adverse effects by offering targeted delivery and controlled release.

IV. THE ROLE OF MUCOADHESIVE GELS IN NASAL DELIVERY

The formulation must have a long enough residence time in the nasal cavity for intranasal medication delivery to be as effective as possible. Reduced medication absorption can result from the quick removal of given formulations from the nasal passages by the normal physiological process of mucociliary clearance, which is the constant movement of mucus and cilia.

Mucoadhesive polymers are macromolecules that can stick to the nasal cavity's mucosal lining by a variety of interactions, such as van der Waals, hydrogen bonding, and electrostatic forces. Carbopol, sodium carboxymethyl cellulose (NaCMC), hydroxypropyl methylcellulose (HPMC), and chitosan are common mucoadhesive polymers. They have important advantages when added to a nasal formulation:

- Prolong Contact Time: Mucoadhesive polymers greatly increase the duration of contact between the drug and the absorption surface by sticking to the nasal mucosa. This increases the chance of drug penetration.
- Reduced Mucociliary Clearance: They enable longer-lasting absorption by physically impeding the formulation's quick removal.
- Controlled Release: A mucoadhesive gel can further alter the drug release profile when paired with nanosponges, creating a synergistic impact of prolonged residency and sustained release.

For intranasal delivery, a gel formulation works especially well. It is a semi-solid solution that can offer a localized, controlled release profile and is often simple to administer and non-irritating. The final formulation gains from the inherent benefits of both sophisticated systems by incorporating drug-loaded nanosponges into a mucoadhesive gel base: the controlled and improved solubility offered by the nanosponges and the extended residence time and enhanced absorption provided by the mucoadhesive gel.

V. EVALUATION

Characterization of Nanosponge:

1. Particle Size and Polydispersity Index (PDI): Dynamic Light Scattering (DLS) should have a low PDI (<0.3) and be in the nanometer range, such as 100–500 nm.
2. Zeta Potential: Shows stability and surface charge, which should be enough to stop aggregation.
3. Morphology: Size, shape, and surface features may be seen using Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM).
4. Encapsulation Efficiency (EE%) and Drug Loading (DL%): Determined by centrifuging the nanosponges, measuring the total drug by dissolving the nanosponges, and checking the supernatant for free drug using UV-Vis or HPLC.

EE% = (Total Drug - Free Drug) / Total Drug * 100
DL% = (Drug in Nanosponges) / (Weight of Nanosponges) * 100

5. Fourier-Transform Infrared Spectroscopy (FTIR) / Differential Scanning Calorimetry (DSC) / X-ray Diffraction (XRD): To verify if the medicine is compatible with the polymer and whether it is crystalline or amorphous in the nanosponges.

In Situ Gel Characterization:

1. Visual Appearance: Homogenous, transparent solution.
2. pH: should be between 5.5 to 6.5, which is the nasal physiological range.
3. Viscosity:

- Sol State: Room temperature viscosity is low, making administration simple.
- Gel State: High viscosity to guarantee retention at body temperature (34°C, nasal cavity temperature). measured with a viscometer.

4. Gelation Temperature (Tgel) and Gelation Time (Tgt): Determined using the inverted tube technique or rheological investigations. Tgt should be quick, and Tgel should be between 30 and 34°C.
5. In Vitro Drug Release: Franz diffusion cell configuration that mimics the nasal environment by utilizing a synthetic membrane or removed nasal mucosa. Analyze the gel's clozapine release.
6. Mucoadhesive Strength: Using mucin discs or removed nasal mucosa in a tensiometer or comparable apparatus.
7. Spreadability: To provide coverage and simple administration into the nasal cavity.
8. Preservative Efficacy Test: To guarantee that the preservative successfully stops the growth of microorganisms.

VI. CONCLUSION

An important discovery in the treatment of schizophrenia is the creation of a mucoadhesive nasal gel filled with Clozapine nanosponge. This approach effectively overcomes the main drawbacks of oral Clozapine treatment by combining the solubility-enhancing properties of nanosponges with the extended contact duration of a mucoadhesive gel.
The "nose-to-brain" route permits:

1. Direct transmission through olfactory nerves is one way to get beyond the Blood-Brain Barrier (BBB).
2. Enhanced Bioavailability: Lower dosages are possible by avoiding hepatic first-pass metabolism, which may lessen the chance of serious adverse effects such agranulocytosis.
3. Enhanced Patient Compliance: The frequency of administration is reduced by sustained release.

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