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Comprehensive Review on Nanosuspension Loaded in Oral Dissolving Film-The Trending Approach to Enhance the Solubility of BCS Class-II Drugs

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Abstract

The significance and bright future of the novel dosage form are discussed in the current paper. A nanosuspension is a colloidal drug dispersion at a size smaller than one micron. Reviewing innovative elements of novel dosage form nanosuspension with oral dissolving films is the aim of this work. Pharmaceutical companies frequently employ nanotechnology-based methods to enhance their water-insoluble medications. This aims to develop nanosuspension with oral fast dissolving films which improves oral bioavailability of drugs. The use of nanosuspension in the manufacture of water-insoluble medications has grown in popularity. The review article describes the advantages, disadvantages, need, features, properties, excipients used, preparation methods, characterization and applications of nanosuspension with oral fast dissolving films.This must be stabilized by surfactants and polymers.This review summarizes the developments in poor soluble drugs. Numerous techniques, including high pressure homogenization, precipitation, solvent evaporation, and media milling, can be used to create nanosuspensions. Oral administration is the common method because of its benefits include low toxicity, low cost of manufacture, highly effective and safe and strong patient compliance. One of the special characteristics of nanosuspensions is their ability to be administered orally, pulmonary, topically, or via a combination of these routes. Oral fast dissolving films provide immediate effect in schizophrenia and dyphasic patients don't need to drink water because the films dissolve in the mouth in 30 seconds. The most crucial approach for creating fast-dissolving oral films is the solvent casting process, which uses film-forming polymers with superior drug contents, faster disintegration times, and better dissolution.

Keywords

Nanotechnology, Nanosuspension, oral fast dissolving films, solvent casting method, water insoluble drugs, enhanced bioavailability.

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INTRODUCTION

The word nano means an object which is 'dwarf'. A nanometre is a billionth of a meter or millionth of millimetre. The study of matters characteristics at the nanoscale is known as nanoscience.[1]

The field of synthesis, engineering and material use known as nanotechnology. The size of the nanoparticles varies from 1 to 100nm. Due to different properties nanoparticles must possess physical, chemical, and biological properties. Nanomaterial shows various properties like optical, magnetic, and electrical properties.[2]

TYPES OF NANOPARTICLES

1. Organic Nanoparticles

Organic nanoparticles are made up of proteins, carbohydrates, lipids and polymers. The nanoparticles are mostly non-toxic and biodegradable. Different parameters are involved to determine potential of nanoparticles such as surface morphology and stability. Common instances of organic nanoparticles include micelles, liposomes, and dendrimers. Applications involved in nanoparticles are utilized in the biomedical area for cancer treatment and tailored medication delivery.[3]

2. Carbon- based nanoparticles

Carbon atoms make up of carbon nanoparticles. Based on carbon nanoparticles shows unique properties of sp2-hybridized carbon bond with physiochemical properties at nanoscale. Examples of nanoparticles are fullerene, carbon black, nano diamond, and quantum dots. Carbon nanoparticles shows various properties like electrical conductivity, electron affinity, optical and thermal properties. Carbon based nanoparticle applications include photovoltaic devices, bioimaging, energy storage and environmental sensing. [4, 5]

3. Inorganic nanoparticles

Organic and carbon-based compounds do not make up inorganic nanoparticles. Inorganic nanoparticles can be either monometallic, bimetallic, or polymetallic according to their pure composition of metal precursors. Metal particles of nanoscale possess thermal, magnetic, and biological properties. Examples of inorganic nanoparticles are metal, ceramics and semiconductors. Inorganic nanoparticles have a wide range of uses, including chemical, biological, medicinal, and physical applications. [6, 7]

NANOSUSPENSION

The term "nanosuspension" refers to the sub-micron colloidal dispersion of discrete, biphasic, nanosized solid medication particles stabilized by surfactants for oral or topical use with smaller particle sizes, accelerating the rate of disintegration and enhancing bioavailability.[8]

Recently formulations of nanosized drugs are rapidly developing as novel drug delivery system. Pharmaceutical nanosuspension acts as equipment used to prepare medications that are insoluble in water. Nanosuspension is mainly favourable for water-insoluble compound which is having high dose and high melting point. There are different kinds of conventional methods are available like surfactant dispersion, micronization and precipitation technique. [9, 10]

Instead of using the lipidic system as a developing technique, medications that are not soluble in water or in inorganic materials are employed in nanosuspension. Nano suspension must focus on effective features like advantages, disadvantages, preparation method, benefits and applications.[11]

ADVANTAGES

1.Nanosuspension has a rapid onset of action and increases bioavailability.

2. Long-term physical stability should be preserved since stabilizers are present.

3.Simplicity of production and increase in size.

4.Medications having a high log P value must be used in the nanosuspension production process.

5.The duration of the drug's content and its absorption are improved when nanoparticles adhere to the GIT mucosa. [12, 13]

NEED OF NANOSUSPENSION

1.Need to use extreme acidic and basic condition to improve the solubility.

2.It involves poor bioavailability.

3.Lack of dose response proportionality.

4.Failed to optimize efficacy and safety.

5.Enhancement of bioavailability can be obtained by following

a) Polymorphism

b) Solid dispersion

c)Particle size reduction

d)Addition of solubilizing excipients.[14]

PREPARATION METHODS OF NANOSUSPNSION

1. BOTTOM-UP TECHNIQUE

This approach is the process of expanding a particle's size from the molecular to the nano scale to produce nanoscale particles.

Advantage:

A) The utilization of basic, inexpensive equipment.

Disadvantages:

A) It isn't utilized for the ineffectively water solvent medications.

B) Physical stability is the major challenging task.[15]

1.1 Emulsification - Solvent Evaporation Technique:
Using this technique, a drug solution that is then emulsified in a separate liquid that isn't the drug's solvent is created. Precipitation of the drug results from the solvent evaporating. Particle and crystal growth and aggregation may be controlled with a powerful shear force and high-speed stirrer.[16]

1.2 Supercritical Fluid Process:
This approach is used to produce nanoparticles from drug solutions. Many methods are employed, such as rapid expansion of supercritical solution (RESS), supercritical anti-solvent process, and precipitation with an anti-solvent process. Non-condensable fluids classified as supercritical fluids (SCF) have temperatures and pressures higher than their critical values. The SCF method has advanced recently, allowing to produce nanoparticulate suspensions featuring particles that range in size from 5 to 2000 nm. To avoid utility of this method which include surfactants in SCF CO2, high pressure and low solubility of poor soluble drugs in pharmaceutical industry.[17]

1.3 Emulsion as Templates:
Drugs with low water miscibility and solubility in volatile organic solvents are treated with emulsions as templates. The medication was combined with the organic solvent and dispersed in a surfactant-containing aqueous phase to create an emulsion. Drug particles quickly precipitated because of the organic phase evaporating, creating a nanosuspension that is stabilized by the surfactant.[18]

1.4 Micro emulsion as template:
A dispersion of two immiscible liquids, such water and oil, that is isotropically transparent and thermodynamically stable known as a micro emulsion is created by the interfacial layer formed by the co-surfactant and surfactant. The medication is either mixed in intimately to produce pre-formed micro-emulsions that are saturated with the medication. The medication is made into nanosuspension by diluting the micro-emulsion.[19]

2. TOP-DOWN TECHNIQUE
This method is the process of obtaining nanoparticles by reducing the dimensions of bigger particles.[20]

2.1 High Pressure Homogenization Technique:
Nanosuspension with poorly soluble medicines involves high pressure homogenization. Homogenization describes the force applied to a suspension under pressure using a narrow-aperture valve. Prior to incorporation, this approach demands tiny sample particles, and homogenization really takes a number of cycles.[21]

2.2 Media milling technique:
A milling shaft, recirculation chamber, and milling chamber make up the media mill. Milling media can be operated under controlled temperature. The diameter of nanosized dispersion is <200nm in 30 to 60 min. The medication acts as an energy source to impactionally split the drug's microparticulate structure into nanoparticles of milling media, which produces high energy and shear force.[22]

2.3 Combined Precipitation and Homogenization Technique:
High shear processing is combined with precipitate. It includes quickly adding medication solution to anti-solvent, which causes the combined solution to become hyper saturated. The amorphous and crystalline solids will result from this. Combining these methods may result in molecules with reduced sizes and improved stability more quickly. The primary flaw with this approach is that it may be used to tackle long-term stability issues as well as crystal development.[23]

2.4 Nanojet Technology:
Opposite stream nanotechnology is another name for it. It uses a chamber to split a suspension stream into more than two pieces, which then collide because of the enormous shear force, under high pressure and smaller particle size created. Large proportion of micro-particles, several runs through the microfluidizer, and lengthy production times are the main disadvantages of this method.[24]

EXCIPIENTS USED IN PREPARATION OF NANOSUSPENSION

1. Organic Solvent:
To prepare the nanosuspension, organic solvents are utilized. Partially water miscible solvents that are needed in the formulation include benzyl alcohol, triacetin, butyl lactate, ethyl acetate, and ethyl format and are pharmaceutical acceptable and less harmful. Other suitable water miscible solvents include menthol, ethanol, and chloroform too. Dichloromethane is an example of a typical hazardous solvent.[25]

2. Stabilizer:
The main purposes of the stabilizer are to completely wet the drug particles and stop the nanosuspension from clumping together. This stabilizer affects the nanosuspension physical stability and in-vivo behavior. Among the several stabilizer kinds that can be used are povidone, lecithin, polysorbates, and poloxomers. The stabilizing ingredient lecithin makes parental-

accepted and autoclaved nanosuspension feasible.[26]

3. Co-surfactants:

When creating a nanosuspension using a micro-emulsion, co-surfactant is essential. Investigations on co-surfactants effects on drug loading and internal phase uptake for micro-emulsions are necessary. By using ethanol and isopropanol as solubilizers and co-surfactants while making nanosuspension.[27]

4. Additional ingredients:

Additives like osmogent, polyols, buffers, and salts may be included in nanosuspension according on the requirements of the drug moiety or the mode of administration.[28]

CHARACTERIZATION OF NANOSUSPENSION

1. Particle size distribution

The particle size distribution provides an explanation for the formulation's physiochemical properties, including saturation solubility, dissolution, velocity, and physical stability. Particle sizes between 3nm to 3µm can be determined using the PCS technique. The LD technique yields a relative size distribution by measuring size ranges of around 0.05 to 80µm.

2. Dissolution rate and saturation solubility

The advantages of nanosuspension over other techniques include the ability to increase the rate of dissolution and saturation solubility. These two parameters are determined by different physiological solutions. These two parameters aid in establishing the formulation's in-vitro behavior.

3. pH value

In order to reduce pH drift and stabilize the pH, the pH of the aqueous preparation must be measured at room temperature.

4. Stability of nanosuspension

Drug crystals aggregating to form large surfaces for nanoparticles. Stabilizers are used to maintain the stability. There are several kind of stabilizers can be used as poloxamers, polysorbates, povidone and lecithin.[29, 30]

APPLICATIONS OF NANOSUSPENSION

1. Pulmonary Drug Delivery

Nanotechnology is largely used in the preparation of medications that are poorly soluble in pulmonary secretions. For lung delivery, nebulization can be performed with an ultrasonic or mechanical nebulizer. For instance, Budenoside [31]

2. Ocular Drug Delivery

Hydrophobic medicines are the primary application for this. The residency time term needs to be extended. Ibuprofen is the most effective example of ocular nanosuspension. When compared to an aqueous solution, ibuprofen's anti-inflammatory efficacy needs to be enhanced.[32]

3. Nanosuspension provide passive targeting

The versatility of nanosuspensions is attributed to their capacity to be included into a variety of dosage forms, including tablets, hydrogels, pellets, and suppositories, for different routes of administration. This is an effective tactic used in the development of a tailored medication delivery system.[33]

The nanosuspension are receptive to damage by aggregation of particles, poor bioavailability and physical stability problems. Here, we decided to convert the nanosuspension into oral fast dissolving films formulation. It facilitates the conversion of particle size to nano size and enhance bioavailability. Oral films are the novel approach which is used to stabilize and optimize nanosuspension.

ORAL FAST DISSOLVING FILMS (OFDFs)

OFDFs is the new technique for administering drugs for oral medication administration. It is defined as “ultra-thin buccal sheet that hydrate and stick to the application site quickly”. It releases medicine into the oral mucosal tissue quickly, dissolving and dissolving in about one minute. Drugs should not undergo first-pass metabolism in the oral cavity due to pre-gastric absorption. OFDFs that contain nanosuspension have better oral bioavailability. Oral dissolving films include patient-friendly features, an economical production process, extended product shelf life, and dose form optimization under the intrinsic control of GIT physiology. [34, 35]

FEATURES OF OFDFs

1.Rapid release
2.Fast disintegration
3.Excellent mucoadhesion
4.Available in various shapes and sizes [36]

IDEAL PROPERTIES OF DRUG TO BE CHOSEN

1.The medication ought to smell good.
2.It need to be able to penetrate the mucosal tissue of the mouth.
3.The medication should only be used in small doses, up to 40 mg.
4.The medication must be well-stabilized and soluble in saliva.[37]

ADVANTAGES OF OFDFs

1.OFDFs can be administered by oral route without need of water.
2.Films provide rapid disintegration and dissolution due to larger surface area in oral region.
3.Stability of OFDFs must be longer duration of time compared to others.

4. Motion sickness, allergic reaction episodes, and severe pain can all be treated with OFDFs.
5.Precise administer dose is ensured from each strip of films.[38]

DISADVANTAGES OF OFDFs

1.The main difficulty is maintaining dosage consistency.
2.High dose of medicament's is not given to patients.
3.This approach cannot be used to provide medications that irritate the mucosal surface.
4.Patients may be administered medications in tiny doses.
5.Expensive packaging of oral films.[39]

PREPARATION METHODS OF OFDFs

Preparation of OFDFs is divided into five types-
1. Semisolid casting
2. Solvent casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling

1. Semisolid casting:

The technique explains about preparation of solution take place which is known as water soluble film forming polymer solution. When making films, acid-insoluble polymers like the following are utilized: Pthalate and butyrate are the derivatives of cellulose acetic acid.[40]

2. Solvent casting:

The main procedure to make OFDFs. Vacuum is utilized for expulsion of entangled air. The arrangement is shaped and afterward cast as a film and pour the arrangement on Petri plate. The arrangement should be dried in stove up to 45-50°C then, cut into desired shape and size.[41]

3. Hot melt extrusion:

The technique talks about polymers which are having minimum molecular weight and minimal viscosity are generally utilized. Zone 1 must be processed at 80°C, zone 2 at 115°C, zone 3 at 100°C, and zone 4 at 65°C. [42]

4. Solid Dispersion Technique:

This method is characterized by the presence of hydrophilic amorphous polymers with one or more active components in the solid state. Glycol is produced below 70°C, and dies are used to form the solid dispersion into films.[43]

5. Rolling method:

This technique may be used to prepare the addition, the active pre-mix, and the film preparation that follows. Once the proper amount of medication has been added to the mixer, combine it with the pre-mix to create a homogeneous matrix.[44]

EXCIPIENTS USED IN PREPARATION OF OFDFs

1. Plasticizer

Plasticizers are used in films to enhance their tensile strength, oral film enlargement, and decreased brittleness. Polymer and drug solvent utilized must be compatible with the plasticizer. Inaccurate plasticizer usage results in film breaking, cracking, and peeling. Examples of plasticizers are castor oil, triacetin, mannitol, glycerine, polyethylene glycol, propylene glycol, glycerol, dimethyl, trimethyl citrate, and acetyl citrate.[45]

2. Film Forming Polymers

The oral cavity uses both synthetic and natural polymers. In comparison to synthetic polymers, natural polymers are less harmful, safer, and have less adverse effects. The water-soluble polymers provide the film **a nice mouthfeel and quick oral cavity dissolution.[46]**

3. Flavouring agents

These agents are the ingredients which are mixed to give flavours in the preparation. Flavours must be chosen according to the kind of medication that is present in the preparation. The several flavours involved are strawberry, raspberry, mint, and orange flavour. Flavouring agents must be extracted from different source like plants, leaves, flowers and fruits. Flavouring agents shows good compatibility with drug and other ingredients.[47]

4. Super disintegrants

Super disintegrants are used to mix in the oral dissolving film preparation which provide rapid disintegration, water absorption and swelling properties. Powerful interaction with saliva is essential for disintegration. Sodium starch glycolate, cross povidone, polyacrylic potassium are some super disintegrants which are used in formulation of film.[48]

CHARACTERIZATION OF OFDFs

1. Thickness:

The thickness measurement is required which associated with the quantity of drug in oral dissolving film. The acceptable thickness is essential for comfortable application of film.[49]

2. Folding Endurance:

Film is folding repeatedly at the same location until its filling breaks to assess the folding endurance. The no. of folds material can withstand before breaking, and its 300-fold folding endurance, which demonstrates exceptional flexibility.[50]

3. Determination of pH value:

It is used to calculate pH in relation to a drug's fast release and solubility or dispersion in the oral cavity. Pour this solution into the petri dish and let it there until the gel solidifies at a standard temperature. The

pH value was determined by touching film using the pH range of 1 to 11, after which the pH paper begins to change colour.[51]

4. Determination of swelling degrees:

The polymeric film's ability to swell is crucial for figuring out how much water it can absorb and for gaining an understanding of its water resistance. Abruptly, a particular number of films are chosen, then each film is individually measured and weighed at several times until the weight achieves the target.[52]

5. Content Uniformity:

The process of determining the standard pharmacopoeia for a certain API is called content uniformity. Each strip API content was estimated to ascertain the content homogeneity. The range for content homogeneity is 85–115%.[53]

6. Dissolution Test:

Dissolution test is carried out employing a standard paddle and basket device. The sink conditions and API dosage will determine the dissolving medium. A difficult dissolving test is required because drugs tend to float in the dissolution media when a paddle equipment is utilized.[54]

7. Disintegration test:

When the film comes into touch with saliva in the oral cavity, this test reveals how quickly it dissolves. To find out how long films take to disintegrate, utilize the disintegration test instrument. It must begin with the movie breaking up in 5 to 30seconds.[55]

APPLICATIONS OF ORAL FAST DISSOLVING FILMS

1. Dissolvable films can be used topically to treat wounds using antibacterial and analgesic agents.
2. To increase the bioavailability of poorly bio-available medications, oral films are utilized.
3. Oral films are used locally to alleviate pain, allergies, problems like sleeping, and central nervous system disorders.
4. Sensitive compounds are integrated into oral dissolving films to allow for regulated release in biological fluid exposure and to provide a synchronized response with a diagnostic equipment.[56]

CONCLUSION AND FUTURE ASPECTS

A novel and practically viable solution to the issue of water-insoluble pharmaceuticals with low solubility and low bioavailability is the use of nanosuspensions. As considering that aggregation might harm the nanosuspension. OFDFs are the novel approach which is used to stabilization and optimized nanosuspension. The conversion of nanosuspension to OFDFs formulation which support in keeping the nanoscale particle size. The OFDFs an ideal dosage form which commonly used for children, geriatric, and paediatric patients. They must show good stability among dosage form. Production techniques are employed in the large-scale manufacturing of nanosuspensions which should be effective in nature. Formulation of film employed with appropriate physical and mechanical properties. Both films additionally nanosuspension are simultaneously dependent on ingredients used in formulation. It provides details on how to conduct evaluation exams. Finally concludes on how well oral dissolving films are being utilized by patients to get instant relief from illnesses and ailments.

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