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FORMULATION AND EVALUATION OF ANTIEPILEPTIC DRUG-LOADED NANOSPHERES: A COMPREHENSIVE OVERVIEW

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ABSTRACT

Epilepsy is a prevalent neurological disorder affecting over 50 million people globally, with approximately 5 million new cases diagnosed each year. It is characterized by aberrant brain activity leading to seizures, often resulting from sudden and excessive neuronal discharges. Despite its widespread impact, epilepsy remains a complex condition with diverse underlying causes and manifestations, affecting individuals across all age groups, particularly Pediatrics and Geriatrics. The delivery of therapeutic agents to specific sites in the brain poses significant challenges in treating epilepsy. However, the emergence of nanotechnology offers promising solutions by enhancing drug performance through nano-sized formulations. Nanospheres, a subset of polymeric nanoparticles with sizes ranging from 10 to 200 nm, are particularly advantageous due to their ability to encapsulate a variety of drugs, enzymes, and genes, and their long circulation time. These nanospheres enable targeted drug delivery, which is crucial for effectively managing epilepsy. Overall, nanotechnology holds significant promise for improving the treatment of epilepsy by enhancing drug delivery and targeting capabilities.

KEYWORDS: Nanospheres, Drug targeting, Drug delivery, epilepsy.

INTRODUCTION

The Nano Drug Delivery System (NDDS) is a dynamic area of scientific research, driven by the rapid advancements in nanotechnology. This field focuses on the innovative development of drug delivery methods that leverage nanoscale materials to enhance therapeutic efficacy and precision.[1] It involves the investigation of individual molecules, atoms, or compounds to

create structures that exhibit unique properties.[2] Nanotechnology with a wide range of nanocarriers such as liposomes and nanoparticles focused on targeted drug delivery has been expanding quickly. [3] Nanoparticles (NPs) are one of the nano system delivery methods which have been developed to accomplish extended or organized drug delivery, to increase the bioavailability, drug stability, and drug targeting to the site of action. Nanospheres are small particles with a size range of 10 to 200 nm.[4]

Epilepsy is considered one of the most prevalent neurological illnesses, affects more than 50 million people worldwide, and each year approximately 5 million new cases are diagnosed. Epilepsy is characterized by aberrant brain activity resulting in convulsions. Depending on basic brain dysfunctions, this neurological disorder comprises numerous etiologies including abrupt and excessive neuronal discharges that result in epileptogenesis. Although it affects people of all ages, the rate of disease is high in children and elderly persons.[5]

Nano Drug Delivery Systems (NDDS) can prolong the presence of drugs in the bloodstream, resulting in reduced fluctuations in plasma levels and consequently minimizing side effects. These nanospheres enable targeted drug delivery, which is crucial for effectively managing epilepsy.[6,7]

Advantages of Nanospheres

- **Efficient Penetration:** Nanospheres can readily traverse even the smallest capillary vessels, ensuring effective distribution throughout the body.
- **Targeted Organ Delivery:** They can be utilized to specifically target organs such as the liver, spleen, lungs, and spinal cord, enhancing therapeutic precision.[8]
- **Decreased Toxicity:** Nanospheres help lower toxicity levels and reduce the frequency of required dosages.
- **Versatile Administration Methods:** They can be administered through multiple routes, including oral, nasal, and parenteral options.
- **Quick Clearance and Targeted Delivery:** Nanospheres enable rapid clearance from the bloodstream while allowing for precise targeting at specific sites within the body.[9]

Disadvantages of Nanospheres

Handling Challenges: Nanospheres can be difficult to manage in both liquid and dry forms.

Manufacturing Expertise Required: The production of nanospheres demands specialized skills and techniques.

Susceptibility to Aggregation: Due to their small size and larger surface area, nanospheres are prone to particle aggregation.[10]

Methods of Preparation of Nanospheres: Several techniques are employed for the preparation of nanospheres, including:

- Polymerization Method
- Solvent Evaporation
- Solvent Displacement Technique
- Double Emulsion Method
- Controlled Gelification Method
- Desolation Technique
- Ionic Gelation Method
- Salting Out Method.[11]

Method of Preparation

Drug nanospheres were prepared using the emulsion followed by solvent evaporation method, incorporating various types of polymers.

Solvent Evaporation Method

A polymer is first dissolved in a suitable organic solvent. The solution is then sonicated for 2 minutes, after which a drug is added and the mixture is sonicated again for another 2 minutes, emulsifying agent like polyvinyl alcohol or gelatine is mixed to create an oil-in-water (O/W) emulsion. This emulsion is subjected to solvent evaporation through continuous mixing, heating, or reduced pressure, resulting in the formation of nanospheres.[12]

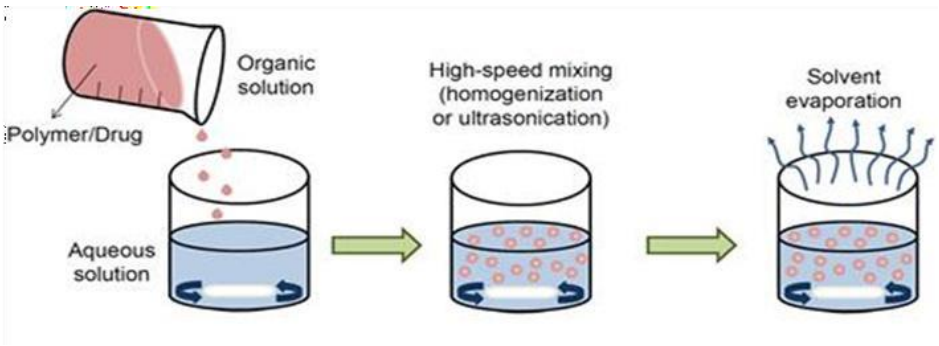

Fig. 1: Solvent evaporation.

Preparation of Polymer and Drug Solution

- Weigh the required amount of polymer and place it in a dry beaker.

- Measure the necessary quantity of solvent (methanol) in a measuring cylinder.
- Gradually add methanol to the beaker containing the polymer.
- Stir continuously with a glass rod to form a polymer solution.
- Accurately weigh 300 mg of drug and mix it thoroughly into the solution.

Preparation of Aqueous Solution: Weigh 1 g of sodium lauryl sulphate (SLS) and dissolve it in 1000 mL of water. Allow the mixture to sit for a short period to remove any air bubbles.

Polymerization

Emulsification polymerization involves creating emulsions of polymers like polymethylmethacrylate and polyethylcyanoacrylate. Another method is interfacial polymerization with polyalkylcyanoacrylate, where monomers form nanospheres in an aqueous solution. The drug can be added by dissolving it in the polymerization medium or by adsorbing it onto the nanospheres afterward. After polymerization, the nanospheres are purified to remove stabilizers, which can be done using centrifugation or by resuspending them in a surfactant-free isotonic solution.[13]

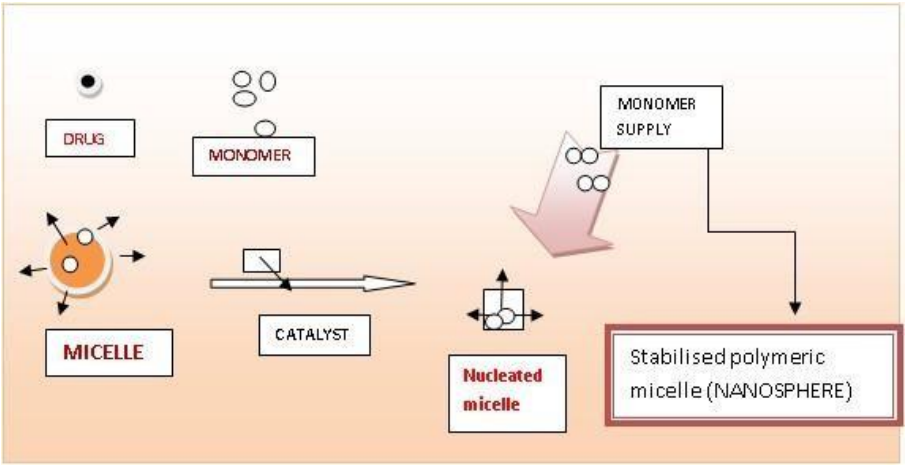

Figure 2: Polymerisation.

Solvent Displacement Technique

The solvent displacement technique allows for the production of nanospheres using a low-energy approach, particularly with biodegradable polyesters and PEG. In this method, a polymer is dissolved in a water-miscible organic solvent and then introduced into an aqueous phase, sometimes with surfactants. As the organic solvent diffuses into the aqueous phase, the polymer precipitates, forming nanospheres. This technique is noted for its simplicity and effectiveness in creating nanoparticles with specific properties.[14]

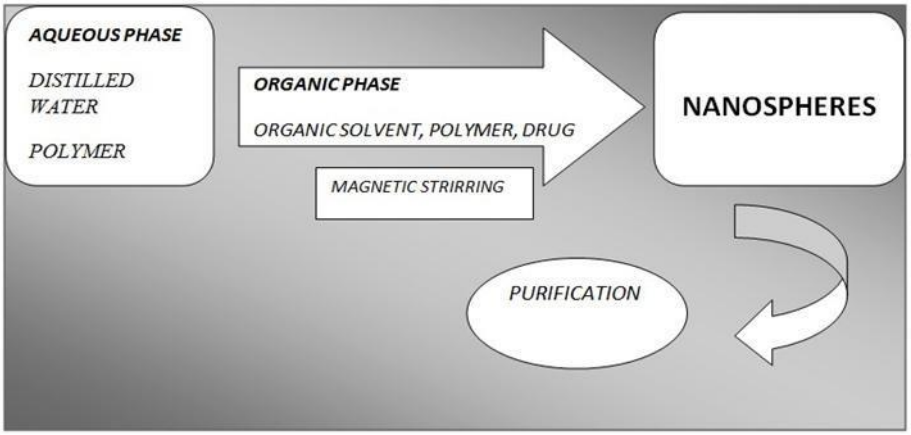

Figure 3: Solvent displacement.

Phase Inversion Temperature (PIT) Method

The phase inversion temperature (PIT) method creates nanospheres by desolubilizing polymers with nano emulsion droplets. Typically, a non-volatile dispersed phase is used, but replacing it with a volatile solvent has proven effective. The authors successfully formed a nanoemulsion by introducing the polymer into the volatile solvent and then evaporating it below the PIT. Currently, there are no other documented formulations of polymeric nanospheres using this method. Additionally, the use of dissolved polymers often requires harmful organic solvents, which undermines one of the PIT method's main advantages: eliminating organic solvents. Thus, interest in modifying this method appears limited.

Nanospheres as targeted drug delivery: There are various ways to using of Nanospheres as targeted drug delivery system.

Targeting on the tumour

Nanospheres are effective in delivering drugs directly to tumours, utilizing the enhanced permeability and retention (EPR) effect and active targeting through surface ligands. This targeted method minimizes toxicity to healthy tissues. However, research shows that a significant amount of the drug, about 56%, accumulates in the liver, with only 1.6% reaching the tumour. This liver uptake poses challenges in avoiding the mononuclear phagocytic system during treatment. Despite this, studies indicate that doxorubicin combined with nanospheres is more effective against liver metastasis than the free drug alone.[15]

Long Circulation of Nanospheres

Nanospheres have the ability to target tumours that are located outside the mononuclear phagocytic system (MPS). A significant advancement in achieving prolonged circulation of

nanospheres occurred with the coating of their surfaces with hydrophilic polymers such as PEG (polyethylene glycol) and poloxamine.[16] This modification produces an opposing effect, reducing uptake by the MPS and allowing for extended circulation time in the bloodstream.[17] The coating creates a hydrophilic and neutral layer around the particle surface, which repels plasma proteins. [18] Consequently, the coated nanospheres become less detectable by the MPS, allowing them to remain in circulation for an extended period.[20]

Nanospheres for Oral Delivery

Utilizing bioactive molecules, such as peptides and proteins, with appropriate carriers poses significant challenges. The bioavailability of these molecules is often limited, and they are prone to degradation by enzymatic action. Polymeric nanospheres provide a viable solution by encapsulating these bioactive molecules, thereby protecting them from enzymatic degradation and enhancing their stability during gastrointestinal transit. This encapsulation ultimately improves the absorption and therapeutic efficacy of the molecules.[21]

Nanospheres for Drug Delivery in the Brain

The blood-brain barrier (BBB) is crucial in drug development for the central nervous system, characterized by tight junctions and selective permeability.[22] This barrier complicates drug delivery, as many drugs cannot penetrate it effectively.[23] Nanospheres can enhance drug transport across the BBB by utilizing receptor-mediated mechanisms. For instance, combining polysorbate 80 with low-density lipoprotein (LDL) has proven effective in facilitating this process.[24] As a result, drugs that typically struggle to cross the BBB can do so more easily when encapsulated in nanospheres, increasing their potential for treating neurological conditions.[25]

There are also other drug delivery systems present for this purpose

- Nanospheres for gene delivery
- Nanospheres targeting to epithelial cells etc.[26]

Benefits of Nanospheres drug delivery system

- Nanospheres can easily traverse the tiniest capillary vessels due to their extremely small size.[27]
- They can evade rapid clearance by phagocytes, allowing for an extended duration in the bloodstream.

- Nanospheres can easily infiltrate cells and tissue gaps to reach target organs such as the liver, spleen, lungs, spinal cord, and lymphatic system.

They exhibit controlled release properties.[28]

- Site-specific targeting is achieved by attaching ligands to the surface of the nanospheres.
- Nanospheres can be administered through various routes, including oral, nasal, and parenteral methods.[29]
- A significant advantage of nanospheres is their ability to reduce toxicity.

Drawback of Nanospheres drug delivery system

- Physical handling of nanospheres can be challenging in both liquid and dry forms.
- The smaller size and larger surface area of nanospheres increase the likelihood of particle aggregation.
- Drug loading and burst release are constrained by the small size and extensive surface area of the nanospheres.[30]

EVALUATION

Assay

It is essential to accurately weigh 3 mg of the nanocrystalline Drug produced. This sample should then be dissolved in 40 mL of methanol and titrated using 0.1 mol/L sodium hydroxide as the volumetric standard (potentiometric titration, with endpoint detection method in Titrimetry). Each millilitre of the resulting solution contains 35.419 milligrams of Drug at a concentration of 0.1 mol/L sodium hydroxide. When dried, drug exhibits a concentration ranging from 99.0% to 101.0%.[31]

Modified Dissolution Test

For the in vitro dissolution studies, a 25 mL nanoparticle solution was combined with a beaker containing 100 mL of a 1% sodium lauryl sulphate (SLS) solution in distilled water. The experiments were conducted over a 24-hour period. A thermostatically controlled water bath maintained the dissolution medium at a temperature of 37 ± 0.05 °C, and the basket's rotation speed was set to 50 rpm. At regular intervals, 3 mL samples were collected, and the drug release was measured spectrophotometrically at 275 nm. To maintain sink conditions, 3 mL of fresh matching medium was added each time a sample was withdrawn from the dissolution flask.[31]

FT-IR Analysis

The potential interactions between the drug and polymers or excipients, IR spectral matching studies were conducted. In this study, FT-IR was employed to evaluate the compatibility of drug with various polymers using a PERKIN ELMER FTI instrument (USA). The samples were scanned with an FT-IR spectrophotometer over a range of 4000 to 400 cm$$^ {-1} $$. Similarly, the IR spectra of each distinct drug and the produced nanocrystals were recorded. The analysis focused on examining the external characteristics of the materials and identifying the presence or absence of peaks in the spectra to detect any possible physical or chemical interactions.[31]

Scanning Electron Microscopy (SEM)

The particle morphology of both untreated and treated drug nanospheres was analysed using scanning electron microscopy. Each drug powder sample was divided into small pieces and affixed to double-sided carbon conductive tape. A Pt-Pd alloy coating, approximately 5 nm thick, was then applied to cover the entire surface of the tape. Micrographs were captured using a Zeiss DSM 982 Field Emission Gun Scanning Electron Microscope (Carl Zeiss AG, Germany).[32]

Particle Size Distribution

Immediately after precipitation, the size of the drug nanospheres was measured using dynamic laser light scattering with a nanoparticle size analyzer (Malvern). The drug solution was diluted to a concentration of 0.2 mg/mL with purified water prior to analysis. The results from the particle size study were interpreted using the graphic mean size (Mz) and calculated surface area.[33,34]

Measurement with Differential Scanning Calorimetry (DSC)

The thermal properties of the lyophilized powder samples were analysed using DSC-41 equipment (Shimadzu, Japan). Each lyophilized powder sample was scanned over a temperature range of 25 to 200 °C at a heating rate of 10 °C/min. A total of 10 mg from each sample was examined in an open aluminium pan, with magnesium used as the control. This thermal analysis was conducted on both the drug and the excipients to evaluate any changes in internal structure resulting from the nanosizing process.[35]

Zeta Potential

The size, size distribution, and zeta potential of the nanospheres were assessed using a zeta

sizer (ZS 90 Malvern). Prior to testing, the lyophilized samples were diluted with PBS to achieve a concentration of 1 mg/mL and a pH of 6.0. These samples were placed in a clean cuvette during the size analysis to obtain multiple peaks, which were then used to calculate the average zeta size. For the zeta potential measurements, the samples were kept in the analysis chamber of the zeta sizer while it was operational to collect accurate data. Typically, the focus is on the monodisperse characteristics of this data rather than its polydisperse aspects.[31,32]

Drug Entrapment Efficiency (EE%) and Drug Loading (DL%)

To determine the drug entrapment efficiency (EE%) and drug loading (DL%), the nanospheres undergo a process of centrifugation, washing, re-centrifugation, and subsequent filtration. An aliquot of the supernatant is taken and diluted for analysis. The concentration of the free drug is measured using a UV-Visible spectrophotometer. The amount of entrapped drug is calculated by subtracting the quantity of free drug from the total amount of drug initially added to the formulation.[36]

Calculating the formula

$$\text{EE (W/W) \%} = \frac{\text{Amount of entrapped drug}}{\text{Total amount of the drug added}} \times 100$$

$$\text{DL (W/W) \%} = \frac{\text{Amount of entrapped drug}}{\text{(amount of polymer + entrapped drug)}} \times 100$$

CONCLUSION

This study concludes that nanospheres hold significant potential for transforming significant potential in enhancing the delivery of poorly soluble and absorbed drugs, such as anti-epileptic medications, by improving solubility and enabling controlled release mechanisms. Their ability to provide site-specific targeting particularly through methods like receptor-mediated transport across the blood-brain barrier (BBB) ensures higher drug concentrations at target sites while minimizing systemic exposure. Additionally, nanospheres protect encapsulated drugs from enzymatic degradation and bodily fluids during transit, enhancing stability and bioavailability. For anti-epileptic drugs, this targeted approach could reduce off-target toxicity and improve therapeutic efficacy by overcoming challenges like BBB impermeability. These advancements highlight nanotechnology's role in transforming traditional drug formulations into precision therapies.

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