"Recent Perspectives of Nanosuspension Drug Delivery System".

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Abstract:

Formulation as nanosuspension is an attractive and promising alternative to solve solubility problems.The only component of a nanosuspension is the medicine itself, which is a poorly water-soluble substance, suspended in a dispersion. Nanosuspension contributes a crucial role in administering the different drug entities through a variety of routes with solving the different issues. Extensive research is now being done on the use of nanosuspensions in various drug delivery methods, including oral, ophthalmic, brain, topical, buccal, nasal, and transdermal routes. Many formulation issues currently faced by protein- and peptide-based medications can be resolved with the advancement of supporting technologies like nanosuspension. The aim of this study was, to employ the nanosuspension technique to produce nanoparticles for oral administration, thereby avoiding the use of harmful additives and enabling to enhance the saturation solubility, dissolution and oral absorption of BCS class 2 drugs. This innovative formulation approach has greatly broadened its application due to the significant improvement in bioavailability, adaptability for surface modification, and mucoadhesion for drug targeting. Several challenges are still present in this approach which need more research.

Keywords-Nanosuspension, Solubility, Nanoparticle, Drug delivery systems.

1. Introduction

The field of nanotechnology includes nanosuspension. Nanotechnology is the branch of science and engineering that focuses on creating and using systems, devices, and structures that can manipulate atoms and molecules at the nanoscale.[9] The issues of hydrophobic drugs, such as poor solubility and poor bioavailability, can be solved using a unique and commercially viable method called nanosuspensions. Nanoparticles have high specific surface areas, consequently increasing the dissolution rate and solubility. BCS class ii have a low solubility and high permeability is therefore to study the solubility enhancement nanosuspension delivery system is used. The colloidal dispersions of pharmaceutical active component particles in a submicron size range are known as nanosuspensions. Liquid phase, size below 1μm, without any matrix material which are stabilized by surfactants and polymers.[1] The diameter of the suspended particle is less than 1 μm in size (i.e. 0.1nm-1000 nm). The solid particles in nanosuspensions typically have a particle size distribution that is less than one micron, with an average particle size of between 200 and 600 nm. It is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators.[2] Nano

means it is the factor of 10-9 or one billionth. The following list includes several nanoscale comparisons,

0.1 nm = Diameter of one Hydrogen atom.
2.5 nm = Width of a DNA molecule
1 micron = 1000 nm.
1 nm = 10 -9m= 10 -7 cm = 10 - 6 mm. Micron = 10 -6m= 10 - 4 cm = 10 -3mm. [3,20,22]

Poor water solubility of drug molecules, insufficient bioavailability, fluctuating plasma levels and high food dependency are the most important and common problems with poorly soluble drug [27]. To improve the solubility and dissolution qualities of drugs, a variety of solubilization techniques have been employed, including the use of surfactants, water-soluble carriers, polymeric conjugates, and solid dispersion. Preparation of drugs in form of nanosuspensions has shown to be a more cost-effective and technically simpler alternative, particularly for poorly soluble drugs, and yield a physically more stable product than liposome dispersions.[14]

1.1. Classification of suspension [5,16]

I. Based on General Classes:
- Oral suspension
- Externally applied suspension
- Parenteral suspension

II. Based on Proportion of Solid Particles:
- Dilute suspension (2 to10%w/v solid)
- Concentrated suspension (50%w/v solid)

III. Based on Electrokinetic Nature of Solid Particles:
- Flocculated suspension
- Deflocculated suspension

IV. Based on Size of Solid Particles:
- Colloidal suspension (< 1 micron)
- Coarse suspension (>1 micron)
- Nano suspension (10 ng) T

Other dosage forms bioavailability is in following order, Solution > Suspension > Capsule > Compressed Tablet

1.2 Need of nanosuspension:
- Major issues associated with poorly water-soluble compounds
- Poor bioavailability.
- Inability to choose lead compounds more effectively and safely
- Variation in bioavailability between fed and fasting
- Inadequate dose-response relationships
- Suboptimal dosing
- Use of harsh excipients, i.e. Excessive use of co-solvents and other excipients
- Use of extreme basic or acidic conditions to enhance solubilization

1.3 Advantages of Nanosuspension:

The following list of unique characteristics of nanosuspension can be used as a potential method for drug delivery.

Reduced particle size, enhance dissolution rate, enhanced rate, and extent of absorption.
- Its general applicability to most drugs and its simplicity.
- Can be applied for the poorly water soluble drugs.
- Can be given by any route.
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.

- I.V. injection can result in rapid breakdown and tissue targeting.
- Rapid onset, a lower fed/fasted ratio, and increased bioavailability are all benefits of oral administration of nanosuspensions.
- The absorption from absorption window of the drugs can be increased, due to reduction in the particle size.
- Higher bioavailability and more consistent dosing in case of ocular administration and inhalation delivery
- Long-term physical stability.
- Drugs having a high log P value can be formulated as nanosuspensions in order to enhance their bioavailability
- Compounds that are insoluble in water but soluble in oil can be used in the formulation of nanosuspension.
- The pharmaceutical nanosuspension can be delivered through various routes such as oral, topical, parenteral, ocular, pulmonary, etc. In fact, nanosuspensions can be incorporated in tablet, pellet, hydrogel, and suppositories.
- Drug nanosuspension can provide passive targeting of the drug.
- It can Improve the in vivo performance due to high dissolution rate and saturation solubility of the drug,
- Ease of manufacturing and scale-up for large scale production.
- The possibility of surface-modification for site-specific drug delivery.
- The nanosuspension technology can increase the amorphous fraction in the particles that may lead to a potential change in the crystalline structure and solubility.

1.4 Limitations of Nanosuspension:

Besides the several advantages, nanosuspension may be subjected to physical instability due to an elevation in the sedimentation rate of dispersed nanoparticles during storage. This may arise as a major problem with nanosuspension, although this crunch can be rectified by the use of suitable polymers. Due to their size, pharmaceutical nanosuspension may also experience wear and tear when handled or transported. Hence, they require sufficient care during handling & transportation.

2. Formulation components [15]

Stabilizers, polymers, surfactants, osmotic agents, organic solvents, cryoprotectants, buffers, complexing agents, buffers, organoleptic agents, and preservatives are the excipients utilised in nanosuspensions the most commonly.

- **Stabilizer**:

The main function of a stabilizer is to wet the drug particles thoroughly, and to by supplying a steric or ionic barrier, one can stop Ostwald's ripening and agglomeration of Nanosuspensions and produce a physically stable formulation. e.g., Lecithin, Povidones, Poloxamers, Polysorbates, Cellulosic, etc. If one wants to create a parenterally acceptable and autoclavable nanosuspension, lecithin is the stabilizer of choice.

- **Organic Solvents**

Organic solvents are used in the formulation of Nanosuspension if emulsions or micro emulsions are used as a template. The pharmaceutically acceptable less

hazardous water miscible solvent, such as methanol, ethanol, chloroform, propanol, carbonate, benzyl alcohol, are preferment in the formulation over the conventional hazardous solvents, such as dichloromethane

- **Surfactants:**

Surfactants are incorporated to improve the dispersion by reducing the interfacial tension. They also act as wetting or deflocculating agents.[2] Widely used surfactants include Tweens and Spans.

- **Co-surfactants** :

The choice of co-surfactant is critical when using micro emulsions to formulate Nanosuspensions e.g., Tweens and Spans - widely used surfactants

- **Other additives**:

Depending on the mode of administration or the characteristics of the drug moiety, nanosuspensions may contain additives including buffers, salts, polyols and cryoprotectant.

2.1. Preparation Methods of Nanosuspension:

The preparation of nanosuspension can be done in one of two ways. They are Top down and Bottom up technologies, respectively.

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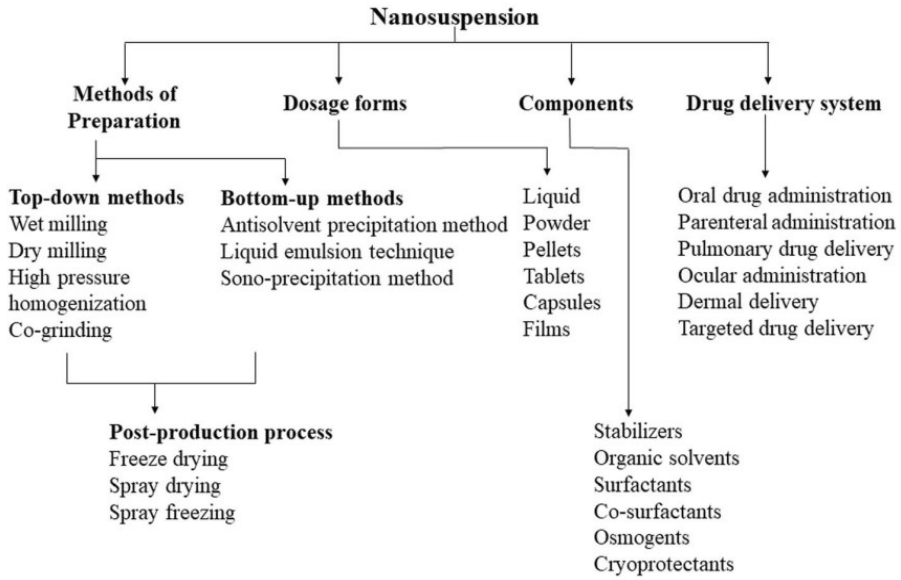

Figure 1: Schematic representation of method of preparation, dosage forms, components and application of nano suspension in drug

2.2. Preparation method of nanosuspension [7]:

1. **Bottom up technology**:[23]

Bottom-up technology refers to a method of creating solid particles that begins at the molecular level and progresses through molecular association [12]

Advantages:

(i) Use of simple and low cost equipment.

(ii) Higher saturation solubility is the advantage for precipitation compared to other methods of Nanosuspension preparation

Disadvantages:

(i) Growing of crystals needs to be limit by surfactant addition.
(ii) The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and in organic media).
(iii) Solvent residues need to be removed, thus increasing production costs.
(iv) It is a little bit tricky to preserve the particle character (i.e. size, particularly the amorphous component). In general, it is recommended that a second consecutive process has to be performed for particle preservation that is spray drying or lyophilisation.

2. **Top-down technology**

The disintegration procedures, or Top-down Technologies, are favoured to the various methods utilised to create nanosuspensions.

There are different methods of Nanosuspensions preparation Homogenization in water (DissoCubes).

i. Media milling (Nanocrystals or Nano systems):[18,19]

In this method the nanosuspensions are produced using high shared media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft and recirculation chamber. The milling medium is framed of a glass, zirconium oxide or highly cross-linked polystyrene resin. The milling media or pearls are rotated at a very high share rate after being charged with water, drug, stabiliser, and milling media.

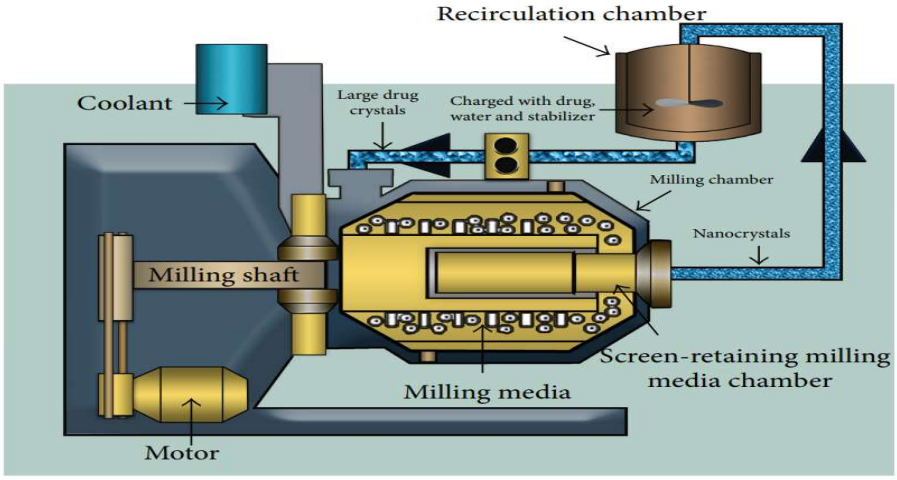

Figure 2: Schematic representation of the media milling process

The milling process is performed under control temperatures. The energy input needed to transform the drug's microparticulate state into nano-sized particles is provided by the high energy and shear pressures created when the drug impaction with the milling media. The unimodal distribution profile and mean diameter of < 200, require time profile of 30-60 min. Drug crystals, both micronized and not, can be successfully processed using the media milling technique. Once the formulation and the process are optimized, very short batch-to-batch variation is observed in a quality of the dispersion.

ii. High pressure homogenization:[21]

High pressure homogenization has been used to prepare nanosuspensions of many poorly wate soluble drugs. The instrument has a volume capacity of 40 ml and can be used at pressures ranging from 100 to 1500 bars (2800 to 21300 psi) (for laboratory scale). This method involves pushing a drug and surfactant suspension through a nanosized aperture valve of a high pressure homogenizer while it is under pressure.

Principle:

The theory is based on aqueous phase cavitation. The drug's microparticles can become nanoparticles thanks to the high particle cavitation forces. Small sample particles prior to loading and the necessity of numerous cycles of homogenization call for the use of this approach.

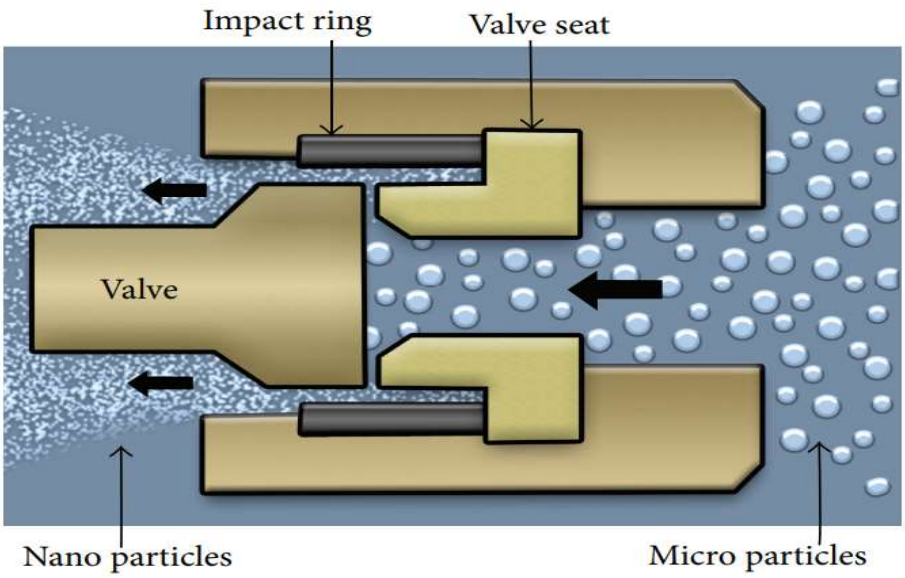

Figure 3: Schematic representation of the high pressure homogenization process.

Advantages:

i. Helpful for the creation of both extremely concentrated and very dilute nanosuspension.
ii. Allows aseptic nanosuspensions to be produced for parenteral delivery.
iii. Low possibility of product contamination.
iv. It is simple to create nanosuspensions out of medications that aren't very soluble in either aqueous or organic environments.
v. Scale-up is simple, and batch variance is minimal.
vi. The final product contains a medication that is a nanoparticulate with a narrow size distribution.
vii. Allows aseptic nanosuspensions to be produced for parenteral administration.

Disadvantages:
(i) micronized drug particles are required.
(ii) The creation of a suspension using high-speed mixers is necessary before homogenization.

iii. Homogenization in Nonaqueous Media (Nanopure)

In the nano pure approach, suspensions are homogenised in media without water or media containing water [57]. At 0 °C and -20 °C, as well as at room temperature, the homogenization can be carried out. Chemically labile pharmaceuticals can be processed using nonaqueous media or water-miscible solutions like polyethyleneglycol-400, PEG 1000, etc. Numerous steroidal drugs, including Hemihydrates, Hydrocortisone, and Diclofenac sodium, were produced using this technique.

iv. Combined Precipitation and Homogenization (Nanoedege)

Drugs with low toxicity that are soluble in non-aqueous fluids, such N-methyl-2-pyrrolidinone, are especially well suited for the nano edge technique. This is accomplished through a combination of high-pressure homogenization and precipitation. Precipitation and homogenization both operate on the same fundamental principle. The precipitating drug nanoparticles frequently continue to form crystals until they are the size of microcrystals. It is necessary to process them using high-energy forces (Homogenization). The precipitated particle dispersion is then homogenised in order to retain the particle size achieved during the precipitation process. The primary limitations of the precipitation method, such as crystal growth and long-term stability, can be mitigated by using Nano edge technology. Particles with better stability and smaller sizes can be produced fast.

v. Homogenization in Water (Dissocubes)[24]

In 1999, Muller created the Dissocubes technology. The device has a 40 ml volume capacity and can be utilised at pressures up to 2000 bars, ranging from 100 to 1500 bars. To avoid obstructing the homogenization gap during the production of the nanosuspension, we must start with drug particles that have been micronized and are smaller than. The homogenization temperature and the dispersion medium affect how the Dissocubes and Nano Pure technologies behave. The dispersion medium for the suspensions was water. The drop in diameter from the big bore cylinder to the homogenization gap (for example, 3 cm) results in an increase in dynamic pressure (streaming velocity), which also results in a decrease in static pressure on the liquid. when the suspension returns after leaving the gap and When returns to its normal pressure, the liquid starts to boil, and gas bubbles appear before collapsing (cavitation). Particle size is decreased by shock waves caused by the formation and deflation of gas bubbles. utilisable homogenizer for piston gaps.

vi. Nanojet Technology (Opposite Stream Technology)

In this method, a chamber is used where a stream of suspension is split into two or more sections that collide at high pressure. As a result of the strong shear forces generated during the operation, the particle size is decreased.

vii. Emulsions as Templates:

For pharmaceuticals that are soluble in either volatile organic solvent or somewhat water-miscible solvent, emulsions can be used as templates. [12] In addition to being a

means of medication delivery, emulsions can also serve as models for the creation of nanosuspensions.

viii. Microemulsions as Templates:

A surfactant and co-surfactant interfacial film stabilises microemulsions, which are thermodynamically stable and isotropically transparent dispersions of two immiscible liquids, such as oil and water (Eccleston 1992).

ix. Solvent Evaporation Technique

In this method, a drug solution is prepared, and it is then emulsified in a liquid that isn't a solvent for the drug. The solvent evaporates, causing the medication to precipitate. High shear forces produced by a high-speed stirrer can be used to control crystal formation and particle aggregation. Successful applications of nanosuspension drug formulation to griseofulvin, diclofenac, acyclovir, and mitotane have been documented.

x. Hydrosol Method:

This method involves dissolving the medication in a solvent, which is then mixed with a non-solvent to start the precipitation of a finely dispersed product. To accomplish this, the solvent is added to a non-solvent (i.e., doing it the other way around would lead to the formation of larger crystals). To prevent the formation of microcrystals, surfactants or polymers must stabilise the produced nanocrystals. To preserve the nano size of the particles, it is typically advised that the product be lyophilized.

xi. Supercritical Fluid Method:

Non condensable dense fluids known as "super critical fluids" (SCF) have critical temperatures and pressures that are higher than their normal operating ranges (Tp).

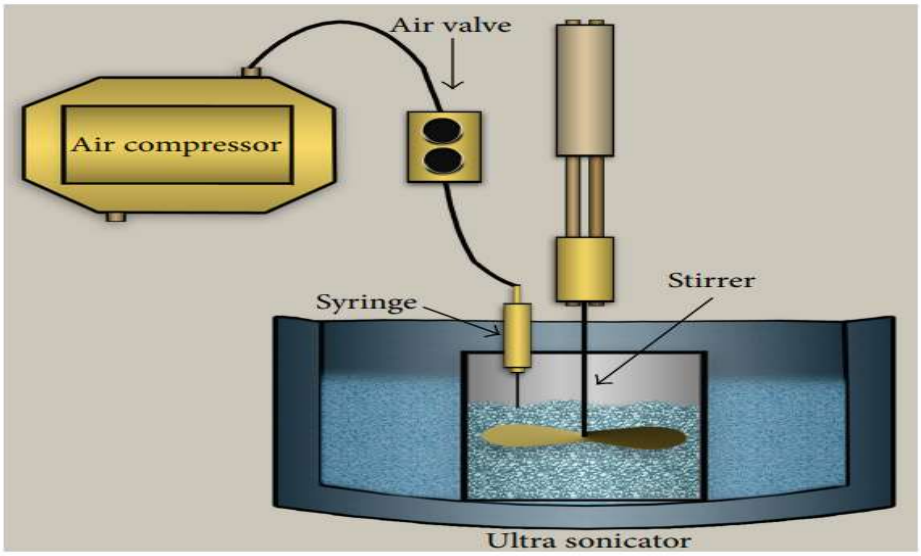

Figure 4: Schematic representation of the Precipitation method.

There are several ways to create nanoparticles, including the rapid expansion of supercritical solution (RESS) process, the supercritical antisolvent process, and the precipitation with compressed antisolvent (PCA) approach. In the RESS technique, drug

solution is expanded through a nozzle into supercritical fluid, causing the supercritical fluid to lose some of its solvent power, precipitating the drug as small particles. Young et al. created cyclosporine nanoparticles with a diameter of 400 to 700 nm using the RESS technique. The medication solution is atomized into the CO2 compressed chamber while using the PCA method. The solution becomes oversaturated when the solvent is removed, which leads to precipitation. Drugs are used in the supercritical antisolvent procedure. The solvent is removed from the supercritical fluid as well as the drug solution, which is then supersaturated.

xii. Melt Emulsification Method:[17]

In this procedure, the medication is mixed with the stabilizer's aqueous solution, heated above the drug's melting point, and homogenised to create an emulsion. The sample holder was wrapped in a heating tape with a temperature controller during this procedure, and the temperature of the emulsion was kept above the drug's melting point. The emulsion was then gradually cooled to room temperature or placed in an ice bath.

Advantage: In comparison to the solvent diffusion approach, the melt emulsification technology completely forgoes the use of organic solvents during manufacture.

xiii. Dry Co-Grinding

Recently, dry milling processes have made it possible to create nanosuspensions. It has been reported that stable Nanosuspensions can be made by dry-grinding insoluble medicines with soluble polymers and copolymers after dispersing them in a liquid medium. There have been many soluble polymers and co-polymers utilised, including cyclodextrin derivatives, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and PVP.

3. Characterization approach/ technologies for nanosuspension [4]

Evaluation of nano-materials including nanosuspension is quite significant for knowing their unique characteristics as well as applications. These techniques are helpful for an efficient comparison among formulations and for the development of an optimized product. As each technique exhibits its own strengths and limitations, the choice of appropriate characterization approaches is a matter of perplexity for researchers and technologists. To overcome these challenges, some of the reliable techniques are required with sufficient reproducibility. Various evaluative techniques that can be efficiently utilized for fabricating the optimum quality products are described in this review article.

1. Particle Size Analyzer:

For the assessment of nanoparticles in nanosuspension, particle size is a key factor. An ideal method for determining particle size in the nanometre (nm) range is to use a particle size analyser. Nanosuspension Technology Recent Patents on Drug Delivery & Formulation which demonstrates high sensitivity to measure the minute particle size of the sample even in nano-range, is the only one employed for this purpose. In contrast to other typical equipment, backscatter optics really aid in identifying the particles with a high concentration. A strategy that is frequently used to estimate the dispersed nanoparticles in nanosuspension is dynamic light scattering (DLS). It is challenging to determine the precise number of aggregates that may be in the sample. Therefore, there is no correlation between the size fractions and a particular composition. This is the

biggest drawback of the DLS instrument. The solvent's refractive index is another need for this method. The analysis is biased toward the more reflective particles because the sample contains a variety of nanoparticles. The average particle size is also depending on the concentration of big or contaminated particles in a sample.

2. Scanning Electron Microscopy (SEM):

For morphology and surface characterization of particles in nanosuspensions, scanning electron microscopy is frequently used as a characterisation tool. For SEM characterization, the nanoparticles of the nanosuspension are converted into a dry form and put on a sample holder coated with a metal such as gold for high conductivity. SEM can create details about particles with a size of less than 5 nm and offers images of a sample surface with excellent resolution.

3. Transmission Electron Microscope (TEM):

Transmission electron microscopy is the powerful characterization technique with high magnification utilized for predicting the morphological characters and surface examination of the samples. It uses a different working principle than SEM but provides similar data. TEM does not provide colourful images as it provides black and white images. Like SEM, it also requires maintaining voltage, current to electromagnetic coils and circulation of cooling water. Additionally, the handling of the instrument needs special training. The samples which are electron transparent, able to tolerate vacuum chamber and sufficiently small to fit in the chamber can only be analysed by transmission electron microscopy.

4. X-Ray Diffraction (XRD):

X-ray diffraction is an effective analytical technique for gaining insightful knowledge about the crystallographic structures of both naturally occurring and artificially created substances, as well as their crystalline structures, lattice structures, and phases. The dual character of X-Rays, i.e., wave or particle, is the foundation of XRD. It is based on the properties of secondary rays that are emitted from substances and are generally used to anticipate certain elements in compounds when activated by a high X-ray energy source. The cathode ray tube in X-ray diffraction generates electromagnetic radiations, which are then filtered to produce monochromatic beams. When the situation satisfies Bragg's law i.e., $n\lambda = 2d \sin\theta$. Where λ is the wavelength of incident X-Rays at a certain angle of diffraction (θ) and the distance between atomic layers in a crystal (d) and n is an integer.

5. Thermogravimetric Analysis (TGA) :

Thermogravimetric analysis is a thermal analytical technique that assesses variations in substance mass and stabiliser content in a controlled setting. With this technology, a nano sample is heated before its components are broken down and vaporised at various degradation temperatures. The TGA equipment then records the temperature and changes in mass. Predicting the properties of substances, such as polymers to consider their degradation temperatures, absorbed moisture content of compounds, the amount of inorganic and organic components in materials, decomposition points of explosives, and solvent residues, is frequently used in research and testing.

6. Ultraviolet (UV) Spectroscopy:

To assess chemicals in the nano-range, ultraviolet spectroscopy or ultraviolet-visible spectroscopy is frequently used. It is based on Lambert-law, Beer's which asserts that as a monochromatic light ray travels through a transparent media, the rate at which its intensity diminishes is directly proportionate to the thickness of the medium. Particularly for those nanoparticles that exhibit optical features sensitive to agglomeration, size, shape, concentration, and refractive index near the surface of nanoparticles, UV spectroscopy is used as a simple and potentially useful defining instrument. It operates by comparing the radiation intensities that pass through the reference substance with those that are reflected from the sample.

7. Zeta Potential [Surface Charge]:

The nature and strength of the surface charge of the dispersed nanoparticles in nanosuspension are estimated using the zeta potential. It aids in determining how they interact with biological systems and how they interact electrostatically with substances that are biologically active. The zeta potential is the potential difference between the liquid's bulk and the surface of solid particles submerged in a conducting liquid. Additionally, it could reveal details about the kind of substance that is coated or encapsulated on the particle's surface. [4] The particle surface charge value reveals the stability of macroscopic nanosuspensions. It is calculated in millivolts (mV) or volts (V). Through zeta potential, colloidal or storage stability of dispersed nanoparticles can be anticipated. For electrostatically stabilised Nanoparticulate dispersion systems nanosuspensions, a minimum zeta potential of 30 mV is needed, while a minimum of 20 mV is needed for steric stabilisation.[10] The electrophoretic mobility of the particle is typically determined, and the electrophoretic mobility is then converted to the zeta potential to determine the zeta potential values. In the field of material sciences, the zeta potential is also determined using the electroacoustic technique [13].

8. Dynamic Light Scattering (DLS):

A popular evaluation method for determining the particle size of disseminated nanoparticles in nanosuspension is dynamic light scattering (DLS). The term "photon correlation spectroscopy" is well-known. John Tyndall developed the first light scattering tests, which assessed light scattering from colloidal solutions with particles larger than the wavelength of incident light. It is based on the idea that light scatters differently depending on the shape and size of the dispersed particles when monochromatic light strikes a solution containing them. It is possible to determine the molecular mass and size of the dispersed particles by measuring the intensity of the scattered light.

9. Differential Scanning Calorimetry (DSC):

The difference between the amount of heat required to raise the temperatures of the sample and the reference as a function of temperature is measured using the thermal analytical technique known as differential scanning calorimetry.

10. Fourier Transform Infrared Spectroscopy (FTIR):

The wonderful technique of Fourier transform infrared spectroscopy is frequently used to study molecules and tiny particles. This method offers important details regarding the three-dimensional data of structures obtained through X-ray diffraction. A given compound's vibration frequencies in FTIR are predicted to occur in a specific location based on the sort of atoms and chemical bonds it contains.

Applications of Nanosuspension [8, 25]: Below are a handful of these applications.

Parenteral Drug Delivery:

Different parenteral delivery routes, including intra-articular, intraperitoneal, and intravenous injection, can be used to administer nanosuspensions.

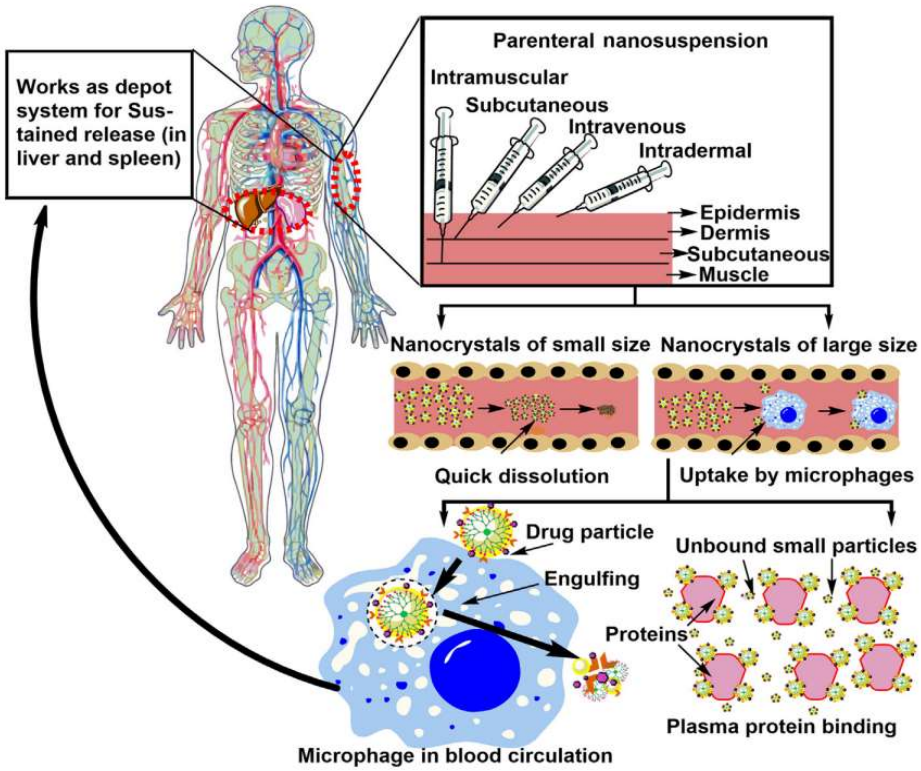

Figure 5: The in vivo fate of drug nanocrystals following intravenous administration.[6]

Oral Drug Delivery:

The oral route is frequently chosen since it has many recognised benefits. Atovaquone and Buparvaquone, two antibiotics that are taken orally, are excellent

examples of this issue. When such medications are nanosized, their oral absorption and consequently bioavailability can both dramatically increase.

Pulmonary Drug Delivery:

Drugs with poor 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 small 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.

Ocular Drug Delivery:

Drugs with weak lachrymal fluid solubility may benefit from nanosuspensions. Drug distribution is challenging without causing tissue damage due to the eyes' defensive barriers. Medication distribution is hampered by poor drug absorption and drug penetration into ophthalmic tissues. For the transport of medications to the intraocular tissues, nanoparticles and nanosuspensions are being produced. Cross-linked polymer nanosuspensions of dexamethasone are one illustration; they exhibit improved anti-inflammatory efficacy in a model of irritation in rabbit eyes.

Targeted Drug Delivery:

Because their surface characteristics and in vivo behaviour may be easily changed by varying either the stabiliser or the milieu, nanosuspensions can be employed for targeted distribution. The future of targeted drug delivery systems lies in the engineering of stealth nanosuspensions (similar to stealth liposomes) by using different surface coatings for active or passive targeting of the desired spot.

Bioavailability Enhancement:

The drug's poor oral bioavailability could be brought about by the digestive tract's poor solubility, permeability, or stability (GIT). By addressing both the issues of poor solubility and poor permeability across the membrane, nanosuspensions are able to address the issue of poor bioavailability. A nanosuspension formulation was used to increase the bioavailability of the hepatoprotective compound oleanolic acid, which is weakly soluble.

Mucoadhesion of the Nanoparticles:

Orally administered nanoparticles in the form of a suspension permeate into the liquid medium and quickly come into contact with the mucosal surface. Prior to particle absorption, the particles initially make direct contact with the intestinal cells through a bio adhesive phase. The nanosuspensions' adhesiveness not only aids in enhancing bioavailability but also enhances targeting of parasites that are still present in the GIT, such as Cryptosporidium parvum.

4. Future perspectives [4]

In recent years, a complementary method called nanosuspension has been used to address problems brought on by poorly soluble medications. Due to their distinct characteristics, the nanosuspensions with greater solubility or redispersibility in the aqueous medium have caught the interest of formulators. Poorly soluble pharmaceuticals can be made into nanosuspensions using a variety of techniques, such as media milling, ultrasonication, high-pressure homogenization, Table 4, and more. The different commercially available formulations created with nanosuspension technology and accepted by the Food and Drug Administration (FDA). However, the nanosuspension produced using such methods may be vulnerable to certain stability issues, such as crystal formation or Ostwald ripening, thus appropriate stabilisers or polymers are added to the nanosuspension to make it stable. The selection of stabilisers is time-consuming and difficult because it requires a lot of work. In fact, well-stabilized nanosuspensions without any stabilisers are in high demand in the field of pharmacy. As a result, nanosuspensions are easier to administer stabilisers through and are also more friendly with the human body. Some scientists are developing the self-stabilization theory for this reason. To build nanosuspensions without stabilisers, this sector must conduct the most extensive study because it is highly difficult and complicated. Due to its ease of use, profitability, better solubility, and dissolution, nanosuspension technology will benefit human society.

5. Discussion and conclusion

The main challenge for formulators is creating pharmaceutical formulations with poorly soluble medicines. Due to the fineness of the dispersed particles' higher dissolving pressure, they dissolve more quickly, increasing the saturation solubility. Comparing this to previous micro particular systems, it may improve the bioavailability of medications. If in vivo dissolution velocity of the drug particles is low enough, the drug nanosuspensions will have the passive targeting advantages of colloidal drug carriers. Nanosuspension is now a potential method for delivering various kinds of therapeutically active substances thanks to a number of noticeable advantages. The issues associated with hydrophobic medicines, such as low solubility and bioavailability, may be resolved by this method. Different pharmacological entities are administered through a range of channels, including oral, transdermal, ophthalmic, parenteral, pulmonary, etc., with the help of nanosuspension. Due to its ease of use, profitability, enhanced solubility, and dissolution, nanosuspension technology may prove to be a successful strategy for improving human condition. This review study's findings suggest that nanosuspension may improve patients' quality of life through improved efficacy, fewer negative treatment side effects, and reduced communal as well as the financial cost of providing healthcare.

References:

1. *P. V. Kamala Kumari, and S. Y Rao, " Nanosuspensions: A Review", Int J Pharm., 2017; vol. 7, no. 2,* ***(2017),*** *pp. 77-89.*

2. *G. V. Yadav and S. R. Singh, " Review Article Nanosuspension", A Promising Drug Delivery System Pharmacophore., 2012, vol. 3, no. 5,* ***(2012),*** *pp. 217-243.*

3. *S. S. Pawar, B. R. Dahifale, S. P. Nagargoje and R. S. Shendge, " Nanosuspension Technologies for Delivery of Drugs", Nanoscience and Nanotechnology Research., vol. 4, no. 2,* ***(2017),*** *pp. 59-66.*

4. *S. Goel, M. Sachdeva and V. Agarwal, "Nanosuspension Technology: Recent Patents on Drug Delivery and their Characterization", Recent Patents on Drug Delivery & Formulation., vol. 13,* ***(2019),*** *pp. 91-104.*

5. *E. Ahire, S. Thakkar, M. Darshanwad and M. Mishra, "Parenteral Nanosuspensions: A Brief Review from Solubility Enhancement to More Novel and Specific Applications", Acta Pharmaceutica Sinica B., vol. 8, no. 5,* ***(2018),*** *pp. 733–755.*

6. *P. Lakshmi, G. A. Kumar, "Nanosuspension Technology: A Review", International Journal of Pharmacy and Pharmaceutical Sciences., Vol. 2, no, 4,* ***(2010),*** *pp. 35-40.*

7. *K. B. Sutradhar, S. Khatun and I. P. Luna, "Review Article Increasing Possibilities of Nanosuspension", Journal of Nanotechnology.,* ***(2013),*** *Article ID 346581, pp. 12 pages.*

8. *A. R. Kumar, "Overview of Nanosuspension Technology", World Journal of Pharmacy and Pharmaceutical Sciences., vol. 8, no. 12, pp. 491-500.*

9. *M. Patel , A. Shah, Dr. N. M. Patel, Dr.. M. R. Patel and Dr. K. R. Patel, " Nanosuspension: A Novel Approach for Drug Delivery System", JPSBR., vol. 1, no. 1,* ***(2011),*** *pp. 1-10.*

10. *S. P. Chaudhari, S. C. Kambale, R. A. Mahajan, S. Jagdale and M. P. Ratnaparkhi , " Nanosuspension -A Novel Approaches in Drug Delivery System", International Journal of Pharma Research & Review., vol. 2, no. 12,* ***(2013),*** *pp. 30-39.*

11. *Ch. Srinivasakumari , P. Sireesha, S. S. Nafees, P. Jagadeesh, S. Dasthagiri and K. S. Basha, " Nanosuspension-An Effective Approach for Solubility Enhancement" , World Journal of Pharmaceutical Research., vol. 5, no. 9, pp. 1518-1544.*

12. *V. R. Patel, Y. K. Agrawal, " Nanosuspension: An Approach to Enhance Solubility of Drugs", Journal of Advanced Pharmaceutical Technology & Research., vol. 2, no. 2,* ***(2011),*** *pp. 81-87.*

13. *M. Nakarani, A. K. Misra, J. K. Patel, and S. S. Vaghani, " Itraconazole Nanosuspension for Oral Delivery: Formulation, Characterization and In Vitro Comparison with Marketed Formulation", DARU Journal of Pharmaceutical Sciences., vol. 18, no. 2 ,* ***(2010),*** *pp. 84-90.*

14. *S. Jacob, A. B. Nair and J. Shah, " Emerging Role of Nanosuspensions in Drug Delivery Systems", Jacob et al. Biomaterials Research., vol. 24, no. 3,* ***(2020),*** *pp. 1- 16.*

15. *J. Hu, K. P. Johnston, and R. O. Williams, " Nanoparticle Engineering Processes for Enhancing the Dissolution Rates of Poorly Water Soluble Drugs". Drug Development and Industrial Pharmacy., vol. 30, no. 3,* ***(2004),*** *pp. 233–245.*

16. *D. Bhowmik, G. Harish, S. Duraive , B. P. Kumar , V. Raghuvanshi and K. P. S. Kumar, " Nanosuspension -A Novel Approaches In Drug Delivery System" ,The Pharma Innovation Journal., vol. 1, no. 12,* ***(2012),*** *pp. 50-63.*

17. *R. Yadollahi, . Vasilev and S, Simovic, " Nanosuspension Technologies for Delivery of Poorly Soluble Drugs", Journal of Nanomaterials.,* ***(2014),*** *pp. 1-14.*

18. *Y. Liu, P. Xie, D. Zhang and Q. Zhang, " A Mini Review of Nanosuspension Development", Journal of Drug Targeting., vol. 20, no. 3,* ***(2012),*** *pp. 209-223.*

19. *F. Flach, S. B. Faes and A. Kwade, " Model Based Process Optimization of Nanosuspension Preparation via Wet Stirred Milling", Power Technology., vol. 331,* ***(2018),*** *pp. 146-154.*

20. *R. L. Shid, S. N. Dhole, N. Kulkarni and S. L. Shid., " Nanosuspension: A Review", Int. J. Pharm. Sci. Rev. Res., vol. 22, no. 1,* ***(2013),*** *pp. 98-106.*

21. *V. B. Patravale, A. A. Date and R. M. Kulkarni, "Nnaosuspension: a Promising Drug Delivery Strategy", JPP., vol. 56,* ***(2004),*** *pp. 827-840.*

22. *G. C. S. Rao, M. S. Kumar, N. Mathivanan and M. E. B. Rao, "Nanosuspensions as the Most Promising Approach in Nanoparticulate Drug Delivery Systems", Pharmazie., vol. 59, no. 1,* ***(2004),*** *pp. 1-5.*

23. *A. A. Tehrani, M. M. Omranpoor, A. Vatanara, M. Seyedabadi and V. Ramezani, "Formation of Nanosuspension in Botton-up-approach: Theories and Optimization", Daru Journal of Pharmaceutical Sciences., vol. 27,* ***(2019),*** *pp. 451-473.*

24. *R. H. Muller, C. Jacobs and O. Kayser, "Nanosuspensions as Particulate Drug Formulations in Therapy Rational for Development and What We Can Expect for the Future", Advanced Drug Delivery Reviews., vol. 47,* ***(2003),*** *pp. 3-19.*

25. *H. M. Patel, B. B. Patel and C. N. Shah, "Nanosuspension : A Novel Approach to Enhance Solubility of Poorly Water Soluble Drugs- A Review", International Journal of Advances in Pharmaceutics., vol. 5, no. 2,* ***(2016),*** *pp. 21-29.*

26. *M. E. Shinde, A. D. Maru, M. P. Sonawane, S. S. Vadje and K. R. Patil, "Nanosuspension: An Promising Approach to Enhance Solubility of Poorly Soluble Drugs", World Journal of Pharmaceutical Research., vol. 9, no. 10,* ***(2020),*** *pp. 131-146.*

27. *S. V. Kadam, D. M. Shinkar and R. B. Saudagar, "Review on Solubility Enhancement Techniques", IJPBS., vol. 3, no. 3,* ***(2013),*** *pp. 462-475.*