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Nanosuspension: A favourable viewpoint for drug delivery of poorly soluble drugs

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Abstract
Many recently produced medications have weak solubility, which causes significant issues during formulation and exhibits poor bioavailability. The issue is significantly more complicated for medications that fall under BCS Class II. Nanotechnology is utilised to increase the solubility and bioavailability of poorly soluble medications in order to solve these issues. The definition of nanotechnology is the use of science and engineering at the Nano scale, or 10-9 metres. Nanotechnology includes Nanosuspensions. As defined by surfactants and polymers, Nanosuspensions are submicron colloidal dispersions of pharmaceutical active component particles in a liquid phase, below 1 m in size, without any matrix material. Nanosuspensions are different from nanoparticles and solid lipid nanoparticles in that they are lipid carriers of medications whereas nanoparticles are polymeric colloidal carriers of pharmaceuticals. All medications that are insoluble in water may be prepared as Nanosuspension, which is a straightforward process. Wet mill, high pressure homogenizer, emulsion solvent evaporation, melt emulsification, and supercritical fluid processes are used to create Nanosuspensions. Delivery methods for Nanosuspensions include oral, parenteral, pulmonary, and ocular. By including Nanosuspensions in mucoadhesive hydrogels and ocular inserts, tailored medication delivery is also possible. In addition to addressing the issues of low solubility and bioavailability, Nanosuspensions also change the pharmacokinetics of the medicine, enhancing its safety and effectiveness.

Keywords: Nanoparticles, Liquid, Surfactants, Stabilizers, Top-down, Bottom-up

1. Introduction
Particles in an aqueous medium, stabilised by surfactants for either parenteral or pulmonary administration or oral and topical usage, with decreased particle size, increasing dissolving rate and resulting in better bioavailability [1]. The typical particle size ranges from 200 to 600 nm [2]. A faster rate of dissolving compared to a product that has been micronized. More than 40% of medicines have low water solubility, making traditional drug formulation difficult. Due to the vapour pressure effect, Nano sized particles enhance solution velocity saturation solubility.

Additionally, the drug nanoparticles' surface diffusional distance is reduced, resulting in an enhanced concentration gradient and a considerably more noticeable dose form. The issue is especially challenging for medications in class that are poorly soluble in organic and aqueous environments. In addition to addressing the issues of low solubility and bioavailability, Nanosuspensions also change the pharmacokinetics of the medicine, enhancing its safety and effectiveness [2].

One definition of a pharmaceutical Nanosuspension is a very finely colloid, biphasic, dispersed, solid drug particles in aqueous vehicle, size below 1 m, without any matrix material, stabilised by surfactants & polymers, prepared by suitable methods for drug delivery applications, through various routes of administration like oral, topical, parenteral, ocular & pulmonary routes.

With the use of Nanosuspension technology, the medicine is kept in a crystalline condition with smaller particles, which increases the pace at which it dissolves and, as a result, improves bioavailability. The pharmaceutical industry accepts either crystalline or amorphous drug states for substances contained inside Nanosuspensions. Brick dust molecules can be effectively formulated in nana suspensions for enhanced solubility & excellent absorption [3].

Nanosuspension has been shown to improve absorption and adsorption, which may enable dose reduction for convectional oral dosage forms. According to the Nernst-Brunner and Levich adaptation of the Noyes-Whitney equation, reducing the size of drug particles

increases surface area, which in turn affects the rate of dissolution. Additionally, the Ostwald-Freundlich equation's explanation of particle size decrease caused by a rise in dissolving pressure hypothesises saturation solubility become greater [3].

Depending on the production process, the crystalline structure of the drug particles may also change. Greater concentrations of the amorphous drug component may result in higher saturation solubility. Additionally, nanoparticles have been said to be generally sticky to tissue [3].

1.1 Advantages

- Generally applicable to most drugs & simplicity.
- Can be applied for poorly water-soluble drugs.
- Can be given by any route.
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Rapid dissolution & tissue targeting by IV route of administration.
- Oral administration provides rapid onset, reduced fed/fasted ratio & improved bioavailability.
- Occular administration & inhalation delivery provides higher bioavailability & more consistent dosing.
- Due to reduced particle size of Nanosuspension, the absorption form absorption window can be enhanced.
- Improvement in biological performance due to high dissolution rate &saturation solubility of the drugs.
- Long-term physical stability (due to absence of Ostwald ripening).
- Nanosuspensions can be incorporated in tablets, pellets, hydrogel & suppositories are suitable for various routes of administration.
- Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure & higher solubility.
- Surface-modification of Nanosuspension possible, for site specific delivery [4].

1.2 Disadvantages

- Physical stability, sedimentation & compaction can cause problems.
- It is bulky sufficient care must be taken during handling & transport.
- Improper dose [4].

2. Nanosuspension

The chart describes the method of preparation, dosage forms, Components and drug delivery system for Nanosuspensions.

2.1 Method of Preparation

The method of preparation of Nanosuspension include following methods:

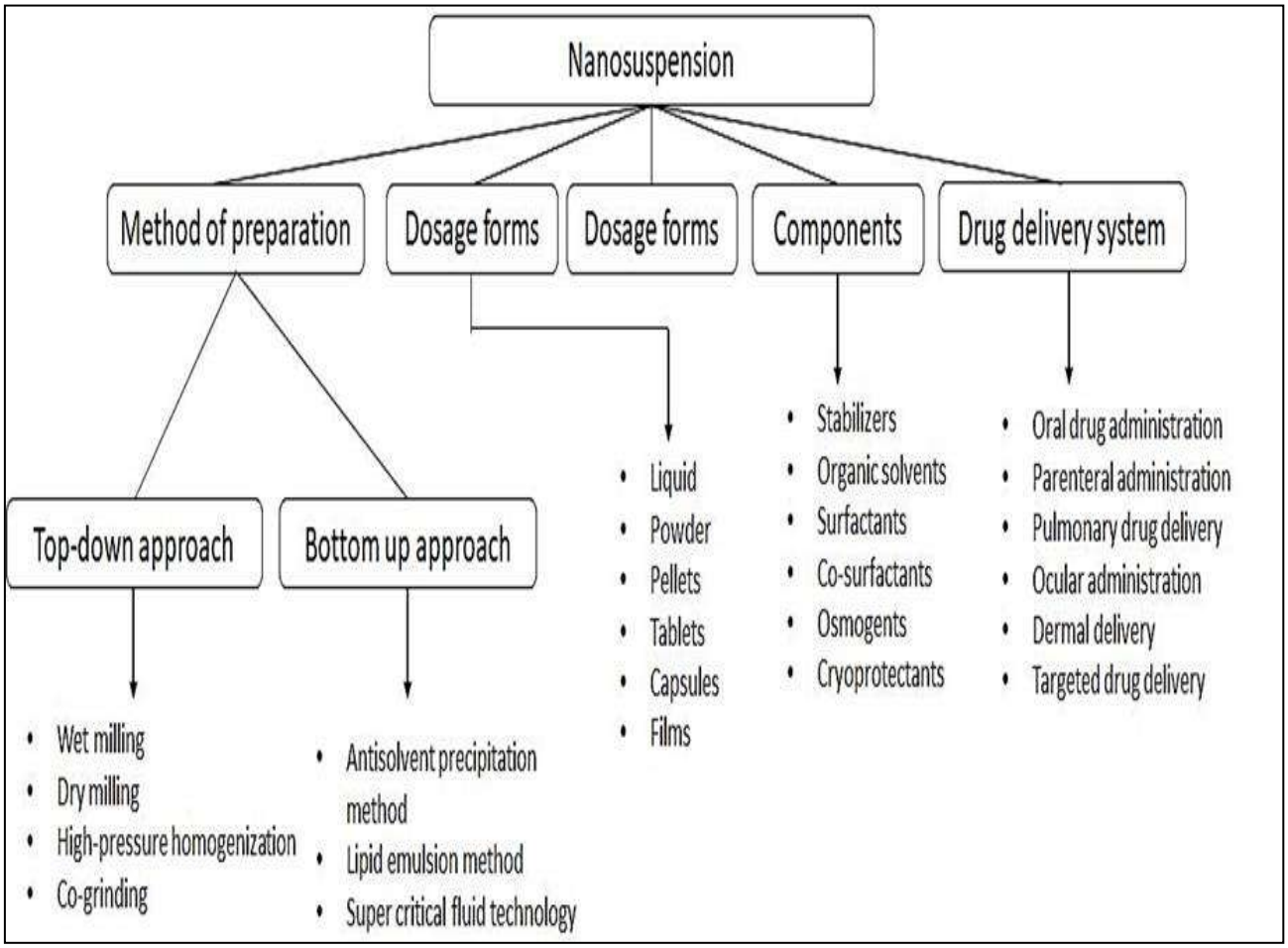

Fig 2: The method of preparation of Nanosuspension

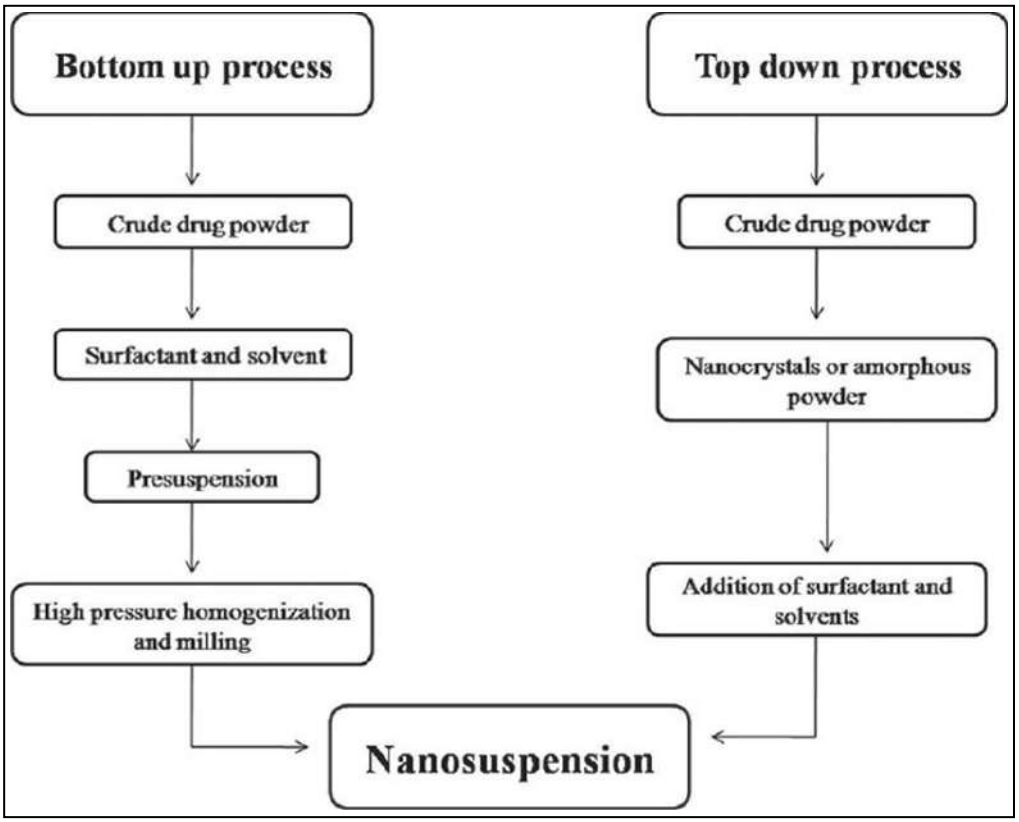

Fig 2: Nanosuspension

2.2.1 Top-Down Method

The top down process involves the disintegration from large particles, micro particles to Nano sized particles.

The techniques used area's follows:

- Wet milling method.
- Dry milling method.
- High pressure homogenization.
- Co-grinding method.

Wet milling method

Liver sedge, *et al.* invented the wet milling method [6, 7]. This approach creates Nanosuspension using high-shear media mills or pearl mills. A milling chamber, a milling shaft, and a recirculation chamber make up the wet mill (Figure 1). Aluminium oxide ceramic sintered in a furnace or strongly cross-linked polystyrene resin surrounds the milling medium or balls. The wet media, which are pearls, spin at a very high shear rate while being supplied into the milling chamber in the form of an aqueous solution of the medication and stabiliser. You can do this technique in a temperature-controlled environment. Nanoparticles are produced by the friction and collisions between drug particles and pearls. The benefits of wet milling are its simplicity in scaling up and its low batch-to-batch variability. The method's drawback is the pearls' erosion, which contaminates the finished product and causes issues when administered [8].

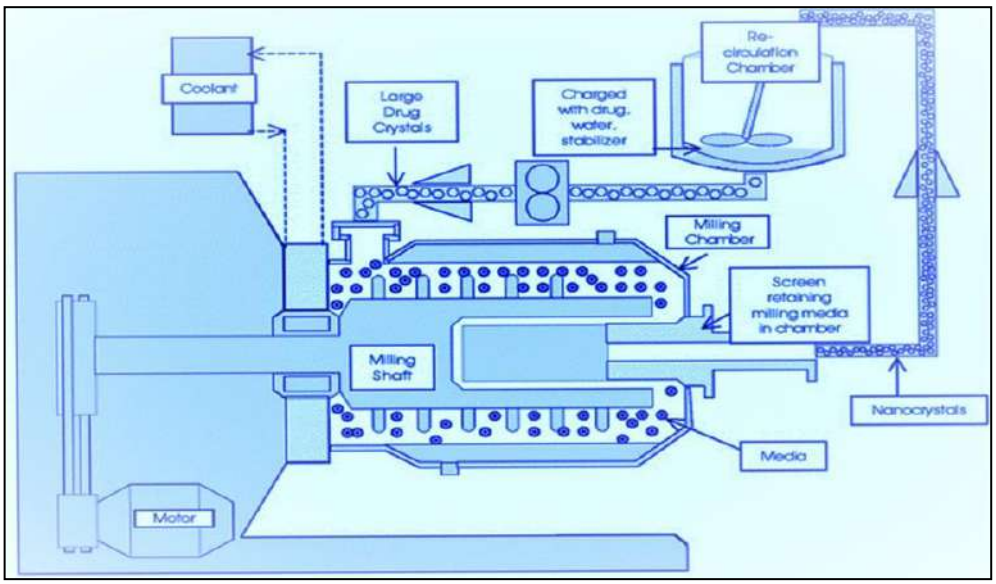

Fig 3: Diagram of media milling method

High Pressure Homogenization [HPH]

The process of HPH is frequently used to create Nanosuspensions of medicines with low solubility [9-14].

HPHG is often classified into two groups:

1. Disso cubes (homogenization in aqueous media),
2. Nano pure (homogenization in water-free media or water mixtures).

Disso cubes operate at high pressures of up to 1500 bar, via a very small hole, where a suspension travels. The boiling point of water is lowered until it approaches room temperature as a result of this decrease in static force and increase in dynamic force. Gas bubbles are created when water boils because it may do so at normal temperature. When the suspension exits the gap and air pressure is re-established, the gas bubbles rupture. This condition is referred to as cavitation. The interaction of cavitation, high shear, and collisions causes the drug micro particles to disintegrate into Nano sized particles [15]. The number of homogenization cycles, drug hardness, and temperature all affect the parameters of the resultant Nanosuspensions when processing thermo sensitive pharmaceuticals, including particle size.

In comparison to media milling, this method has less noticeable metal contamination caused by erosion. A safe method for creating Nanosuspensions is high pressure homogenization. Under processing conditions of 20 cycles and 1500 bar pressure, less than 1 ppm metal contaminations were found [15-17].

The primary drawbacks of this approach are the several cycles of homogenization and the requirement for pre-treatment in order to obtain micro particles before beginning the homogenization process [18, 19]. For a variety of uses, Liquid Nanosuspensions are dispersed in non-aqueous liquids or media with decreased water content, such as dispersing medication Nano crystals in low molecular weight polyethylene glycol or oil. The pressure decrease is insufficient to cause cavitation because of the high boiling point and low vapour pressure of oily fatty acids and oils, hence it has no impact on this process.

The Nano pure procedure, also known as the "deep-freeze" method, is carried out at low temperature in order to make up for an inadequate reduction in pressure [20].

Co-Grinded

For a long time, pearl ball mills have been used to manufacture Nanosuspensions using wet grinding methods. Dry milling techniques may now be used to create Nanosuspensions. After dispersion in a liquid media, poorly soluble drugs are dry ground with soluble copolymers and polymers to create stable Nanosuspensions. Itoh *et al.* have demonstrated how sodium dodecyl sulphate and polyvinylpyrrolidone, which act as stabilisers, cause numerous weakly water-soluble medications, such as nifedipine, griseofulvin, and glibenclamide, to form colloidal particles [21-23].

2.2.2 Bottom-Up Method

The traditional approaches to hydrosol precipitation are referred to as "Bottom-Up Technology." A common technique for creating submicron, insoluble drug particles is precipitation. Since the medication cannot dissolve in the presence of the solvent itself during this process, it must first be dissolved in a solvent. Ultrafine amorphous or crystalline medications are produced by quickly adding solution to such a solvent, which is frequently water. This process involves the development of crystals and the nucleation of atoms, both of which are incredibly temperature-dependent processes. To create a stable solution with small particle sizes, a high nucleation rate and a low crystal growth rate are required. The technique's constraint is the need that the drug be soluble in at least one solvent and that this solvent be miscible with no solvent [5].

Bottom-up process is an assembly method forms nanoparticles from molecules:

Examples includes

- Antisolvent precipitation method.
- Lipid emulsion technique.
- Supercritical Fluid Technology.

Anti-solvent precipitation method:

Particularly for medications that are poorly soluble, precipitation has been utilised to produce submicron particles. The drug is first dissolved in a solvent, and this solution, which still contains surfactants, is then combined with a miscible antisolvent. When a drug solution is hastily added to an antisolvent, it abruptly becomes super-saturated and generates ultrafine crystalline or amorphous drug solids. The two steps of the precipitation process are crystal growth and nuclei production. To produce a stable suspension with the lowest feasible particle size, a high nucleation rate but a low growth rate is necessary. Both rates are influenced by temperature. To employ this approach, the medication must be soluble in at least one solvent that is miscible with non-solvent [24].

Lipid emulsion method

Drugs that are soluble in partly water miscible solvents or volatile organic solvents can be used with this approach. Here, the drug was dissolved in the proper organic solvent before being emulsified in the correct aqueous phase with a surfactant. The drug particles precipitated in the aqueous phase and formed the required particle size for the aqueous suspension as a result of the organic solvent progressively evaporating under reduced pressure. To make Nanosuspensions, the produced suspension can be properly diluted. Additionally, Nanosuspensions may be created using templates from micro emulsions. An interfacial surfactant and surfactant coating hold together micro emulsions, which are thermodynamically stable, isotropically transparent dispersions of two immiscible liquids, such as water and oil. Either the medicine can be intimately mixed with the pre-formed micro emulsion or it can be put into the internal phase. The drug Nanosuspension is produced once the micro emulsion is properly diluted [25].

Supercritical fluid technology

Traditional procedures, such as solvent extraction-evaporation, solvent diffusion, and methods for organic phase separation, call for large (massive) quantities of organic solvents. In order to create biodegradable nanoparticles, supercritical fluid technology is used as an alternative. A solvent is described as a supercritical fluid if it is above its critical temperature and stays a single phase regardless of pressure. Due to its moderate critical conditions, nontoxicity, in flammability, and affordable price, supercritical CO2 (SC CO2) is the most often

employed supercritical fluid. Since the precipitate is essentially solvent free, SCF method is used as clean. For the production of polymeric nanoparticles, RESS (Rapid Expansion of Supercritical Solution) and its modified technique have been employed.

SCF can be used for various purposes in the nanoparticle production as follows

[A] solvent-rapid expansion from supercritical solutions process.

[B] Swelling and plasticizing agent-gas saturated solutions process.

[C] An antisolvent-gas antisolvenor supercritical antisolvent process or aerosol solvent system process and solution-enhanced dispersion by SCF process.

[D] A solvent for polymerization in dispersed media [26].

2.3 Dosage Forms

The dosage forms of Nanosuspension includes

- Liquid
- Powder
- Pellets
- Tablets
- Capsules
- Films

2.3.1 Liquid dosage form

In the liquid nan suspension, the drug nanoparticles are distributed in the suitable solvent medium. Liquid dosage forms provide advantages over other dosage forms, including less irritation, quicker absorption, simpler dose division, and increased drug bioavailability (27). For oral delivery, liquid Nanosuspensions of the poorly soluble medicines can be made. Aripiprazole [28], febuxostat [29], paclitaxel [30], myricetin [32], pranlukast [33], albendazole [34], fenofibrate, itraconazole, probucol, revaprazan hydrochloride are some recent examples [34].

2.3.2 Powder dosage form

Most solid dosage forms, including granules, pills, and capsules, start off as powders during manufacture. Various powder dosage forms are often generated from poorly soluble drug Nanosuspensions for oral delivery.

The most basic dose form is a powder, which also serves as the foundation for many additional solid dosage forms including tablets and capsules. Before processing, many medications or chemicals are also in powder form. In order to quickly restore the original particle size after agglomerates developed during drying, an effective redispersants should quickly disperse the agglomerates. Before drying, redispersants must be applied to the Nanosuspensions.

Succrose, trehalose, maltodextrin, lactose, and mannitol are common redispersants that are also utilised as cry protectants during lyophilisation. When compared to coarse powder and a commercial product (Norvir®), ritonavir Nanosuspension in rats shown a substantial increase in Cmax and AUC0 t values when studied among fed group volunteers [35].

2.3.3 Pellets

Pellets, which are multiparticulate dosage forms, have a number of benefits. The fluid bed coating approach was used to spray the dried indomethacin Nanosuspensions onto pellets. Drug Nanosuspensions and dry pellets containing Nanosuspension both showed comparable dissolving characteristics [36]. Ketoprofen Nanosuspension-containing pellets for long-lasting drug release of up to 24 hours have been revealed [37].

By using the high-pressure homogenization method, mucoadhesive hydrocortisone Nanosuspension was created. Pellets were initially spray coated with Nanosuspensions and then coated with enteric polymers to maintain a controlled medicine release. Studies on the solubility of drugs in vitro found that the Nano crystals in the pellets had an improved rate of dissolution and drug release [38].

Spray coating pellets with a Nanosuspension containing a water-soluble binder and then coating them with an enteric coating is the most likely way to control how quickly high dose drugs are released into the body. Similar to how matrix cores are made using the same spheronization-extrusion method, pellets may also be utilised to deliver tiny doses of medicine [39].

2.2.4 Tablets

Pharmaceutical tablets are solid unit dose forms that typically include medicinal ingredients compressed with the help of appropriate pharmaceutical excipients. Granules were created using freeze drying or spray drying procedures in the majority of the experiments. By using these techniques, Nanosuspension may be converted to dry powder and then crushed as tablets by moulding or compression. It is also feasible to convert Nanosuspension into tablet. In order to give the drug, the necessary defence and stability during the freezing and drying stages, a number of stabilisers, including sugars, sugar alcohols, polymers, and amino acids, are frequently utilised (s). To produce crystalline or amorphous freeze-dried Nanosuspension formations, these excipients are frequently used together.

In contrast to electrostatic stabilisers, are unaffected by the presence of electrolytes and other excipients used in the manufacture of tablets. Therefore, after oral administration, a stable Nanosuspension at variable gastrointestinal tract pH may be produced by choosing the suitable steric stabilisers based on the characteristics of the API. The optimal zeta potential for a Nanosuspension system stabilised by both steric and electrostatic mechanisms is thought to be 20 mV [40].

Above a specific threshold, when crushed during the tableting process, Nano crystals can mix more thoroughly in a tablet. This might significantly down the rate of absorption and dissolution, particularly for BCS II medications that are just marginally water soluble. It is effective to release low-dose medications into the solution as a fine Nanosuspension by making them with a total nanoparticle concentration of less than 1 % in relation to the weight of the whole tablet [41].

2.2.5 Capsules

It was demonstrated that both Novartis compound A and itraconazole Nanosuspension had improved bioavailability when administered orally to rats [43] or beagle dogs [42], respectively. The bioavailability of glimepiride Nano crystal-loaded capsules was much higher than that of the commercial formulation, according to both in vitro dissolution tests and in vivo rat investigations [44].

2.2.6 Films

Oral films, also known as or dispersible films, offer significant benefits over other oral dosage forms because they quickly dissolve in the mouth, quickly traverse the oral mucosa, and skip hepatic metabolism, increasing the drug's bioavailability.

By combining the chemical film-forming agents HPMCE5 and PVA with Nanosuspensions of buspirone, oral films that dissolve quickly were created. In in vitro studies, buspirone oral film demonstrated exceptional physic mechanical qualities, high stability, and burst release followed by sustained drug release [45]. Many weakly water-soluble medications might have their dissolution and permeability properties improved by adding nanoparticles to fast-dissolving oral films. The drug lercanidipine, which is poorly soluble in water and has a low bioavailability, was synthesised as nanoparticles in fast dissolving oral films using the antisolvent evaporation method. The formulations were shown to significantly improve ex vivo steady state flow and in vitro dissolving rate [46].

Maltodextrin were used as the film-forming material and glycerine served as the plasticizer in feasibility experiments of low bioavailable, quickly dissolving oral films containing quercetin, which showed that the addition of Nano crystals had no effect on the elasticity and ductility. It was discovered that the dissolving rate was higher than that of bulk medication [47]. Additionally, the oral films made of Nano crystals that quickly dissolve had an AUC0-24 h that was about 2-times greater than that of the oral solution, demonstrating a considerable increase in the rate and breadth of bioavailability [48].

Recently, a mucoadhesive film based on Nanosuspension that contains carvedilol was created and sandwiched between backing and mucoadhesive layers. Using PEG400 as a plasticizer, Nanosuspension was added to a hydrogel made of HPMC and Carbopol 934P. When compared to commercial tablets, in vivo investigations on rabbits showed a considerable increase in the relative bioavailability [49].

2.3 Components

2.3.1 Stabilizers

Without a suitable stabiliser, the high surface energy of nanoparticles might cause the drug crystals to aggregate or clump together. In order to provide a physically stable formulation, a stabiliser must fully wet the drug particles and prevent Ostwald's ripening and agglomeration of Nanosuspensions by supplying steric or ionic barriers. The kind and quantity of the stabiliser significantly affects the in vivo behaviour and physical stability of Nanosuspensions. In some circumstances, a combination of stabilisers is necessary to provide a stable Nanosuspension Polysorbate (Tween/Span series), povidone, cellulose, poloxomers, and lecithin are examples of commonly used stabilisers [50].

2.3.2 Organic solvent

The high surface energy of nanoparticles might cause the drug crystals to agglomerate or aggregate if they aren't stabilised properly. A stabiliser must completely moisten the drug particles and offer steric or ionic barriers to prevent Ostwald's ripening and agglomeration of Nanosuspensions in order to produce a physically stable formulation. In vivo behaviour and physical stability of Nanosuspensions are greatly influenced by the kind and quantity of the stabiliser. To create a stable Nanosuspension in some cases, a combination of stabilisers is required. Stabilisers that are often used include polysorbate (Tween/Span series), povidone, cellulose, poloxomers, and lecithin [50].

2.3.3 Surfactants

To enhance the dispersion by lowering the interfacial tension, surfactants are added to formulations. Surfactants can also act as wetting or deflocculating agents. In Nanosuspension, surfactants like Tweens and Spans are routinely used [52].

2.3.4 Co-surfactants

When creating Nanosuspensions using micro emulsions, the choice of co-surfactant is crucial. The impact of co-surfactant on internal phase uptake and drug loading for certain micro emulsion compositions should be studied since it has a significant impact on phase behaviour [53]. Other solubilizes, such as Transcutol, glycofurol, ethanol, and isopropanol, can be used in the production of micro emulsions without running the risk of causing harm, despite the fact that bile salts and dipotassium glycerrhizinate are referenced in the literature as co-surfactants [54, 55].

2.3.5 Other additives

The presence of additives such buffers, salts, polyols, osmogent, and cry protectants in Nanosuspensions might vary depending on the administration route or the properties of the drug moiety [56].

2.4 Drug Delivery System

The drug delivery system of Nanosuspension includes:

- Oral Drug Administration.
- Parenteral Administration.
- Pulmonary Drug Delivery.
- Oculare Administration.
- Dermal delivery.
- Targeted drug delivery.

2.4.1 Oral drug administration

The main issue with oral medication delivery is poor solubility, inadequate dissolution, and insufficient effectiveness. Oral Nanosuspensions are specifically utilised to boost the absorption rate and bioavailability of poorly soluble medicines due to their smaller particle size and much higher surface to volume ratio [57].

In comparison to 20 % of micronized medicines, more than 65 % of azithromycin Nanosuspensions were reported to disintegrate in 5 hours [58]. Low intersubject variability, dosage proportionality, and better oral absorption are some benefits of the Nanosuspension. Drug Nanosuspensions may be easily included into a variety of dosage forms, such as tablets, capsules, and rapid melts, by employing normal production procedures. Ketoprofen's Nanosuspension was effectively combined into pellets enabling a 24-hour sustained release of the medication [59].

2.4.2 Parenteral administration

In some circumstances, such as in emergency scenarios, parenteral administration is preferable over other drug-delivery methods. This is because it has various benefits, including the avoidance of first-pass metabolism, improved bioavailability, and consistent dosing.

Parenteral delivery, which offers better control over the dosage and pace than oral administration, results in more predictable pharmacodynamics and pharmacokinetic characteristics. Typically, the size of medication particles delivered should be less than 5 m to prevent capillary occlusion [60].

It was shown that oridonin in the form of Nanosuspension may significantly increase the rate of tumour inhibition by about 20 % when compared to the standard form of oridonin in a research on the evaluation of oridonin Nanosuspension's capacity to inhibit tumour growth [61]. With the use of Nanosuspension, therapeutic effectiveness is increased while costs are significantly decreased.

2.4.3 Pulmonary drug delivery

Drugs with limited pulmonary secretion solubility may be delivered most effectively by Nanosuspensions. Mechanical or ultrasonic nebulizers can be used to nebulize aqueous Nanosuspensions for lung administration. Given their tiny size, it is likely that each aerosol droplet contains at least one drug particle, resulting in a more even dispersion of the medication throughout the lungs.

The drug's Nano particulate structure enables quick diffusion and disintegration at the site of action. In addition, the drug's improved ability to stick to mucosal surfaces allows it to stay at the absorption site for a longer period of time. Most lung disorders require this ability of Nanosuspensions, which initially has a fast beginning of action followed by a regulated release of the active moiety. Using an ultrasonic nebulizer, budesonide medicinal nanoparticles were effectively nebulized [62].

2.4.4 Ocular administration

For a prolonged release of the medications, Nanosuspensions are utilised. Using Eudragit, Liang and colleagues created cloricromene Nanosuspension for ocular administration. An experiment revealed that the rabbit eye's aqueous humour has a greater drug availability. Therefore, Nanosuspension formulation offers a potentially effective technique to increase the drug's bioavailability and shelf life [63].

Significant issues with ocular treatment include

- Poor drug solubility in lachrymal fluids.
- Frequent use of regular eye drops owing to nasolacrimal duct leakage.
- Repeated instillation and systematic drug absorption often causing side effects [64].

2.4.5 Dermal delivery

The Nano crystals show better permeation and bio-adhesiveness as a result of higher Nano crystal penetration into a membrane. Investigations into inject ability and rapid dissolving are necessary to create intravenous formulations. The utilisation of adhesion, rapid dissolution, or greater penetration for cutaneous and mucosal applications, however, has not been used by researchers for years [65].

In order to boost the penetration of drug Nano crystal, the concentration of the poorly soluble drug was raised, which may have increased the concentration gradient between the formulation and the skin [66].

It was discovered during research on a penetration barrier that lutein Nano crystals have a fourteen-fold more capacity than raw powder to pass through cellulose nitrate membranes. Due to its lipophilicity, these lutein Nano crystals remained in the pig ear skin after entering [67].

2.4.6 Targeted drug delivery

Because of their surface characteristics, Nanosuspensions are good for targeting certain organs. Additionally, by adjusting the stabiliser, in vivo behaviour may be easily modified. The mononuclear phagocytic system will pick up the medication, enabling distribution to targeted areas. If the infections remain intracellular, this can be utilised to direct antifungal, ant mycobacterial or antileishmanial medications to macrophages [68].

Aphidicolin Nanosuspension created by Kayser increased medication targeting to Leishmania-infected macrophages. He claimed that the drug's EC50 in its Nanosuspension form was 0.003 g/ml as opposed to 0.16 g/ml in its traditional form [69]. Atovaquone Nanosuspension was used by Scholer *et al*. to treat toxoplasmic encephalitis employing improved medication targeting to the brain [70].

2.5 Characterization of Nanosuspension

Assay, associated impurities, particle size, zeta potential, crystalline morphological status, dissolving tests, and in vivo research are used to assess Nanosuspensions.

Among these the essential characterization techniques were discussed.

1. Mean particle size and particle size distribution.
2. Surface charge (Zeta potential).
3. Crystalline state and particle morphology.
4. Saturation solubility and Dissolution velocity.
5. Stability.
6. Osmolarity.
7. PH.
8. Drug content.

2.5.1 Mean particle size and particle size distribution

The mean particle size and particle size distribution affect Nanosuspensions' physical stability, dissolving rate, saturation solubility, and even in vivo behaviour. The particle size distribution may be determined using laser diffraction, photon correlation spectroscopy, and the Coulter counter multisizer, among other methods [71].

Additionally, the width of the particle size distribution may be determined using PCS (polydisperity index, PI). PI values between 0.1 and 0.25 denote a very tight size distribution, whereas values over 0.5 suggest a very large distribution [72]. When measuring the contamination of Nanosuspensions by micro particulate medicines, the coulter-counter is more effective and appropriate than LD since it provides the exact number of particles per volume unit for the various size classes.

2.5.2 Surface charge (zeta potential)

The stability of Nanosuspension is governed by surface charge. A Nanosuspension's zeta potential is controlled by both the stabiliser and the medication. Zeta potential should be at least 20Mv for combined steric and electrostatic stabilisation and at least 30mV for electrostatically stabilised Nanosuspension [73].

2.5.3 Crystalline state particle morphology

Due to the possibility of polymorphism during Nanosuspension storage, it is crucial. Therefore, it is important to research the drug's crystal shape when it is in

suspension. For these research, differential scanning Colorimetry (DSC) is most frequently employed [74].
It is crucial to gauge the amount of amorphous drug produced during the creation of Nanosuspensions since drug particles may become amorphous when Nanosuspensions are created. The amount of the drug's amorphous form is frequently assessed using the X-Ray Diffraction (XRD) technique [75].

2.5.4 Saturation solubility and dissolution velocity
In order to predict any changes in the in vivo performance of the medication (blood profiles, plasma peaks, and bioavailability), it is crucial to determine the saturation solubility and dissolution velocity. The measurement of the saturation solubility rather than a rise in saturation solubility remains a significant investigative criterion since Nanosuspensions are known to improve the drug's saturation solubility.
According to procedures described in the pharmacopoeia, the saturation solubility and dissolution velocity of drug Nanosuspensions in various physiological buffers and at various temperatures should be evaluated. When creating sustained release dosage forms based on Nano particulate medicines, the analysis of the dissolution velocity of Nanosuspensions shows the benefits that may be realised over traditional formulations [76].

2.5.5 Stability
The stability of the suspensions is influenced by particle size. As the particles get Nano sized, their surface energy increases, and they begin to cluster together. In order to improve the stability of the suspension and reduce the likelihood of Ostwald ripening, stabilisers are utilised. These stabilisers act as an ionic or steric barrier. Stabilizers such cellulosics, poloxamer, Polysorbate, lecithin, polyoleate, and povidones are frequently utilised in Nanosuspensions. When creating parenteral Nanosuspensions, lecithin may be chosen [77].

2.5.6 Osmolarity
Utilizing an osmometer, one may determine the Osmolarity of a Nanosuspension. The formulation of the Nanosuspension was evaluated for osmolality since the intravenous dose form should be isoosmolar with the blood. Osmolarity was actually tested using an ohmmeter, and theoretically it was computed using the formula below.

Osmolarity (mOsmol) =weight in gm/lit. No. of species * 1000molecular weight*100 [78].

2.5.7 ph
The pH value of an aqueous formulation should only be measured at a certain temperature and once settling equilibrium has been reached in order to minimise "pH drift" and electrode surface coating with suspended particles. Electrolyte shouldn't be added to the formulation's outer phase in order to stabilise pH [79]. Prepared Nanosuspension was taken in 10ml beaker and pH was measured using pH meter.

2.5.8 Drug content
The drug content of the Nanosuspension formulation was assessed using lyophilized powder (equivalent to 5 mg of drug), an appropriate solvent mixture such as Methanol: THF (1:1) mixture, shake well, and centrifuge.
The absorbance is measured at an appropriate max after the supernatants are separated and diluted with the same solvent combination. The calibration curve is used to determine the medication content.
Total volume of nanosuspention = total volume of nanosuspention x amount of drug in aliquot/volum of aliquot [80].

3 Conclusions
The delivery of hydrophobic medications, particularly those that are poorly soluble in aqueous as well as organic media, can cause issues like low bioavailability, which Nanosuspensions look to be a novel and yet economically feasible solution to. To increase medication absorption and bioavailability, the challenges associated with poorly water-soluble medicines dissolving have mostly been resolved. Surfactant-stabilized submicron colloidal dispersions of drug particles at the Nano scale are known as Nanosuspensions. Tablets, capsules, pellets, and parenteral medicines can all be made using Nanosuspension technology in addition to conventional dosage forms. Nanosuspensions will continue to be of interest as oral formulations and non-oral administration grow in the future in order to take advantage of Nanosuspension drug delivery, easy formulation methods, and various uses.

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