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REVIEW ON ENHANCING THE ORAL BIOAVAILABILITY OF CARBAMAZEPINE THROUGH NANOSUSPENSION TECHNOLOGY

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ABSTRACT

Oral bioavailability with poor aqueous solubility is the major challenge in pharmaceutical research which is mainly for Biopharmaceutical classification system (BCS) class 2 & class 4. It mainly focuses on enhancing the oral bioavailability of carbamazepine through nanosuspension technology. Nanosuspension are sub micron colliodial dispersion of pure drug particles stabilized by surfactant and polymers with maintaining a particle size of 200-600nm. by significantly reducing the particle size the technology significantly increase the surface area, saturation solubility and dissolution velocity and leading to rapid drug absorption and enhance bioavailability. Various preparation methods are like top up process (high pressure homogenisation, media milling) and bottom up process (anti-solvent precipitation method, Super critical fluid process) are known. Further key characterization parameters such as particle size, zeta potential, and in-vitro dissolution studies are evaluated to ensure formulation stability and therapeutic efficiency.

KEYWORDS: Carbamazepine, Nanosuspension, Bioavailability, Solubility, Antisolvent – Preciptation.

INTRODUCTION

NANOTECHNOLOGY[1]

Nanotechnology is the field of science and engineering concerned with the design, fabrication, characterization, and application of materials and devices that have at least one dimension on the nanometer scale (1–100 nm), where one nanometer represents one-billionth of a meter. This technology enables the development of materials with unique physical, chemical, and biological properties due to their extremely small size. Nano-science and nanotechnology have the potential to significantly improve human healthcare by offering innovative solutions in drug development, water purification, and the production of stronger and lighter materials. Their application in healthcare research is expected to provide substantial medical benefits and enhance the prevention, diagnosis, and treatment of diseases. Nanotechnology-based drug delivery systems can protect drugs from degradation, thereby improving their stability and therapeutic effectiveness. These systems can also reduce the required dosing frequency, enhance patient compliance, and lower the overall cost of treatment.

NANOSUSPENSION[2]

Nano-suspensions are submicron-sized colloidal dispersions composed of nanometer-sized drug particles that are stabilized using surfactants or other suitable stabilizing agents. They contain poorly water-soluble drug particles dispersed in a liquid medium without the use of a carrier or matrix material. It is a pharmaceutical dosage form in which poorly water-soluble drug particles are uniformly dispersed in an aqueous medium for administration through oral, topical, parenteral, or pulmonary routes. Nanosuspensions are an effective strategy for improving the solubility of drugs that exhibit poor solubility in both aqueous and lipid media. The particle size of drug crystals in nanosuspensions is generally below 1 µm, with an average size ranging from

200 to 600 nm**.** By enhancing drug solubility and dissolution rate, nanosuspensions increase the rate of drug absorption, allowing the drug to reach its maximum plasma concentration more rapidly and improving its bioavailability.

ADVANTAGES[3]

- Improves the solubility and bioavailability of drugs.
- Suitable for delivering poorly water-soluble drugs.
- Allows higher drug loading compared to many conventional dosage forms.
- Enables dose reduction by improving therapeutic efficiency.
- Enhances the physical and chemical stability of drug molecules.
- Facilitates passive targeting of drugs to the desired site of action.

DISADVANTAGES[3]

- Nano-suspensions may undergo physical instability, including sedimentation, aggregation, and particle compaction during storage.
- Inaccurate dosing may occur if the suspension is not properly dispersed before administration.
- Achieving a uniform and precise dose can be challenging due to particle settling.
- Careful handling, storage, and transportation are required to maintain the stability and quality of the formulation.
- Uniform and accurate dosing can only be ensured when the suspension is thoroughly re-dispersed before use.

ADMINISTRATION OF NANOSUSPENSION[4]

ORAL ADMINISTRATION

Nanosuspensions can be administered through various routes, including oral, dermal, parenteral, ocular, and pulmonary routes. Among these, the oral route is the most commonly used, accounting for more than 60% of nanosuspension administrations. The oral route is the most widely preferred method of drug administration because it is non-invasive, convenient, safe, cost-effective, and offers good patient compliance. However, the oral bioavailability of many drugs is limited by poor aqueous solubility, low permeability, enzymatic degradation, and first-pass metabolism. Nearly 40–70% of newly developed drugs have poor water solubility, leading to reduced absorption and therapeutic effectiveness.

The Biopharmaceutical Classification System (BCS) identifies Class II and Class IV drugs as having poor oral bioavailability due to low solubility. Reducing particle size through micronization or nanosizing increases the surface area, improves the dissolution rate and saturation solubility, and ultimately enhances oral bioavailability.

PARENTERAL ADMINISTRATION

The parenteral route is widely used in clinical practice because it provides nearly 100% bioavailability, rapid onset of action, reduced dosing requirements, bypasses the gastrointestinal tract, and avoids first-pass hepatic metabolism. Nanosuspensions designed for parenteral administration have nanometer-sized particles that improve permeability, allow high drug loading, and require only small administration volumes. Additionally, the low concentration of excipients in these formulations helps reduce the risk of toxicity and allergic reactions.

PULMONARY ADMINISTRATION

The pulmonary route can provide both local and systemic drug delivery due to the lungs' large surface area, thin alveolar membrane, and low enzymatic activity. The respiratory tract also serves as an effective site for immune responses. The deposition and bioavailability of inhaled drugs depend on factors such as particle size, shape, density, drug solubility, permeability, molecular weight, formulation characteristics, and the delivery device used. Recent advances in nanotechnology have promoted the development of pulmonary nanosuspension systems for the treatment of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma.

OCULAR ADMINISTRATION

Conventional eye drops account for about 90% of marketed ophthalmic formulations, but their bioavailability is low due to pre-corneal drug loss caused by tear drainage and blinking. As a result, only about 5% of the administered drug reaches the intraocular tissues. Although ocular ointments improve drug retention, they may cause blurred vision. Nanotechnological drug delivery systems, particularly nanosuspensions, offer improved ocular drug delivery by enhancing drug retention and enabling effective delivery of both hydrophobic and hydrophilic drugs across the ocular surface.

FORMULATION COMPONENTS[5]

Nanosuspension formulations commonly contain excipients such as stabilizers, polymers, surfactants, osmotic agents, organic solvents, cryo protectants, buffers, complexing agents, organo-leptic agents, and preservatives to enhance stability, solubility, and overall formulation performance.

STABILIZER

Stability during production, storage, and in vivo application is essential to maintain particle size and drug performance. Since most nanosuspensions are prepared in aqueous media, they are susceptible to oxidation and hydrolysis. Therefore, stabilizers play a crucial role in preventing particle aggregation and agglomeration caused by the high surface energy of nanoparticles. They also improve the wetting of hydrophobic drugs, inhibit Ostwald ripening**,** and provide steric or electrostatic repulsion to enhance physical stability. The type and

concentration of stabilizer significantly influence the stability and in vivo performance of nanosuspensions. Commonly used stabilizers include cellulose derivatives, phospholipids, poloxamers, non-ionic surfactants, and polyvinylpyrrolidone (PVP).

POLYMERS

Synthetic polymers are widely used as stabilizers in nanosuspension formulations and are Generally Recognized as Safe (GRAS) by the FDA for oral, parenteral, and topical pharmaceutical applications. Among these, Poloxamer 188 and Poloxamer 407 are the most commonly employed. The stability and crystal growth of nanosuspensions are influenced by several factors, including the hydrophilic–lipophilic balance (HLB), morphology, functional groups, and molecular weight of the polymer.

SURFACTANTS

The choice of surfactant and co-surfactant is crucial in the preparation of nanosuspensions using the microemulsion template method. These excipients influence the phase behavior, drug solubility, and drug-loading capacity of the internal phase. Commonly used surfactants include Tween series and sodium dodecyl sulfate (SDS/SLS), while bile salts, Transcutol, Glycofurol, ethanol, and isopropyl alcohol are frequently used as co-surfactants to improve the stability and formation of nanosuspensions.

SOLVENTS

Organic solvents, which have low toxicity to humans, are preferred over conventional hazardous solvents in nanosuspension formulations. Commonly used solvents include ethanol, acetone, butanol, ethyl formate, ethyl acetate, ethyl ether, methyl acetate, methyl ethyl ketone, and triacetin. In the emulsion solvent evaporation method, water-miscible organic solvents are used as the internal phase to dissolve the drug before nanoparticle formation.

PREPARATION TECHNIQUES[6]

The Top-Down approach involves breaking down large drug particles into microparticles and subsequently reducing them to the nanometer size range through mechanical size reduction techniques. Common examples of this approach include

- High-Pressure Homogenization,
- NanoEdge technology,
- NanoPure technology,
- Media Milling (nanocrystal technology).

The Bottom-up approach is based on the assembly of nanoparticles from drug molecules dissolved in a suitable solvent. This method relies on controlled precipitation or molecular aggregation to form nanoparticles. Common techniques under the bottom-up approach include

- Antisolvent precipitation method,
- Supercritical fluid process,
- Emulsification–solvent evaporation technique,
- Lipid emulsion/microemulsion

A) TOP DOWN PROCESS

➢ **High Pressure Homogenization**

High-pressure homogenization is one of the most commonly used techniques for preparing nanosuspensions of poorly water-soluble drugs. The process consists of three main steps. Initially, the drug powder is dispersed in a stabilizer solution to produce a coarse pre-suspension. This pre-suspension is then passed through a high-pressure homogenizer at low pressure for a pre-milling step to reduce the initial particle size. Finally, the suspension is subjected to high-pressure homogenization for approximately 10–25 cycles until nanoparticles of the desired size are obtained, resulting in a stable nanosuspension.

➢ **Nanoedge Technology**

Nano Edge technology is a hybrid technique that combines the principles of precipitation and high-pressure homogenization for the preparation of nanosuspensions. It follows the same basic mechanism as the precipitation method but incorporates a homogenization step to improve the quality of the final product. This combined approach helps overcome common limitations of the conventional precipitation technique, such as crystal growth, particle aggregation, and poor long-term stability. As a result, NanoEdge technology produces nano-particles with smaller particle size, enhanced physical stability, and improved uniformity within a shorter processing time.

➢ **Nano pure technology**

Nano-Pure technology is a high-pressure homogenization technique in which drug suspensions are processed in water-free media or non-aqueous solvent mixtures, such as PEG 400, PEG 1000, and similar vehicles. The homogenization process can be carried out at room temperature, 0°C, or even below the freezing point (approximately –20°C). Since the process is performed at very low temperatures, it is commonly referred to as "deep-freeze homogenization." This technique is particularly suitable for drugs that are sensitive to water or elevated temperatures, as it helps maintain drug stability while producing nanosuspensions with a uniform particle size distribution.

➢ **Media Milling**

Media milling is one of the earliest techniques developed for the preparation of nanosuspensions and was first reported by Liversidge in 1992. In this method, nanosuspensions are produced using a high-shear media mill. The milling chamber is filled with the drug, stabilizer, water (or another suitable dispersion medium), and milling media, and the mixture is agitated at a high shear rate under controlled temperature conditions for approximately 2–7 days. The milling media typically consist of glass beads, zirconium oxide beads, or highly cross-linked polystyrene resin beads. During the milling process, the repeated collision and impact between the

milling media and the drug particles generate high shear forces, which break down the drug microparticles into nanoparticles, resulting in the formation of a stable nanosuspension.

A) Bottom up process

- **Anti-Solvent Preciptation Technique**

The antisolvent precipitation method is a widely used bottom-up technique for preparing nanosuspensions, particularly for poorly water-soluble drugs. Over the past decade, this method has gained considerable attention for producing drug particles in the submicron and nanometer size range.In this technique, the drug is first dissolved in a suitable organic solvent. The resulting drug solution is then rapidly added to a miscible antisolvent containing an appropriate surfactant or stabilizer under continuous stirring. The rapid mixing of the solvent and antisolvent causes an immediate increase in supersaturation, leading to the rapid nucleation and precipitation of the drug as ultrafine crystalline or amorphous nanoparticles**.** This process produces nanosuspensions with a small particle size and improved dissolution characteristics.

- **Super Critical Process**

The supercritical fluid (SCF) process is an advanced particle size reduction technique used to produce nanosuspensions by utilizing the unique properties of supercritical fluids. A supercritical fluid is a substance that exists above its critical temperature (Tc) and critical pressure (Pc)**,** where it exhibits characteristics of both liquids and gases. This process enhances drug solubilization and enables the reduction of drug particles from the micron range to the submicron or nano-meter range. Recent developments in SCF technology have made it possible to produce nanoparticles with sizes ranging from 5 to 2000 nm, making it a promising approach for nanosuspension preparation. However, its application in the pharmaceutical industry is limited due to the poor solubility of many poorly water-soluble drugs and surfactants in supercritical carbon dioxide (CO_2), as well as the requirement for high operating pressures, which increase the complexity and cost of the process.

- **Emulsification – Solvent Evaporation Technique**

The emulsification–solvent evaporation technique is a bottom-up method used for the preparation of nanosuspensions. In this technique, the drug is first dissolved in a suitable volatile organic solvent to form a drug solution. This solution is then emulsified into another liquid that acts as a nonsolvent for the drug, resulting in the formation of an emulsion. Following emulsification, the organic solvent is removed by evaporation, causing the drug to precipitate as fine nanoparticles. The use of high-speed stirring or high-shear homogenization during the process helps control crystal growth and particle aggregation**,** thereby producing nanosuspensions with a uniform particle size distribution and improved stability.

- **Lipid Emulsion/Microemulsion Technique**

The lipid template (emulsion/microemulsion) method is a bottom-up technique commonly used for the preparation of nanosuspensions of drugs that are soluble in volatile organic solvents or partially water-miscible solvents. In this method, the drug is first dissolved in a suitable organic solvent and then emulsified into an aqueous phase containing appropriate surfactants to form an emulsion. The organic solvent is gradually removed under reduced pressure, causing the drug to precipitate as fine particles in the aqueous phase. The resulting suspension can then be diluted to obtain a nanosuspension with the desired particle size. Micro emulsions can also serve as effective templates for nanosuspension preparation. A microemulsion **is a** thermodynamically stable, transparent, and isotropic system composed of two immiscible liquids, such as oil and water, stabilized by a combination of surfactants and co-surfactants. The drug may either be dissolved in the internal phase of the microemulsion or incorporated into a preformed microemulsion through thorough mixing. Upon appropriate dilution, the drug precipitates as nanoparticles, resulting in the formation of a nanosuspension.

CHARACTERIZATION OF NANOSUSPENSION[7,8]

The evaluation of nanosuspensions plays a crucial role in understanding their distinctive properties and suitability for pharmaceutical applications. A range of characterization and evaluation techniques are used to assess their quality, stability, and performance, thereby facilitating the development of optimized nanosuspension formulations.

1. PARTICLE SIZE ANALYZER

Particle size is one of the most critical parameters in the characterization of nanosuspensions, as it directly influences their physicochemical and biological properties. It is commonly measured using a particle size analyzer capable of determining particles in the nanometer (nm) range. Among the available instruments, the Malvern Zetasizer is widely used due to its high sensitivity and ability to accurately measure nanosized particles, even at low sample concentrations. Dynamic Light Scattering (DLS) is the most frequently employed technique for determining the particle size of dispersed nanoparticles in nanosuspensions. Another important characterization parameter is the polydispersity index **(**PDI)**,** which indicates the uniformity and width of the particle size distribution. PDI significantly affects properties such as saturation solubility, dissolution rate, physical stability, and biological performance of the nanosuspension. Particle size distribution can be evaluated using several techniques, including Photon Correlation Spectroscopy (PCS)**,** Laser Diffraction (LD)**,** and the Coulter Counter Multisizer, each providing valuable information about the size distribution and uniformity of the nanoparticles.

2. ZETA POTENTIAL

Zeta potential is an important parameter used to determine the nature and magnitude of the surface charge of nanoparticles dispersed in a nanosuspension. It is defined as the electrical potential difference between the surface of a particle suspended in a conducting liquid and the bulk of the surrounding medium, and it is expressed in volts (V) or millivolts (mV). Zeta potential serves as a key indicator of the colloidal and storage stability of nanosuspensions, as it reflects the degree of electrostatic repulsion between dispersed particles. It may also provide information about the presence of materials adsorbed or coated on the particle surface.

For a nanosuspension stabilized primarily by electrostatic repulsion, a zeta potential of at least ±30 mV is generally considered necessary to ensure adequate stability. Surface charge develops mainly through the ionization of functional groups on the particle surface or the adsorption of charged species, such as surfactants. The zeta potential is measured at the hydrodynamic shear plane by evaluating the electrophoretic mobility of particles under an applied electric field. Particle mobility depends on the effective surface charge and is also influenced by the concentration of electrolytes present in the dispersion medium.

3. DIFFERENTIAL SCANNING CALORIMETRY

Differential Scanning Calorimetry (DSC) is a thermal analysis technique used to measure the difference in the amount of heat required to increase the temperature of a sample relative to a reference as a function of temperature. During the analysis, both the sample and the reference are maintained under identical temperature conditions while the temperature is increased at a controlled linear rate. One of the major advantages of DSC is that it requires only a small quantity of sample for analysis. The principle of DSC is based on the fact that when a material undergoes a physical change, such as a phase transition, melting, or crystallization, it either absorbs or releases heat. To maintain both the sample and the reference at the same temperature, the instrument measures the difference in heat flow between them. The direction and magnitude of this heat flow depend on whether the thermal event is endothermic (heat absorption) or exothermic (heat release), providing valuable information about the thermal behavior and physical properties of the sample.

4. SCANNING ELECTRON MICROSCOPY

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are widely used to characterize the particle size, shape, surface morphology, and surface topography of drug nanoparticles. These microscopic techniques provide high-resolution images that enable detailed visualization of the structural and morphological characteristics of nanosuspensions. SEM primarily examines the surface features of particles, whereas TEM provides detailed information about the internal structure and morphology of nanoparticles.

5. IN-VITRO DISSOLUTION STUDY

The dissolution rate of a nanosuspension is defined as the amount of drug that dissolves in a solvent per unit time under standardized conditions of temperature, solvent composition, and liquid–solid interface. Drug dissolution is considered a heterogeneous process involving the net transfer of solute molecules from the solid surface into the surrounding medium. The rate of dissolution is determined by the balance between the release of drug molecules from the particle surface and their deposition back onto it.

In vitro dissolution studies are an essential part of the evaluation of nanosuspensions, as they provide preliminary information on the biopharmaceutical performance of nanoformulations. For orally administered nanosuspensions, dissolution testing is generally performed using simulated gastric fluid (SGF) to mimic the conditions of the stomach and to assess the influence of gastric contents on drug dissolution. For poorly soluble drugs that are expected to dissolve predominantly in the intestine, additional studies using simulated intestinal fluid (SIF) offer valuable insights into their expected in vivo performance.

Due to their reduced particle size and increased surface area, nanosized drug particles typically exhibit a significantly faster dissolution rate than their conventional counterparts. Before conducting in vitro dissolution studies, any undissolved drug particles should be removed to ensure accurate analysis. This is commonly achieved by filtration through membranes with an appropriate pore size or by ultracentrifugation, which effectively separates undissolved particles from the dissolved drug fraction.

6. SATURATION SOLUBILITY AND DISSOLUTION VELOCITY

Saturation solubility is a critical parameter for predicting the in vivo performance of a drug, including its plasma concentration, blood profile, and overall bioavailability. Nanosuspensions significantly enhance both the saturation solubility and dissolution velocity of poorly water-soluble drugs. The reduction in particle size increases the dissolution pressure due to the enlarged surface area and higher surface energy of the particles. Even a relatively small decrease in particle size can improve saturation solubility, primarily because of changes in surface tension at the particle–liquid interface, resulting in enhanced drug solubility and improved dissolution characteristics.

CONCLUSION[2]

The present study demonstrates that nanosuspension technology is a promising strategy for improving the oral bioavailability of carbamazepine, a poorly water-soluble drug. Reduction of particle size to the nano meter range

enhanced the saturation solubility and dissolution rate, which are expected to increase gastrointestinal absorption and improve oral drug delivery. The developed carbamazepine nanosuspension exhibited satisfactory physio-chemical characteristics, indicating the suitability of the selected formulation and preparation method. Overall, the findings suggest that nanosuspension technology can effectively overcome the solubility limitations of carbamazepine and enhance its oral bioavailability, thereby improving its therapeutic potential. Further in vivo pharmacokinetic studies and long-term stability evaluations are recommended to confirm its clinical efficacy and support its successful pharmaceutical development.

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