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Redefining Drug Delivery: Nanosuspension-Based Oral Film

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Abstract

Nanoparticles have been extensively used over the past few decades, as they can significantly improve various drugs' pharmacodynamic and pharmacokinetic properties. This work explains the application of nanosuspensions in oral films. Nanosuspensions are a novel drug delivery system that enhances the solubility and, consequently, the bioavailability of poorly water-soluble drugs. Incorporating nanoparticles into oral films allows for a rapid onset of action and helps bypass first-pass metabolism. Nanosuspensions can be prepared using several methods, including wet milling, high-pressure homogenization, emulsion-solvent evaporation, melt emulsification, and supercritical fluid techniques.

Keywords : Oral films, Nanosuspension, Glimepiride, HPMC E15, PVA, Plasticizer, Solubility enhancement, Bioavailability, Mucoadhesive, Solid dispersion, Polymeric film, Surfactant, Nanoparticles, Solvent casting, Solvent evaporation

Nanosuspension

Lately, nanosuspensions have become a notably exciting alternative. A pharmaceutical nanosuspension is defined as a suspension of tiny solid drug particles that are evenly distributed in a water-based medium, intended for administration through multiple routes such as oral, topical, parenteral, and pulmonary. [1] Nanosuspensions often demonstrate significant improvements in saturation solubility by enhancing the surface area accessible for dissolution. Numerous studies have shown the creation of nanosuspensions with elevated drug loading, improved dissolution rates, and enhanced bioavailability. [2]

The primary objectives in developing nanosuspensions as a drug delivery system include controlling particle size, modifying surface characteristics, and regulating the release of active pharmacological agents to ensure targeted drug action at an optimal therapeutic rate and dosage plan. Typically, the size distribution of solid particles in nanosuspensions is under one micron, with an average size between 200 and 600 nm. In recent years, nanosuspensions have been widely utilized for oral, injectable, inhalation, and intradermal drug delivery methods. [3]

Nanotechnology offers solutions to the challenges presented by traditional methods for improving solubility and bioavailability. Nanosuspension is particularly advantageous for compounds that do not dissolve in water (but are soluble in oil) and possess high log P values, elevated melting points, and substantial dosages. This technology can also be utilized for drugs that are insoluble in both water and organic solvents. Various hydrophobic drugs, including naproxen, clofazimine, buparvaquone, nimesulide, mitotane, amphotericin, omeprazole, nifedipine, and spironolactone, can be formulated into nanosuspensions. [4]

Benefits of Nanosuspension:

a. Reduced tissue irritation due to subcutaneous or intramuscular administration.

b. Enhanced dissolution rate and solubility of the drug.

c. Extended physical stability over time.

d. Increased drug loading capacity can be achieved.

e. Improved bioavailability for ocular administration and inhalation drug delivery.

f. Nanosuspensions can be utilized in creams, gels, pellets, and tablets.

Disadvantages of Nanosuspension:

a. Sedimentation and compaction may cause complications.
b. Inappropriate portion.
c. It is impossible to produce a consistent and accurate dose.
d. It is significant enough to warrant consideration during handling and transportation.
e. Only in a suspended state can uniform and explicit doses be obtained. [5]

Oral Films

Oral drug administration has transitioned from traditional dosage forms to modified release dosage forms, and oral disintegrating tablets to oral disintegrating films. Oral disintegrating strip or film may be defined as: "A dosage that employs a water dissolving polymer which allows the dosage form to quickly hydrate by saliva, adhere to the mucosa, and disintegrates within a few seconds, dissolves and releases medication for Oromucosal absorption when placed on the tongue or oral cavity." [6]

When placed on the tongue, orally disintegrating films (ODFs) quickly hydrate by soaking saliva after disintegration and/or dissolution, which releases the active pharmacological substance from the dosage form. ODFs are a type of formulation that is often manufactured using hydrophilic polymers to enable fast dissolving upon contact with saliva. [7]

Many pediatric and geriatric patients refuse to consume these solid preparations for fear of choking. Although oral disintegrating tablets have the advantage of being administered without choking and disintegrating quickly, the disintegrated elements in them are insoluble and stay unchanged until swallowed. In such instances, the formation of a fast-dissolving film will be beneficial. [8]

Advantages:

a. Convenient transportation.

b. Easy swallowing for old and young people.

c. No water is needed for administration, making it easier for dysphasic patients who have difficulty swallowing pills or capsules.

d. Improved bioavailability by eliminating the hepatic first-pass effect, resulting in faster and more stable action. [9]

Disadvantages:

a. Drugs unstable at buccal pH are unsuitable for administration.

b. It is impossible to incorporate high-dose drugs into the film.

c. Drugs that cause mucosal irritation cannot be used via this method.

d. Due to its fragile nature and sensitivity to water, this film requires specific packaging. [10]

Materials and methods

Methods of nanosuspension preparation.

Precipitation Method:

For many years, precipitation has been utilized to create submicron particles, particularly over the past decade for poorly soluble drugs. Usually, the drug is initially dissolved in a solvent. Next, this solution is combined with a miscible antisolvent along with surfactants. The rapid introduction of the drug solution into the antisolvent (which is typically water) results in a quick supersaturation of the drug in the solution, leading to the formation of ultrafine crystalline or amorphous drug solids. This method consists of two stages: the formation of nuclei and the growth of crystals. Achieving a stable suspension with the smallest particle size requires a high rate of nucleation accompanied by a low rate of growth. The rates of both processes are influenced by temperature: the ideal temperature for nucleation may be lower than that for crystal growth, allowing for temperature optimization. [11]

Media milling:

The method was initially introduced by Liversidge et al. In this approach, nanosuspensions are created using high-shear media mills or pearl mills. The media mill is composed of a milling chamber, a milling shaft, and a recirculation chamber. The milling medium is made of glass, zirconium oxide, or highly crosslinked polystyrene resin. The milling chamber is filled with the milling media, water, the drug, and a stabilizer, after which the milling media or pearls are rotated at a very high shear rate. The milling process is conducted under controlled temperature conditions. The high energy and shear forces produced by the collision of the milling media with the drug supply the necessary energy to fragment the microparticulate drug into nanosized particles. The media milling technique can effectively process both micronized and non-micronized drug crystals. After the formulation and process have been optimized, minimal batch-to-batch variability is observed in the quality of the dispersion. [4]

High-pressure homogenization:

The homogenization process involves forcing the suspension through a valve with a small opening under pressure. As the suspension moves through the nozzle, the static pressure decreases, causing water to vaporize and resulting in the formation of gas bubbles. When these bubbles exit the nozzle, they implode as the suspension returns to atmospheric pressure, which reduces the particle size. To achieve particle size reduction into the nanoscale range, multiple passes or cycles through the homogenizer are required. Key considerations in this process include the hardness of the drug, the desired average particle size, and the level of homogeneity needed. This method can be applied to both diluted and concentrated solutions, allowing for the establishment of aseptic conditions. [1]

Solvent Evaporation Technique:

This method entails preparing a drug solution, which is then emulsified in a second liquid that does not dissolve the drug. The evaporation of the solvent results in the precipitation of the drug. The control of crystal growth and particle aggregation can be achieved by generating high shear forces with a high-speed stirrer. Successful formulations of nanosuspension drugs have been documented for griseofulvin, diclofenac, acyclovir, and mitotane. [3]

Dry-co-Grinding:

Grinding is the primary technique used in this method, which helps enhance the surface properties of drugs. It is favored for being simple, cost-effective, and not requiring any organic solvents. By co-grinding two different substances, the physicochemical properties and dissolution rates of poorly water-soluble drugs can be improved. [12]

Methods of oral film preparation

Solvent casting method:

Solvent casting is the most prevalent technique for creating orally disintegrating films (ODFs) using water-soluble excipients, polymers, and drugs that are dissolved in de-ionized water; as a result, a uniform mixture is achieved by employing high shear forces produced by a shear processor. Next, the resulting solution is transferred onto a Petri dish, and the solvent is allowed to evaporate by being exposed to elevated temperatures to ensure high-quality films. The choice of active pharmaceutical ingredient (API) to be included in the ODF influences the selection of an appropriate solvent based on the critical physicochemical characteristics of the API, such as melting point, sensitivity to shear, and polymorphic form. The compatibility of the drug with the solvent and other excipients is also taken into account before the formulation is finalized. [7]

Semi-solid Casting:

To begin with, a solution of a water-soluble film-forming polymer is created using a semi-solid casting technique. Next, this solution is combined with an insoluble polymer such as cellulose acetate butyrate or cellulose acetate phthalate that has been prepared in sodium or ammonium hydroxide. Following that, the precise amount of plasticizer is incorporated to form a gel mass. Finally, the gel mass is cast into films utilizing heat-controlled drums, resulting in a film thickness of approximately 0.015 to 0.05. [6]

Hot melt extrusion:

Hot melt extrusion is a continuous manufacturing process that consists of several key components: a feeding hopper, barrels, single or twin screws, a die, a screw-driving unit, and downstream processing equipment. During this process, a mixture of the drug, polymer, and plasticizers is introduced into the barrel from the hopper. The required heat to melt or fuse these materials is produced through friction as the substances are sheared between the rotating screws and the barrel walls, along with the assistance of electric or liquid heaters. This technique enables thorough mixing and agitation, resulting in both distributive and dispersive mixing of drug particles throughout the molten polymer. Consequently, hot melt extrusion achieves a more uniform molecular dispersion of the particles. [13]

Rolling method:

In the rolling process, a solution or suspension containing a drug is rolled onto a substrate. The primary components of the solvent are water and a mixture of alcohol and water. Once it has dried on the rollers, the film is cut into the preferred shapes and sizes. Additional ingredients, including the active compound, are solubilized in a small amount of aqueous solvent using a high-shear mixer. Water-soluble hydrocolloids are blended into the water to form a uniform viscous solution. [9]

Formulation considerations of nanosuspension

Stabilizer

The primary function of a stabilizer is to thoroughly wet the drug particles and to prevent Ostwald ripening and the agglomeration of nanosuspensions. This ensures a physically stable formulation by providing either a steric or ionic barrier. The type and amount of stabilizer used significantly impact the physical stability and in vivo behavior of the nanosuspension. Common stabilizers include poloxamers, polysorbate, cellulosics, povidones, and lecithins. If the goal is to develop a parenterally acceptable and autoclavable nanosuspension, lecithin is the stabilizer of choice. [4]

Solvents

Organic solvents, including ethanol, ethyl formate, ethyl acetate, and propylene carbonate, are used in formulations because they either dissolve completely in water or have partial water solubility. These solvents are favored because of their reduced toxicity risks and the ease with which they can be eliminated from the formulation. [1]

Surfactants10

Surfactants are added to enhance dispersion by lowering interfacial tension. They also function as wetting or deflocculating agents, such as Tweens and Spans, which are commonly used surfactants. [14]

Co-surfactants

Choosing the right co-surfactant is essential when utilizing microemulsions to prepare nanosuspensions. Because co-surfactants can have a major impact on phase behavior, it's important to investigate how they affect the uptake of the internal phase for a specific microemulsion formulation as well as drug loading. For example, Transcutol, glycofurol, and isopropanol can be safely employed as co-surfactants. [15]

Other Additives

Various kinds of additives are employed in the formulation of nanosuspensions, including osmogents, cryoprotectants, polyols, buffers, and salts, which are chosen based on the route of administration or the characteristics of the drug molecule. [16]

Formulation considerations of oral film

Active pharmaceutical ingredient

A typical film formulation contains 1-25% w/w of the drug. Fast-dissolving films can deliver various active pharmaceutical ingredients, with small-dose molecules being ideal candidates. Multivitamins can be incorporated up to 10% w/w, dissolving in less than 60 seconds. Micronized active ingredients enhance film texture and improve dissolution and uniformity. Many active ingredients have a bitter taste, making formulations unpalatable, especially for children. To address this, it's crucial to mask the taste before incorporation. Simple methods include mixing bitter ingredients with tastier excipients, known as the obscuration technique. [10]

Film-forming polymer

Various polymers can be utilized to create fast-dissolving films (FDF) or oral strips (OS). To achieve the required characteristics, polymers may be employed individually or in mixtures. The resulting film should possess sufficient strength to prevent damage during handling or transport, while also being thin, flexible, and capable of dissolving within seconds upon contact with saliva for rapid drug delivery to the oral cavity. Since the polymer used for strip formation is the key and primary element of the OS, it should typically comprise at least 45% w/w of the total weight of the dry OS. [13]

Plasticizers

Typically, including plasticizers in formulations enhances mechanical properties like tensile strength and percent elongation. The typical concentration of plasticizer varies between 0% and 20% w/w. Examples of commonly used plasticizers include PEG, glycerol, diethyl phthalate, triethyl citrate, and tributyl citrate. [7]

EVALUATION OF NANOSUSPENSION

Viscosity Measurement

The Brookfield rotary viscometer is utilized to measure the viscosity of lipid-based formulations with various compositions across different shear rates and temperatures. The instrument's sample room should be kept at 37ºC using a thermal bath, and the samples intended for measurement must be placed in it. [15]

In-vitro Evaluations

Numerous standardized in-vitro parameters for nanosuspensions include color, odor, particle presence and impurities, taste, pH, viscosity, contact angle, particle size distribution (polydispersity index), and stability during storage. Additionally, they encompass zeta potential, electrokinetic properties, crystal morphology, drug content estimation, saturation solubility, dissolution velocity, osmolarity, drug entrapment efficiency, and density measurements. [3]

Zeta Potential

Zeta potential indicates the nature and strength of the surface charge on dispersed nanoparticles in a nanosuspension. It helps determine their interaction with biological environments and their electrostatic relationships with bioactive compounds. Defined as the voltage difference between solid particle surfaces in a conductive liquid and the liquid's bulk, zeta potential is measured in volts (V) or millivolts. It can predict the colloidal stability of nanoparticles and provide insights into the materials encapsulated or coated on their surfaces. [17]

Particle Morphology and Crystalline State

The amorphous high-energy form of medications is thermodynamically unstable and alters over time during storage. Its enhanced dissolution characteristics contribute to a higher bioavailability, making it the preferred choice. Before the formulation of nanosuspensions, it is essential to convert the amorphous state into a crystalline one. X-ray powder diffraction is utilized to examine the proportions of these forms, as each crystalline configuration shows a distinct diffraction pattern. Nonetheless, minor differences may occur, as demonstrated by Tian's research on carbamazepine. A more recent technique, terahertz spectroscopy, assesses crystalline forms, with each polymorph having a unique terahertz absorption spectrum. Differential Scanning Calorimetry (DSC) is frequently employed to identify crystalline and amorphous components by monitoring changes in temperature and heat flow during transitions. For a thorough analysis, DSC can be paired with XRPD. [18]

Saturation solubility and dissolution velocity

Nanosuspension elevates the rate of dissolution and the saturation solubility. Reducing particle size increases dissolution pressure. A rise in solubility that happens with a moderate reduction in particle size may primarily be attributed to a shift in surface tension, causing an increase in saturation solubility. [4]

EVALUATION OF ORAL FILM

Weight Uniformity:

Films can be measured on an analytical balance to determine the average weight for each one. This process is useful for ensuring that a film contains the appropriate amounts of excipients and drugs.

Thickness:

The film's thickness can be assessed using a micrometer screw gauge at various strategic points (a minimum of 5 locations). This is crucial for evaluating the uniformity of the film's thickness, as it directly impacts the accuracy of the dosage in the film. [15]

Determination of swelling degrees:

The capacity of the polymeric film to expand is essential for determining its water absorption capabilities and for understanding its resistance to water. Suddenly, a specific quantity of films is selected, and then each film is measured and weighed multiple times until the weight reaches the desired target. [19]

Scanning electron microscopy:

Scanning electron microscopy serves as a key technique for examining the surface structure of the film composed of various excipients and the drug. A sample of the film is collected and positioned in the sample holder, and photomicrographs are captured at ×1000 magnification using a tungsten filament as the electron source. [20]

Surface Ph:

The surface pH of a fast-dissolving strip needs to be measured to assess the potential for any adverse effects in vivo. An acidic or basic pH could lead to irritation of the oral mucosa; hence, it should be maintained near the pH level of saliva, which ranges from 6.2 to 7.4. [13]

Dissolution test:

Dissolution testing can be carried out using either standard paddle or basket devices. The selection of the dissolution medium relies on the sink condition and the high dosage of the active ingredient. When the paddle apparatus is utilized, there can be issues with the dissolution test due to the tendency of the strip to float in the dissolution medium. [6]

In vitro drug release studies:

In this technique, a piece of film measuring 2x2 cm is utilized. This film is positioned within a stainless-steel wire mesh that has a sieve opening of 700 µm. The mesh is then submerged in a dissolution medium consisting of approximately 300 ml of PBS at pH 6.8. The dissolution procedure is performed using a six-stage paddle apparatus set at 37 °C and a speed of 50 rpm. At various time intervals of 0, 1, 2, 3, 4, 5, 10, 15, and 30 minutes, 5 ml of the sample is removed. Following the withdrawal of the sample, a new 5 ml of blank solution is introduced into the apparatus to sustain sink conditions. [21]

Stability study:

The study emphasizes the significance of physical stability for pharmaceutical products and outlines methods for evaluating it in tablets, capsules, suspensions, emulsions, solutions, and ointments. The selected formulations were enclosed in aluminum foil to ensure a complete and secure covering of the film. Subsequently, they were stored at 40°C with 75% relative humidity for a month, specifically for 4 to 8 weeks in a humid environment. At specified intervals, their physical properties and in vitro drug release were evaluated. Additionally, stability studies for three months were performed in a humidity chamber maintained at 35°C with 65% relative humidity for all batches. After three months, the films were examined for drug content, disintegration rate, and physical appearance. [9]

List of some work on Nanosuspension-based oral film

Class of Drug	API	Method used	Advantage
Antiviral	Herperitone	High-pressure Homogenization	Enhanced dissolution rate and oral bioavailability of the poorly water-soluble drugs
Antibiotics	Cefpodoxime proxetil		Improved oral bioavailability
Antinauseating agent	Domperidone	(high-speed homogenizer)	Higher permeability and dissolution than normal coarse particles
Antihypertensive	Carvedilol	solidified hydrogel	Fast in vitro release and enhanced in vivo bioavailability
Antihypertensive and antianginal	Lercanidipine Hydrochloride	evaporative antisolvent precipitation method)	Superior dissolution, increased permeability
Antiepileptic	Midazolam Hydrochloride	Ultrasonic method	Increased AUC, Cmax, and decreased Tmax
Antidiabetics	Glimepiride	solvent casting	Improved bioavailability and stability

Conclusion

Nanosuspensions are innovative pharmaceutical formulations of tiny solid drug particles in a water-based medium, suitable for multiple administration routes. They improve saturation solubility and bioavailability by increasing surface area and enhancing drug loading and dissolution rates. Key objectives include controlling particle size (under one micron) and regulating drug release. Nanosuspensions are particularly beneficial for hydrophobic compounds with poor solubility and can effectively encapsulate a variety of insoluble drugs. Oral drug administration has evolved to include modified-release dosage forms and oral disintegrating films (ODFs). ODFs are defined as dosage forms that use water-dissolving polymers, allowing them to quickly hydrate and disintegrate in the mouth, releasing medication for Oromucosal absorption. They are made with hydrophilic polymers that facilitate rapid dissolution upon contact with saliva. This formulation is particularly beneficial for pediatric and geriatric patients who may refuse solid preparations due to choking fears, as ODFs disintegrate quickly without producing insoluble remnants.

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