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Research Article

Nanosuspension: An Approach to The Solubility of Poorly Soluble Drugs

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ABSTRACT

Proper drug solubility is a significant issue in pharmaceutical development that limits drug bioavailability and therapeutic efficacy. Nanosuspension has proved to be a potential approach to address these issues. This method consists of preparing the poorly soluble drug into submicron drug particles dispersed in a liquid medium resulting in improved solubility, stability, and bioavailability. The abstract summarizes the fundamentals, techniques, and opportunities associated with nanosuspension by discussing its role in enhancing the solubility of poorly soluble drugs.Drugs that are poorly soluble in water and nonaqueous media, such as carbamazepine, simvastatin, and itraconazole, fall under the biopharmaceutical classification system's BSC class II, making the issue even more complicated. In addition to addressing issues with poor solubility and bioavailability, nanosuspension modifies the pharmacokinetics of the medication, enhancing its safety and effectiveness. The benefits, challenges, and future directions of this innovative approach are also discussed.

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Introduction:

In the modern era of drugs discovery is very simple and successful at chosing any types of drugs molecules and rejecting non-promising ones with high technology and various methods of preparation[1]. Butsum of the drugs molecules may not satisfy both the therapeutical and formulation. It occurs the slow rate of solubility in the pharmaceutical industry. The drugs that are insoluble in aqueous as well as in organic solvents. The formulation of following parameters such as solubility and stability at various temperature are playing a vital role in the development of drugs formulation[2]. Up to this point over 40% of the new chemical entities being synthesized through drug discovery programs are poorly water-soluble or lipophilic compounds. Nanosuspension technology has been applied to drugs insoluble in water and organic solvents[3]. Drugs which are administered via oral route in the solid dosage from converting the larger drugs particles with isintegrated into smaller

particle or primary particle to which drug molecules are freely dissolve into gastrointestinal tract[4].

One of the most important objectives of contemporary culture and one of the main goals of drug development in recent decades has been to increase the bioavailability of poorly water-soluble medications[5].The objective of nanosuspension is to studie and investigate the possibility producing the nanosuspension to increase the dissolution rate of drugs of oral bioavailability[6].Nanosuspension can solve be different unique drug delivery issues in pharmaceutical fields.nanosuspension can be described as a biphasic, systems it can increase the tablets[7].

Need of suspension

It has Poor availability of the organism

- Lack of dose-responsibility equilibrium
- Utilizing extremely basic or acidic conditions to improve solubilization
- for both readily water-soluble and inadequately organic-soluble medications
- Need of nano suspension

Features of nanosuspensions

Particle sizes can range from 300 nm to 10 microns.

- Low levels of dose volumes in nanosuspension are 10 to 200 mg/ml
- Safety is increased due to the removal of co-solvents.
- It havea long term stability in room temperature or 5°**C** it may be upto 2 years
- Oral, respiratory, intramuscular, ID, and other routes for administering dosage forms
- It can be applied to targeted or controlled substances.

Advantages

- When it comes to poorly water-soluble medications, nanosuspension is simple to use.
- IV route administration allows for rapid tissue targeting for dissolution.
- Nanosuspensions administered orally offer enhanced and expedited bioavailability.
- Long-term physical stability because nanosupensionscontain stabilizers.
- Tablets, pellets, and hydrogels can all include nanosuspension.

Disadvantages

- Nanosuspensions can have issues regarding chemical stability, the formation of sediments and compacting
- they are heavy, and handling and transportation require extra caution
- uniform and precise dosage is impossible. Absent suspension

Methods of preparations of nanosuspension

- Mediamilling (nanocrystals)
- Precipitation methods
- Microemulsion templateDry co-grinding
- Liquid emulsion/microemulsion template
- Melt emulsification methods
- Homogenization in nonaqueous media [Nano-pure]
- Bottom-up process
- Top-down process
- Homogenization in aqueous media (Dissocubes)
- Nanojet technology

High-pressure homogenisation

A high pressure Homoginization method.Since the high pressure homogenization method reduces larger particles in the stabilizer substance to smaller ones that range in size from the nanoscale, it is thought of as a top-down strategy[8].This reversed Methods used for micronization can be classified in two types like highenergy.Low energy media mills and high pressure homogenization[9]. Due to its simplicity and suitability of the majority of poorly soluble medicines, this technique is the most widely used method for creating nanosuspension formulations[10]. This method is performed step by step. Step one dry powder of drug is prepared, step two pre suspension is pre milled at low pressure and then high pressure[11].unless the desired particle size is achieved, the final step involves 10 to 25 cycles at higher pressure[12].

Media milling

Drug synthesis frequently produces billions of poorly soluble drugs that are overlooked for further development due to solubility issues. Over the past two decades, nanolization through mechanical milling has been successfully commercialized to rescue these neglected drugs by solving solubility problems in a cost-

effective manner[13]. Both industry and academic laboratories have explored milling alone as well as combined with other techniques to reduce particle size and hasten drug dissolution kinetics[14]. Milling provides a straightforward production process and efficient means for enhancing bioavailability without chemically altering the drug itself. High-throughput screening occasionally discovers a drug with insolubility so severe that it appears useless clinically despite otherwise desirable properties[15]. Through meticulous optimization of milling conditions on a nano-scale level, scientists have occasionally been able to recover such compounds and advance them to market[16].Milling allows for a facile manufacturing process, enabling precise regulation of fabrication variables from compact to expansive amounts. It permits yielding intensely concentrated suspensions and augments steadiness of the ultimate merchandise[17]. Investigations into nano-comminuted dispersions demonstrated encouraging outcomes both in artificial and living systems, significantly multiplying bio-accessibleness. In media milling method have two methods have wet media melling methods. The high-speed rotation of the mill stirrer includes turbulent motion in the suspension[18].

Precipitation methods.

The precipitation methods is a general, methods for preparing the drug is dissolved in a solvent using this method, and the solvent is then combined with the drug, which is insoluble in the presence of a surfactant[19].Rapid supersaturation of the drug into the solution and ultrafine amorphous/crystalline form is achieved by increasing the solvent (typically water) without a gap.The nucleation and crystallization of these compounds primarily on temperature[20].

Microemulsion

Microemulsion method of nanoparticles synthesis is of great interest nowadays. Ever since the discovery of microemulsions, they have gained more and more importance both in basic science and in various industrial applications. due to their unique properties, which include their capacity to solubilize immiscible liquids, large interfacial area, thermodynamic stability, and ultralow interfacial tension.Microemulsions have several uses and applications from chemical to biological areas[21].These nanoparticles not only provide basic scientific interest, have led to significant technological uses like drug delivery, high density magnetic recording, microelectronic devices, high performance ceramic materials, and catalysts[22]. One of its general preparation techniques, the microemulsion method offers the potential to control the characteristics of the particles, such as their size control mechanisms, geometry, morphology, homogeneity, and surface area[23].

Dry grinding

However, pearl ball mill has been used for several years for preparation of nanosuspensions through wet grinding processes. Dry milling techniques can now be used to create nanosuspensions13. For this, stable nanosuspensions are made by dry grinding poorly soluble drugs with soluble polymers and copolymers, then dispersing them in a liquid medium[24]. Itoh et al. have reported the formation of colloidal particles of several poorly water-soluble drug compounds, including glibenclamide, griseofulvin, and nifedipine, using polyvinylpyrolidone as a stabilizer and sodium dodecyl sulphate as a stabilizer 23.

Homogenization in-aqueous media

Muller created the Dissocubes technology in 1999. The device has a 40 ml (for laboratory scale) volume capacity and operates at pressures between 100 and 1,500 bars (2 800 and 21 300 psi) up to 2,000 bars[25]. A high-speed stirrer must be used to prepare a pre-suspension of the micronized medication in a surfactant solution. According to Bernoulli's Law, the fluid's flow volume in a closed system remains constant across all of its cross sections. The dynamic pressure rises as the 3 cm diameter decreases to 25 μm, while the static pressure falls below the room temperature boiling point of water[26]. Water boils at room temperature as a result, and gas bubbles form that burst when the suspension exits the gap (cavitation) and the air pressure returns to normal. Temperature, the number of homogenization cycles, the homogenizer power density, and the homogenization pressure all have a significant impact on the final size of the drug nanocrystals[27]. The cost of the entire dosage form is increased by drug micronization and expensive preprocessing equipment. Several medications, including Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine, and Dexamethasone, were prepared as nanosuspensions using this technique.

Liquid emulsion(Vermaa S, Lan Y, Gokhale R, Burgessa DJ05.2006)

A One option is an emulsion, which uses a solvent that is partially water-miscible as the dispersed phase and only needs to be diluted to create nanosuspensions. The emulsion method works for medications that are soluble in volatile organic solvents or partially water miscible. Additionally, microemulsion templates can be used to create nanosuspensions. Microemulsions are dispersions of two immiscible liquids, like water and oil, that are thermodynamically stabilized by a surfactant or cosurfactant[28]. The drug can be saturated through close drug mixing and is loaded in internal phase, microemulsion, or preformed form. A griseofulvin nanosuspension is made by the microemulsion technique with water, butyl lactate, lecithin, and the sodium salt of Tauro deoxycholates[29].

Melt emulsification method(Nagaraju P, Krishnachaithanya K, Srinivas VD, Padma SV)

Melt emulsification is the primary method used to create solid lipid nanoparticles. First, Kipp and colleagues use the melt emulsification method to create ibuprofen nanosuspensions[30]. The process consists of four steps. First, the drug is added to an aqueous solution that contains a stabilizer. To create an emulsion, the solution is heated to a temperature higher than the drug's melting point and then homogenized using a high-speed homogenizer[31]. Throughout the entire process, the temperature is kept above the drug's melting point. The particles are finally precipitated by cooling the emulsion. The primary determinants of nanosuspension particle size include drug concentration, stabilizer type and concentration, cooling temperature, and homogenization procedure[32].

Homogenization in nonaqueous media

Nanosuspension is a homogenized suspension in a water-free medium. Drug suspensions in nonaqueous media are homogenized at 0°C, or occasionally lower, using a process known as "deep-freeze" homogenization. The drop of static pressure is insufficient to initiate cavitation in nanosuspension technology due to the extremely high boiling point and low vapor pressure of water, oils, and fatty acids.[33]Patents on the homogenization procedures and additional homogenization technologies.

Melt emulsification method

The melt emulsification method is a fascinating technique used for the preparation of nanosuspensions, especially for drugs with poor solubility. Here's a breakdown of the process. Drug and Stabilizer Solution: The process begins by adding the drug to an aqueous solution containing a stabilizer[34]. The stabilizer helps to prevent the particles from aggregating.Heating The mixture is then heated to a temperature that is higher than the melting point of the drug. This step ensures that the drug is in a melted state and can be easily emulsified.Homogenization: The heated solution is homogenized using a high-speed homogenizer. This step is crucial for the formation of a stable emulsion. During homogenization, the drug particles are dispersed uniformly throughout the stabilizer solution[35].Cooling The emulsion is then cooled, which leads to the precipitation of the drug particles. This step solidifies the dispersed drug particles, forming a nanosuspension.

Oral route	**Paliperidone palmitate Griseofulvin Aphidicolin Fenofibrate Rapamune**	**Anti schizophrenia Antifungal Antileishmanial Lipid lowering Immunosuppressant**	**Johnson and Johnson Boris Y. Shekunov O. Kayser SkyePharma Elan Nanosystems**
Parental Intravenous	Oridonin	Anticancer	Lei Gao
Pulmonary	Budesonide	Asthma	Jerry Z. Yang
Intrathecal Topica	Silver	Eczema	Nucryst

PHARMACEUTICAL APPLICATION OF NANOSUSPENSION

Nanosuspensions are made into a variety of dosage forms through postproduction processing. Because of its larger surface area and smaller particle size, nanosuspension accelerates the drug's absorption and rate of dissolution. The commercially available medications in the form of nanosuspensions and the methods by which they are administered

Following application are use in nanosuspension

Oral Drug Delivery

Parental Drug Delivery

Pulmonary Drug Delivery

Targeted Drug Delivery

Oral Drug Delivery

The main problems with oral drug delivery are low solubility rate, incomplete dissolution, and low efficacy. Because of their smaller particle size and significantly higher surface to volume ratio, oral nanosuspensions are especially used to increase the rate of absorption and bioavailability of medications with low solubility[36]. Compared to 20% of micronized medications, over 65% of azithromycin nanosuspensions dissolved in 5 hours. Benefits of the nanosuspension include low intersubject variability, dose proportionality, and improved oral absorption[37]. Drug nanosuspensions are easily incorporated into various dosage forms, including tablets, capsules, and fast melts, using standard manufacturing techniques. Ketoprofen's nanosuspension was successfully loaded into pellets for a 24-hour drug release.

Parental Drug Delivery

Micellar solutions, salt formation, co-solvent solubilization, cyclodextrin complexation, and, more recently, vesicular systems like liposomes and niosomes are the current parental delivery techniques[38]. However, these methods have limitations, including high manufacturing costs, parental acceptability, and solubilization capacity. The nanosuspension technology is used to get around the aforementioned difficulties. Numerous parent routes, including intraarticular, intraperitoneal, intravenous, etc., are used to administer nanosuspensions[39]. Additionally, parenteral drug administration is made more effective by nanosuspensions. It was discovered that paclitaxel nanosuspension excelled at reducing the median tumor burden. In female mice infected with Mycobacterium avium, clofazimine nanosuspension demonstrated improved stability and efficacy compared to liposomal clofazimine.In contrast to the solution formulation, Rainbow et al. showed that intravenous nanosuspension of itraconazole exhibited superior antifungal activity in rats[40].

Pulmonary Drug Delivery

Both mechanical and ultrasonic nebulizers can be used to nebulize nanosuspensions for pulmonary delivery systems. Drug nanoparticles are present in all aerosol droplets due to the large number of tiny particles. For pulmonary administration, budesonide or fluticasone has been successfully made as a nanosuspension[41]. Because of their minuscule particle size, drug aqueous suspensions are easily nebulized and administered via the pulmonary route. Nebulizers come in a variety of types that can be used to administer liquid solutions[42]. Several medications have been successfully tested via the pulmonary route, including budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, and doxorubicin[43].

Targeted drug delivery

Because of their surface properties, nanosuspensions can be used to target particular organs. Furthermore, altering the stabilizer or the in vivo behavior is straightforward[44]. The mononuclear phagocytic system will absorb the medication, allowing for region-specific delivery. If the pathogens are still intracellular, this can be used to target macrophages with antifungal, antimycobacterial, or antileishmanial medications[45]. Kayser created an aphidicolin nanosuspension that improved the drug's ability to target Leishmanian macrophages. He claimed that the drug's EC50 in nanosuspension was 0.003 µg/ml, whereas the traditional form was 0.16 µg/ml. Scholer et al. reported that an atovaquone nanosuspension improved drug targeting to the brain in the treatment of toxoplasmic encephalitis[46].

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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