Nanosuspensions: A Novel Approach Towards the Drug Delivery System

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ABSTRACT

Nanotechnology has emerged as a tremendous field in the medicine. Nano refers to particles size range of 1-1000nm. Nanosuspensions are part of nanotechnology. Many of the drug candidates are exhibiting poor aqueous solubility. Solubility is an essential factor for drug effectiveness, independent of the route of administration. Poorly soluble drugs are often a challenging task for formulators in the industry. Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. One of the critical problems associated with poorly soluble drugs is too low bioavailability. Nanosuspension technology can be used to improve the stability as well as the bioavailability of poorly soluble drugs. Nanosuspensions contain submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants. Production of drugs as nanosuspensions has been developed for drug delivery systems as an oral formulation and non-oral administration. Currently, efforts are being directed to extending their applications in site-specific drug delivery. The study is focused on the various method of preparation of nanosuspension with their advantages and disadvantages, evaluation of nanosuspension, their application in drug delivery system and current marketed products of nanosuspension.

Keywords: Nanotechnology, Nanosuspension, Solubility, bioavailability.

INTRODUCTION

Nanosuspensions can be defined as colloidal dispersions of nano-sized drug particles that are produced by a suitable method and stabilized by a suitable stabilizer. They can also define as the biphasic system consisting of pure drug particle dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1um in size.[1] Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability. An increase in the dissolution rate of micronized particles (particle size <
Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient. The increases in surface area and concentration gradient lead to a much more pronounced increase in the dissolution velocity as compared to a micronized product. Furthermore, the saturation solubility is increased as well. Another possible explanation for the increased saturation solubility is the creation of high energy surfaces when disrupting the more or less ideal drug microcrystals to nanoparticles. Dissolution experiments can be performed to quantify the increase in the saturation solubility of a drug when formulated into a nanosuspension.\[^{2-5}\]

The term stability is most important in concern of nanosuspension as differences in particle size in nanosuspension always hamper the stability and influences the phenomenon, like Ostwald ripening, that causes further transformation of nanosized particles to microparticle through crystal growth. Thus, uniform particle size is essential for formulation of nanosuspension with required stability.\[^{5}\] The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programmes are poorly water-soluble. The problem is even more intense for drugs such as itraconazole and carbamazepine as they are poorly soluble in both aqueous and organic media, and for drugs having a log \(P\) value of 2. Such drugs often have an erratic absorption profile and highly variable bioavailability because their performance is dissolution-rate limited and is affected by the fed/fasted state of the patient.\[^{6}\]

Traditional strategies, such as micronization, solubilization using co-solvents, the use of permeation enhancers, oily solutions and surfactant dispersions, which evolved earlier to tackle the formulation challenges, have limited use. Although reasonable success has been achieved in formulating water-insoluble drugs using liposomes, emulsions, microemulsions,
solid dispersion technology and inclusion complexes employing cyclodextrins there is no universal approach applicable to all drugs. Hence, there is a growing need for a unique strategy that can tackle the formulation-related problems associated with the delivery of hydrophobic drugs in order to improve their clinical efficacy and optimize their therapy with respect to pharmacoeconomics.\(^{[7,8]}\)

Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly water- and lipid-soluble drugs, and are unique because of their simplicity and the advantages they confer over other strategies. This review focuses on the various aspects of nanosuspensions and their potential as a promising strategy in drug delivery. Nanosuspensions can be defined as colloidal dispersions of nano-sized drug particles that are produced by a suitable method and stabilized by a suitable stabilizer.\(^{[9,10]}\)

**Preparation of nanosuspensions:**

Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols)\(^{[11,12]}\) are called ‘Bottom Up technology’. In Bottom Up Technology the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. Sucker and co-workers used a precipitation technique to produce nanoparticles by dissolving the drug in a solvent and adding the solvent to a nonsolvent that cause precipitation of the fine drug particle. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles.\(^{[13,14]}\)

The limitation of this precipitation technique is that the drug needs to be soluble in atleast one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous. The ‘Top Down Technologies’ are the disintegration methods and are preferred over the precipitation methods. The ‘Top Down Technologies’ include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (NanoedegE).\(^{[13,14]}\)
**Figure 1**
Two differing manufacture processes of nanosuspensions ‘bottom-up’ process, ‘top-down’ process.\(^{[15]}\)

**Preparation method of nanosuspensions:**

There are different methods of Nanosuspensions preparation like,

1. Media milling (Nanocrystal or Nanosystems).
2. Homogenization in water (Dissocubes).
3. Homogenization in nonaqueous media (Nanopure).
5. Nanojet technology
7. Hydrosol method

8. Supercritical fluid method

1. Media milling (Nanocrystal or Nanosystems)

The method is first developed and reported by Liversidge et.al. (1992). The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene resin. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles.\[^{5,16}\]

Advantages:

- Media milling is applicable to the drugs that are poorly soluble in both aqueous and organic media.
• Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.

• Nanosize distribution of final nanosize products.

Disadvantages:

• Nanosuspensions contaminated with materials eroded from balls may be problematic when it is used for long therapy.

• The media milling technique is time consuming.

• Some fractions of particles are in the micrometer range.

• Scale up is not easy due to mill size and weight.

2. Homogenization in water (Dissocubes)

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. Dissocubes was developed by Muller et al. in 1999.\textsuperscript{[17]} The instrument can be operated at pressure varying from 100 – 1500 bars (2800 –21300psi) and up to 2000 bars with volume capacity of 40ml (for laboratory scale).

Principle

In piston gap homogeniser particle size reduction is based on the cavitation principle. Particles are also reduced due to high shear forces and the collision of the particles against each other. The dispersion contained in 3cm diameter cylinder; suddenly passes through a very narrow gap of 25Bm. According to Bernoulli’s Law the flow volume of liquid in a closed system per cross section is constant. The reduction in diameter from 3cm to 25Bm leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure, are reached. The size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenization cycles, and power density of homogeniser and homogenization pressure.
Figure 3: Schematic Cartoon of the High-Pressure Homogenization Process

Advantages:
- It does not cause the erosion of processed materials.
- Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity\textsuperscript{[19]}
- It is applicable to the drugs that are poorly soluble in both aqueous and organic media.
- It allows aseptic production of nanosuspensions for parenteral administration\textsuperscript{[20]}

Disadvantages:
- Preprocessing like micronization of drug is required.
- High cost instruments are required that increases the cost of dosage form.

3. Homogenization in nonaqueous media (Nanopure)
Nanopure is suspensions homogenized in waterfree media or water mixtures.\textsuperscript{[16]} In the Dissocubes technology, the cavitation is the determining factor of the process. But, in contrast to water, oils and oily fatty acids have very low vapour pressure and a high
boiling point. Hence, the drop of static pressure will not be sufficient enough to initiate cavitation.

Patents covering disintegration of polymeric material by high-pressure homogenization mention that higher temperatures of about 80°C promoted disintegration, which cannot be used for thermolabile compounds. In nanopure technology, the drug suspensions in the nonaqueous media were homogenized at 0°C or even below the freezing point and hence are called "deep-freeze" homogenization. The results obtained were comparable to Dissocubes and hence can be used effectively for thermolabile substances at milder conditions.

4. Combined precipitation and homogenization (Nanoedge)
The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation technique, such as crystal growth and longterm stability, can be resolved using the Nanoedge technology. In this technique, the precipitated suspension is further homogenized, leading to reduction in particle size and avoiding crystal growth.

5. Nanojet technology
This technique, called opposite stream or nanojet technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction.

Equipment using this principle includes the M110L and M110S microfluidizers (Microfluidics). Dearn prepared nanosuspensions of atovaquone using the microfluidization process.\[13\] The major disadvantage of this technique is the high number of passes through the microfluidizer and that the product obtained contains a relatively larger fraction of microparticles.

6. Emulsification-solvent evaporation technique
This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.
7. Hydrosol method
This is similar to the emulsification- solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug antisolvent.[21] Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size.

8. Supercritical fluid method
Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process and precipitation with compressed anti-solvent process (PCA). The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. Young et al. prepared cyclosporine Nanoparticles in the size range of 400-700 nm using this process.[22] In the PCA method, the drug solution is atomized into a chamber containing compressed CO2. As the solvent is removed, the solution gets supersaturated and thus precipitates as fine crystals. The supercritical anti-solvent process uses a supercritical fluid in which a drug is poorly soluble and a solvent for the drug that is also miscible with the supercritical fluid. The drug solution is injected into the supercritical fluid and the solvent gets extracted by the supercritical fluid and the drug solution gets supersaturated. The drug is then precipitated as fine crystals. Nanoparticles of griseofulvin, a drug with poor solubility, were prepared by Chattopadhyay et al. using this method. The disadvantages of the above methods are use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques, particle nucleation overgrowth due to transient high super saturation, which may also result in the development of an amorphous form or another undesired polymorph.

Formulation consideration :

1. Stabilizer
Stabilizer plays an important role in the formulation of nanosuspensions. In the absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald’s ripening and agglomeration of
nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. In some cases, a mixture of stabilizers is required to obtain a stable nanosuspension. The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case. Stabilizers that have been explored so far include cellulosics, poloxamers, polysorbates, lecithins and povidones. Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable nanosuspension.\[23\]

2. Organic solvents

Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion as a template. The acceptability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. The pharmaceutically acceptable and less hazardous water-miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. Additionally, partially water-miscible organic solvents can be used as the internal phase of the microemulsion when the nanosuspensions are to be produced using a microemulsion as a template.\[23\]

3. Co-surfactants

The choice of co-surfactant is critical when using microemulsion to formulate nanosuspensions. Since co-surfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycercrizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions.

4. Other additives

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety.
5. Temperature
Maintaining optimum temperature conditions while carrying out the formulation of nanosuspensions is important. Optimally it is very important to carry out the formulation at low temperature conditions while carrying out homogenization. For nanosuspensions manufactured using the emulsion technique, it is significant that when the drug loaded organic solvent is added to the aqueous surfactant solution, homogenization is carried out in an ice bath or other provisions are made for lowering the temperature. The reason behind this is that since organic solvents are involved in the formulation, keeping a higher temperature will lead to rapid removal of the solvent from the system leading to formation of irregular particles. On the other hand in low temperature conditions, the solvent diffuses slowly out of the system leading to the formation of spherical and complete nanoparticles.

6. Stirring Speed
Stirring speed is also an important formulation variable. The homogenization of nanosuspensions leads to maintenance of low particle size and this is achieved either through High Pressure Homogenization (HPH) or High Shear Homogenization (HSH). It has been observed that on an average, increasing the speed of stirring during HSH or increasing the number of cycles during HPH leads to a reduction in the particle size towards the nano-sized range. However, it has been noted that operating the instruments at high speed conditions is not always optimum and an average speed has to be maintained. Optimally, for HSH 20000 RPM and for HSH around 5 to 6 cycles have been recommended. This is because higher agitation speeds often lead to formation of a huge amount of foam in the suspension which often leads to early separation of the solid nanoparticles from the aqueous medium. As a result, this can lead to ineffective size reduction and insufficient formation of the nanoparticle.\textsuperscript{[24]}

Post-production processing
Solidification Techniques
The nanosuspensions usually have the stability issues involved in the physical (e.g. Ostwald ripening and agglomeration) and chemical (e.g. hydrolysis) processes. In this case, solid dosage forms are considered more attractive, due to their patient convenience (marketing aspects) and good stability. Therefore, transformation of nanosuspensions into
the solid dosage form is desirable. Solidification methods of the nanosuspensions include some unit-operations such as pelletization, granulation, spray drying or lyophilization.\[25\] As the primary objective of the nanoparticulate system is rapid dissolution, disintegration of the solid form and redispersion of the individual nanoparticles should be rather rapid, so that it does not impose a barrier on the integrated dissolution process. Drying of nanoparticles can create stress on the particles that can cause aggregation. For example, drying may lead to crystallization of the polymers such as poloxamers, thereby compromising their ability to prevent aggregation. Drying can also create additional thermal stresses that may destabilize the particles. Due to the above considerations, adding matrix-formers to the suspension prior to solidification is necessary. Van Eerdenbrugh et al. had successfully used microcrystalline cellulose to displace sucrose as a matrix former during freeze-drying of itraconazole nanosuspensions\[26\] and had again evaluated four alternative matrix formers [Avicel®PH101, Fujicalin® (CaHPO4), Aerosil®200 SiO2) and Inutec®SP1] for their capability in preserving rapid dissolution after spray-drying of nanosuspensions.\[27\] In addition, the effect of surface hydrophobicity on drug dissolution behaviour upon redispersion had been investigated, indicating the more intense hydrophobicity, the more aggregation of the nanoparticles and the slower the drug’s dissolution after solidification.\[28\]

Surface Modification Techniques

Nanosuspensions have the particular characteristics to increase the saturation solubility and dissolution rate for the poorly soluble drugs. But in some cases, the rapid or burst release of nanosuspensions may result in the side effect and toxicity. As a colloid nanoparticle system, nanosuspensions usually can target the monocyte phagocytic system (MPS), which can aid in the treatment of lymphatic-mediated diseases \[29\], like Mycobacterium tuberculosis, Listeria monogyna, Leishmania sp. The action is called as ‘passive targeting’. However, the passive targeting process could pose an obstacle when either macrophages are not the desired targets or accumulated drug is toxic to MPS cells. Hence, in order to bypass the phagocytic\[30,31\] uptake of the drug, its surface properties need to be tuned, just like stealth liposomes and nanoparticles.\[32,33\] Faced with the above problems, the surface modification of nanosuspensions will be very necessary. In the case of burst release and passive targeting, the controlled release and long residence at site of
action may be effective. For example, Tan et al. had prepared layer-by-layer self-
assembly coated procaine hydrochloride.

Evaluation of nanosuspensions

Nanosuspensions evaluation is done in similar ways as those used for conventional
suspensions such as appearance, color, odor, assay, related impurities, etc. Apart from the
aforementioned parameters, the nanosuspensions should be evaluated for their particle
size, zeta potential, crystalline status, dissolution studies and in vivo studies.

A) In-Vitro Evaluations

1. Particle size and size distribution.
2. Particle charge (Zeta Potential).
3. Dissolution velocity and saturation solubility.
4. Crystalline state and morphology.

B) In-Vivo Evaluation

C) Evaluation for surface-modified Nanosuspensions\(^{[34]}\)

1. Surface hydrophilicity.
2. Adhesion properties.
3. Interaction with body proteins.

1. mean particle size and particle size distribution

The mean particle size and the span of particle size distribution (polydispersity index, PI)
are two important characteristic parameters because they affect the saturation solubility,
dissolution rate, physical stability, even in-vivo behavior of nanosuspensions.\(^{[35]}\) It has
been indicated by Müller & Peters (1998) that saturation solubility and dissolution
velocity show considerable variation with the changing particle size of the
drug.\(^{[36]}\) Particle size distribution determines the physicochemical behavior of the
formulation, such as saturation solubility, dissolution velocity, physical stability, etc. The
particle size distribution can be determined by photon correlation spectroscopy (PCS),
laser diffraction (LD) and coulter counter multisizer.\(^{[37]}\) PCS can even be used for
determining the width of the particle size distribution (polydispersity index, PI). The PI is
an important parameter that governs the physical stability of nanosuspensions and should
be as low as possible for the long-term stability of nanosuspensions. A PI value of 0.1–
0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5
indicates a very broad distribution.\cite{36}\ The coulter-counter gives the absolute number of
particles per volume unit for the different size classes, and it is a more efficient and
appropriate technique than LD for quantifying the contamination of nanosuspensions by
microparticulate drugs.\cite{35}

2. Surface charge (zeta potential)

![Surface Charge (Zeta Potential)](image)

Zeta potential gives certain information about the surface charge properties and further
the long-term physical stability of the nanosuspensions. The zeta potential of a
nanosuspension is governed by both the stabilizer and the drug itself.\cite{36}\ For a stable
 suspension stabilized only by electrostatic repulsion, a minimum zeta potential of 30 mV
is required whereas in case of a combined electrostatic and steric stabilizer, a zeta
potential of 20 mV would be sufficient.\cite{37}

3. crystalline state and particle morphology
The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing.\(^{[35]}\) Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high-pressure homogenization.\(^{[37]}\) The changes in the solid state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis\(^{[38]}\) and supplemented by differential scanning calorimetry.\(^{[39]}\) In order to get an actual idea of particle morphology, scanning electron microscopy is preferred (Mu¨ller & Bo¨hm 1998)

4. saturation solubility and dissolution velocity

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs.\(^{[36]}\) The assessment of saturation solubility and dissolution velocity helps in determining the in vitro behavior of the formulation.\(^{[37]}\)

Properties of nanosuspensions

Physical Long-term Stability

Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is caused due to the difference in dissolution velocity/ saturation solubility of small and large particles. In nanosuspensions all particles are of uniform size hence there is little difference between saturation solubility of drug particles because of that Ostwald ripening is totally absent in nanosuspension which is also responsible for long-term physical stability of nanosuspensions.\(^{[12]}\)

Increase in Saturation Solubility and Dissolution Velocity of drug

Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation
(Equation no.1) dissolution velocity increase due to increase in the surface area from micron size to particles of nanometer size.

\[ \frac{dx}{dt} = \left(\frac{D \times A}{h}\right) \left(\frac{C_s - X}{V}\right) \] -----(1)

Where D is diffusion coefficient, A is surface area of particle, dx/dt is the dissolution velocity, V is volume of dissolution medium and X is the concentration in surrounding liquid.

Internal Structure of Nanosuspensions

The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenisation particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of homogenisation cycles chemical nature of drug and power density applied by homogenizer.[5,12]

Applications

1. Intravenous administration

The parenteral route of administration provides a quick onset of action, rapid targeting and reduced dosage of the drug. It is the preferred route for drugs undergoing first-pass metabolism and those that are not absorbed in the GIT or degraded in the GIT. One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic cosolvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages.[40]

2. Bioavailability enhancement

The poor oral bioavailability of the drug may be due to poor solubility, poor permeability or poor stability in the gastrointestinal tract (GIT). Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension formulation. The therapeutic effect was significantly enhanced, which indicated higher bioavailability.
This was due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min).[36]

3. Pulmonary administration
Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Because of their small size, it is likely that in each aerosol droplet at least one drug particle is contained, leading to a more uniform distribution of the drug in lungs. They also increase adhesiveness and thus cause a prolonged residence time. Budenoside drug nanoparticles were successfully nebulized using an ultrasonic nebulizer.[41]

4. Ocular administration
Ocular delivery of the drugs as nanosuspensions to provide a sustained release of drug. Pignatello et al. prepared Eudragit retardnanosuspensions of cloricromene for ocular delivery. They observed that the drug showed a higher availability in rabbit aqueous humor and the formulation appeared to offer a promising means of improving the shelf-life and the bioavailability of this drug after ophthalmic application.[42]

5. Drug targeting
Nanosuspensions can also be used for targeting as their surface properties and changing of the stabilizer can easily alter the in vivo behavior. The drug will be up taken by the mononuclear phagocytic system to allow regional-specific delivery. This can be used for targeting anti-mycobacterial, fungal or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly.[43]

6. Mucoadhesion of the nanoparticles
Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion." From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption.[44] The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT.
### TABLE 1: SOME RECENT WORKS ON NANOSUSPENSION TO BE MARKETED

<table>
<thead>
<tr>
<th>Drug</th>
<th>Used for</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Anticancer</td>
<td>Intravenous</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Antiasthamatic</td>
<td>Pulmonary</td>
<td>Phase I</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Anticancer</td>
<td>Intrathecal</td>
<td>Phase I</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Hypolidemic</td>
<td>Oral</td>
<td>Phase I</td>
</tr>
<tr>
<td>Thymectacin</td>
<td>Anticancer</td>
<td>Intravenous</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Insulin</td>
<td>Antidiabetic</td>
<td>Oral</td>
<td>Phase I</td>
</tr>
<tr>
<td>Calcium Phosphate</td>
<td>Mucosal vaccine adjuvant for Herpes</td>
<td>Oral</td>
<td>----------</td>
</tr>
<tr>
<td>Silver</td>
<td>Eczema, atopic dermatitis</td>
<td>Topical</td>
<td>Phase I</td>
</tr>
<tr>
<td>Cytokine Inhibitor</td>
<td>Crohn’s disease</td>
<td>Oral</td>
<td>Phase</td>
</tr>
</tbody>
</table>

### TABLE 2: CURRENT MARKETED NANOSUSPENSION PRODUCTS

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug compound</th>
<th>Uses</th>
<th>Company</th>
<th>Nanoparticle technology</th>
</tr>
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<tbody>
<tr>
<td>RAPAMUNE®</td>
<td>Sirolimus</td>
<td>Immunosuppressant</td>
<td>Wyeth</td>
<td>Elan Drug Delivery</td>
</tr>
<tr>
<td>EMEND®</td>
<td>Aprepitant</td>
<td>Antiemetic</td>
<td>Merck</td>
<td>Elan Drug Delivery</td>
</tr>
<tr>
<td>TriCor®</td>
<td>Fenofibrate</td>
<td>Treatment of hypercholesterolemia</td>
<td>Abbott</td>
<td>Elan Drug Delivery</td>
</tr>
<tr>
<td>MEGACEES®</td>
<td>Megestrol acetate</td>
<td>Appetite stimulant</td>
<td>PAR Pharmaceutical</td>
<td>Elan Drug Delivery</td>
</tr>
<tr>
<td>Triglide™</td>
<td>Fenofibrate</td>
<td>Treatment of hypercholesterolemia</td>
<td>First Horizon Pharmaceutical</td>
<td>SkyPharma IDD®-P technology</td>
</tr>
</tbody>
</table>
CONCLUSION
By this we conclude that the drugs which are belonging to the BCS CLASS II & IV were most eligible to prepare in the form of Nanosuspension so that solubility problem we can overcome and ultimately bio availability also increases.

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