

A Review on Nanosuspensionspromising Drug Delivery Strategy.***Toshi Chaurasia, Divya Singh, Nimisha, Dipti Srivastava.**

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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 of a drug can be a limiting factor for its formulation into a suitable dosage form and it influences the effectiveness of a drug to a large extent. Nanosuspensions are defined as the sub-micron colloidal dispersions of pure drug particles stabilized by surfactants. Nanosuspensions differ from nanoparticles and solid lipid nanoparticles with respect to the fact that nanoparticles are polymeric colloidal carrier of drugs while SLN (solid-lipid nanoparticle) are lipidic carrier of drugs. Nanosuspensions can be successfully utilized for the delivery of poorly water soluble drug candidates. Formulation of lipophilic drugs into nanosuspensions improves their stability and also enhances their bioavailability significantly. Nanosuspensions have unique advantages for which they have been utilized for the production of dosage forms suitable for administration through oral, parenteral, ocular and pulmonary routes. Nanosuspensions can be manufactured using the 'Top Down' or 'Bottom's up' technology and employ a variety of components including surfactants for stability purposes and polymers for sustained release of drug in certain formulations.

Key Words

Nanosuspension, Dissolution, Lipophilic Drugs, Colloidal drug delivery, Bioavailability Enhancement.

Introduction

Nanotechnology refers to the projected ability to construct items from the bottom up, using techniques and tools being developed today to make complete, high performance products. More than 40 percent of the drugs coming from High-throughput screening are poorly soluble in water. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms.

One of the main problems responsible for the low turnout in the development of new molecular entities as drug formulations is low solubility and low bioavailability of the lead compounds. The increasing frequency of poorly water soluble new chemical entities exhibiting therapeutic activity is of major concern to the pharmaceutical industry. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability. The approaches include micronization, solubilization using co-solvents, use of permeation

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enhancers, oily solutions, surfactant dispersions, salt formation and precipitation techniques. These techniques for solubility enhancement have some limitations and hence have limited utility in solubility enhancement. These techniques are not applicable to the drugs, which are not soluble in both aqueous and organic Media. Hence there is need of some different and simple approach to tackle the formulation problems to improve their efficacy and to optimize the therapy with respect to pharmacoeconomics.

Nanosuspension

A Nanosuspension is a submicron colloidal dispersion of drug particles. A pharmaceutical nanosuspension is defined as very finely colloid, Biphasic, dispersed, solid drug particles in an aqueous vehicle, size below 1 μ m, without any matrix material, stabilized by surfactants and polymers, prepared by suitable methods for Drug Delivery applications, through various routes of administration like oral, topical, parenteral, ocular and pulmonary routes. A nanosuspension not only solves the problem of poor solubility and bioavailability but also alters the pharmacokinetics of drug and that improves drug safety and efficacy. Nanosuspensions differ from nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid lipid nanoparticles (SLN), which are lipidic carriers of drug. In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems nanosuspensions are used as a formulation approach.

Nanosuspension formulation approach is most suitable for the Compounds with high log P value, high melting point and high dose. The use of nanotechnology to formulate poorly water soluble drugs as nanosuspension offers the opportunity to address nature of the deficiency associated with this class of drugs. Nanosuspension has been reported to enhance absorption and bioavailability it may help to reduce the dose of the conventional oral dosage forms. Therefore to maintain the therapeutics, metronidazole may be used as nanosuspension with a nanoparticle size in the nano range typically between 1-1000nm is proposed. Drug particle size reduction leads to an increase in surface area and consequently in the rate of dissolution as described by the Nernst–Brunner and Levich modification of the Noyes–Whitney equation. In addition, an increase in saturation solubility is postulated by particle size reduction due to an increased dissolution pressure explained by the Ostwald–Freundlich equation. The problem is even more intense for drugs such as itraconazole and carbamazepine (belonging to class III as classified by Washington 1996), 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.

Preparation of Nanosuspensions

The most common approach that has been used for preparing nanosuspensions is micronization by colloid or jet milling. This method increases the dissolution rate of the drug but does not have any impact on the saturation solubility and thus cannot improve the bioavailability of drugs. Sucker and co-workers used a precipitation technique to produce nanoparticles by dissolving the drug in a solvent and adding the solvent to a non-solvent that cause precipitation of the fine drug particle. This has the advantage of using relatively simple and low-cost equipment. However, this created problems in stirring and mixing when taken up for large-scale production. The major challenge of this technique is to avoid crystal growth that occurs on storage due to Ostwald ripening. The principle techniques used in recent years for preparing nanosuspensions can be classified into four basic methods: (a) wet milling, (b) homogenization, (c) emulsification-solvent evaporation and (d) supercritical fluid method.

a) Wet Milling

Nanosuspensions are produced by using high-shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls/pearls. As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined

forces of friction and impact produce a high degree of particle size reduction. The milling media or balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. Planetary ball mills is one example of equipment that can be used to achieve a grind size below 0.1 μm . A nanosuspension of Zn-Insulin with a mean particle size of 150 nm was prepared using the wet milling technique. The major drawbacks of this technology include the erosion of balls/pearls that can leave residues as contaminants in the final product, degradation of the thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles $\geq 5 \mu\text{m}$.

b) Homogenization 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. In this case, the suspension of the drug is made to pass through a small orifice that result in a reduction of the static pressure below the boiling pressure of water, which leads to boiling of water and formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding part containing the drug particles rushes to the centre and in the process colloids, causing a reduction in the particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of drug, the desired mean

particle size and the required homogeneity. The major advantage of high- pressure homogenization over media milling is that it can be used for both diluted as well as concentrated suspensions and also allows aseptic production.

Nanopure

Nanopure is suspensions homogenized in water-free media or water mixtures. 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 non- aqueous 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.

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 collide 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). 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.

c) 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.

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 anti-solvent. Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size.

d) 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.

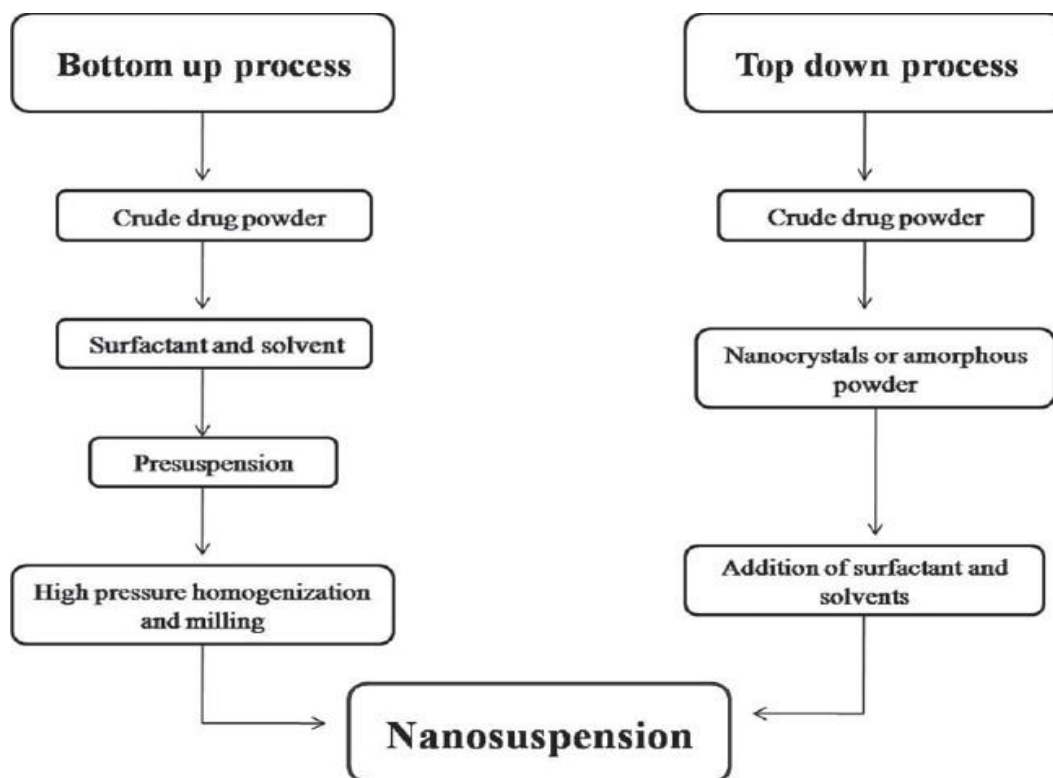


Fig.1: Two differing manufacture processes of nanosuspensions ‘bottom-up’ process, ‘top-down’ process.

Formulation Considerations

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 cellulose, poloxamers, polysorbates, lecithin, and povidone. Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autoclavable nanosuspension.

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.

3. Co-surfactants

The choice of co-surfactant is critical when using microemulsions 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 glycyrrhizinate 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, osmogen 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.

Post-production processing

Post-production processing of nanosuspensions becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also require, when the best possible stabilizer is not able to stabilize the nanosuspension for a longer period of time or there are acceptability restrictions with respect to the desired route. Considering these aspects, techniques such as lyophilization or spray drying may be employed to produce a dry powder of nano-sized drug particles. The effect of post-production processing on the particle size of the nanosuspension and moisture content of dried nano-sized drug should be given due consideration.

Advantages of Nanosuspensions

1. Increase in the dissolution velocity and saturation solubility of the drug

This is an important advantage that makes nanosuspensions amenable to numerous applications. The reason behind the increase in the dissolution

velocity and saturation solubility of the nanosuspensions can be given as follows. According to the Nernst-Brunner and Levich modification of the Noyes Whitney dissolution model equation, the dissolution velocity of the nanosuspension increases due to a dramatic increase in the surface area of the drug particles from microns to particles of nanometer size:

$$dX/dt \propto \frac{D \cdot A}{h} (C_s - X/V)$$

Where, dX/dt is the dissolution velocity,

D is the diffusion coefficient,

A is the surface area of the particle,

h is the diffusional distance,

C_s is the saturation solubility of the drug,

X is the concentration in the surrounding liquid,

V is the volume of the dissolution medium.

2. Improved biological performance

An increase in the dissolution velocity and saturation solubility of a drug leads to an improvement in the in-vivo performance of the drug irrespective of the route used.

3. Ease of manufacture and scale-up

Unlike nanoparticulate carriers such as polymeric nanoparticles, which were investigated earlier, nanosuspensions are easy to manufacture. The production processes described earlier are easily scaled up for commercial production. The introduction of nanosuspension products such as Rapamune and the NanoCrystal colloidal ketoprofen is sufficient to substantiate this.

4. Long-term physical stability

Another special feature of nanosuspensions is the absence of Ostwald ripening, which is suggestive of their long-term physical stability. Ostwald ripening has been described for ultrafine dispersed systems and is responsible for crystal growth and subsequently formation of microparticles. Ostwald ripening is caused by the differences in dissolution pressure/saturation solubility between small and large particles. It is in practice an effect based on the higher saturation solubility of very small particles as compared to larger ones. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles. The diffusion process of the drug from the small particles to the large particles leaves an area around the small particles that is not saturated any more, consequently leading to dissolution of the drug from the small particles and finally completes disappearance of the small particles.

Versatility

The flexibility offered in the modification of surface properties and particle size, and ease of post production processing of nanosuspensions enables them to be incorporated in various dosage forms, such as tablets, pellets, suppositories and hydrogels, for various routes of administration, thus proving their versatility.

Characterization of Nanosuspension

1. Mean particle size and 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 behaviour of nanosuspensions. It is indicated that saturation solubility and dissolution velocity show considerable variation with the changing, particle size of the drug. Particle size distribution determines the physiochemical behaviour of the formulation, such as saturation solubility, dissolution velocity and physical stability. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. 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. 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.

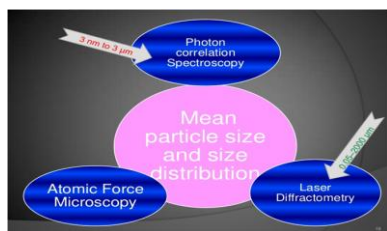


Fig.2: Mean Particle size.

2. Surface charge (zeta potential)

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. 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.

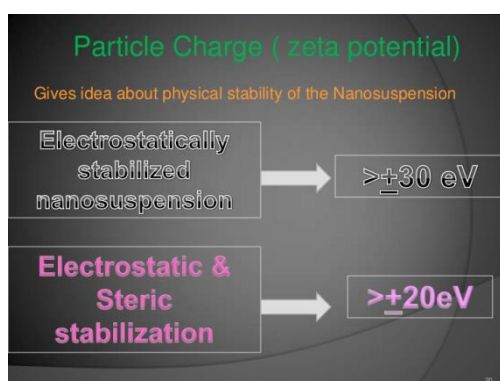


Fig.3: Surface Charge (Zeta Potential).

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. 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. 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 and supplemented by differential scanning calorimetry. In order to get an actual idea of particle morphology, scanning electron microscopy is preferred.

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.

5. Dissolution Studies

An USP dissolution apparatus (Electrolab, India) Type II (paddle method) at rotation speed of 50 rpm was used for in vitro testing of drug dissolution from the various formulations obtained after each size reduction step.

Stability of Nanosuspensions

The high surface energy of nanosized particles induces agglomeration of the drug crystals. The main function of the stabilizer is to wet the drug

particles thoroughly to prevent Ostwald ripening and agglomeration of the nanosuspension and form a physically stable formulation by providing a steric or an ionic barrier. Typical examples of stabilizers used in nanosuspensions are celluloses, poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral nanosuspensions.

Pharmaceutical Application of Nanosuspension

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.

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).

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. Budesonide drug nanoparticles were successfully nebulized using an ultrasonic nebulizer.

4. Ocular administration

Ocular delivery of the drugs as nanosuspension provides a sustained release of drug. Pignatello et al. prepared Eudragit retard nanosuspensions of chloricromene 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.

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* behaviour. 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.

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. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT.

7. Targeted drug delivery

The need to target drugs to specific sites is increasing day by day as a result of therapeutic and economic factors. Nanoparticulate systems have shown tremendous potential in targeted drug delivery, especially to the brain. Successful targeting of the peptide dalargin to the brain by employing surface modified poly isobutyl cyanoacrylate nanoparticles has been a major achievement in targeted delivery. Likewise,

nanosuspensions can be used for targeted delivery as their surface properties and *in vivo* behaviour can easily be altered by changing either the stabilizer or the milieu. Their versatility and ease of scale-up and commercial production enables the development of commercially viable nanosuspensions for targeted delivery. Overall nanosuspensions have indicated a good potential in targeted drug delivery but this has yet to be fulfilled.

Conclusion

The nanosuspensions technology can be successfully utilized for overcoming problems associated with poorly soluble drugs or lipophilic drugs insoluble in both organic and aqueous media. Large scale production methods of production of nanosuspensions like media milling or high pressure homogenization have been employed for manufacture. There exist a number of technologies which have a huge commercial application and can be utilized for further advancements in the area of formulation of poorly soluble drugs. The recent advancements in the work being done related to nanosuspensions show that many formulations are being developed on a laboratory scale which have a potentially important clinical significance and can be used for the mitigation of diseases.

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Table 1: Current Marketed Pharmaceutical Products Utilizing Nanosuspension Formation.

Product Drug	compound	Indication	Company	Nanoparticle Technology
RAPAMUNE	Sirolimus	Immunosuppressant	Wyeth	Elan Drug Delivery Nanocrystals
EMEND	Aprepitant	Antiemetic	Merck	Elan Drug Delivery Nanocrystals
TriCor	Fenofibrate	Treatment of Hypercholesterolemia	Abbott	Elan Drug Delivery Nanocrystals
MEGACERES	Megestrol acetate	Appetite stimulant	PAR Pharmaceutical	ElanDrug Delivery Nanocrystals
Triglide	Fenofibrate	Treatment of Hypercholesterolemia	First Horizon Pharmaceutical	SkyePharma IDD-P Technology

Conflict of Interest: Not Declared
