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Nano-Suspension A Tool for Enhancing Bioavailability : A Systematic Review

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Abstract: *Nanosuspension technological know-how solved the drawback of medications which are inadequately watery dissolvable and less bioavailability. Steadiness and bioavailability of the medications can be expanded by means of the Nanosuspension technology. Coaching of Nanosuspension is simple and relevant to all medicinal drugs which are fluid insoluble. Nanosuspensions are readied through utilizing wet mill, high strain homogenizer, emulsion□solvent evaporation, melt emulsification approach and super significant fluid systems. Nanosuspension can be prepared with the aid of using stabilizers, natural and organic solvents and different components such as buffers, salts, polyols, osmogent and cry protectant. Nanosuspensions can likewise be delivered with the aid of oral, parenteral, aspiratory and visual courses. Nanosuspensions can additionally be used for distinct drug supply when included in the ocular inserts and mucoadhesive hydrogels.*

Keywords: Nanosuspension, Lipid solubility, Particle size, Oral bioavailability

I. INTRODUCTION

Nanotechnology has the potential to drastically alter our lives in general, and our health situation in particular. In today's world, it is one of the most critical areas of research and development. Nanotechnology is a subset of the larger field of nanoscience, which is one of the most promising, demanding, and rewarding research areas in today's scientific landscape. [1] It's the study of small particles with distinct properties that vary as the particle's size changes. [2] A pharmaceutical nanosuspension is characterised as very finely colloid[3] , biphasic[4] , dispersed solid drug particles in an aqueous vehicle with a size less than 1 m, stabilised by surfactants[5] and polymers[6], and prepared for drug delivery[7] applications using appropriate methods. Reduced particle size (10-1000nm) leads to increased dissolution rate and therefore enhanced bioavailability. [8] Used for oral or topical application, as well as parentral and pulmonary administration. [9] Nanosuspension has been shown to improve adsorption and bioavailability, which could lead to lower doses in convectional oral dosage types. [10] Micronization, solubilization with co-solvents, salt form, surfactant dispersions, precipitation procedure, and oily solution are only a few of the traditional methods for improving the solubility of poorly soluble drugs. Liposomes, emulsions, microemulsions, solid dispersion, and inclusion complexation with cyclodextrins are examples of other techniques. More than 40% of drugs are poorly soluble in water, rendering typical dosage forms difficult to formulate. The problem is even more complicated for class II drugs, which are poorly soluble in both aqueous and organic media. Nanosuspensions are preferred in the cases described above. [9] Drugs that are insoluble in both water and organic solvents will benefit from nanosuspension technology. [11] Nanosuspension not only eliminates the issue of low solubility and bioavailability, but it also changes the drug's pharmacokinetics, improving its protection and efficacy. [12]

Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs such as Atorvastatin, [13] Famotidine, [14] Simvastatin, [15] Revaprazan, [16] Aceclofenac, [17] are formulated as Nanosuspension .Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size. The Nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a Nanosuspension can also be incorporated in a solid matrix [18-23].

Nano is a Greek word, which means ‘dwarf’. Nano means it is the factor of 10-9 or one billionth. Some comparisons of nanoscale are given below,

0.1 nm = Diameter of one Hydrogen atom.

2.5 nm = Width of a DNA molecule

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1 micron = 1000 nm.
1 nm = 10-9m= 10-7 cm = 10-6 mm.
Micron = 10-6m= 10-4 cm = 10-3mm 4.
For a long duration of time micronization of poorly soluble drugs by colloid mills or jet mills was preferred. The overall particle size distribution ranges from 0.1µm to approximately 25µm, only negligible amount being below 1µm in the nanometer range.

When to go for Nano Suspensions Approach

- Preparing nano suspensions is preferred for the compounds that are insoluble in water (but are soluble in oil) with high log P value.
- Conventionally the drugs that are insoluble in water but soluble in oil phase system are formulated in liposome, emulsion systems but these lipidicformulation approaches are not applicable to all drugs. In these cases nano suspensions are preferred.
- 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.[24,25]

Potential Benefits of Nanosuspension Technology for Poorly Soluble Drugs

- Reduced particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, area under plasma versus time curve, onset time, peak drug level, reduced variability, reduced fed/fasted effects.
- Nanosuspensions can be used for compounds that are water insoluble but which are soluble in oil. On the other hand, Nanosuspensions can be used in contrast with lipidic systems, successfully formulate compounds that are insoluble in both water and oils.
- Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the drug and thereby enhancing its absorption.
- A pronounced advantage of Nanosuspension is that there are many administration routes for Nanosuspensions, such as oral, parenteral, pulmonary, dermal and ocular.
- Nanosuspension of nanoparticles (NPs) offers various advantages over conventional ocular dosage forms, including reduction in the amount of dose, maintenance of drug release over a prolonged period of time, reduction in systemic toxicity of drug, enhanced drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, suitability for poorly water-soluble drugs and smaller particles are better tolerated by patients than larger particles, therefore nanoparticles may represent auspicious drug carriers for ophthalmic applications.
- Nanosuspension has low incidence of side effects by the excipients.
- Nanosuspensions overcome delivery issues for the compounds by obviating the need to dissolve them, and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability.
- Increased resistance to hydrolysis and oxidation, increased physical stability to settling.
- Reduced administration volumes; essential for intramuscular, subcutaneous, ophthalmic use.
- Finally, Nanosuspensions can provide the passive targeting.[26-29]

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II. METHODS OF PREPARATION OF NANOSUSPENSION

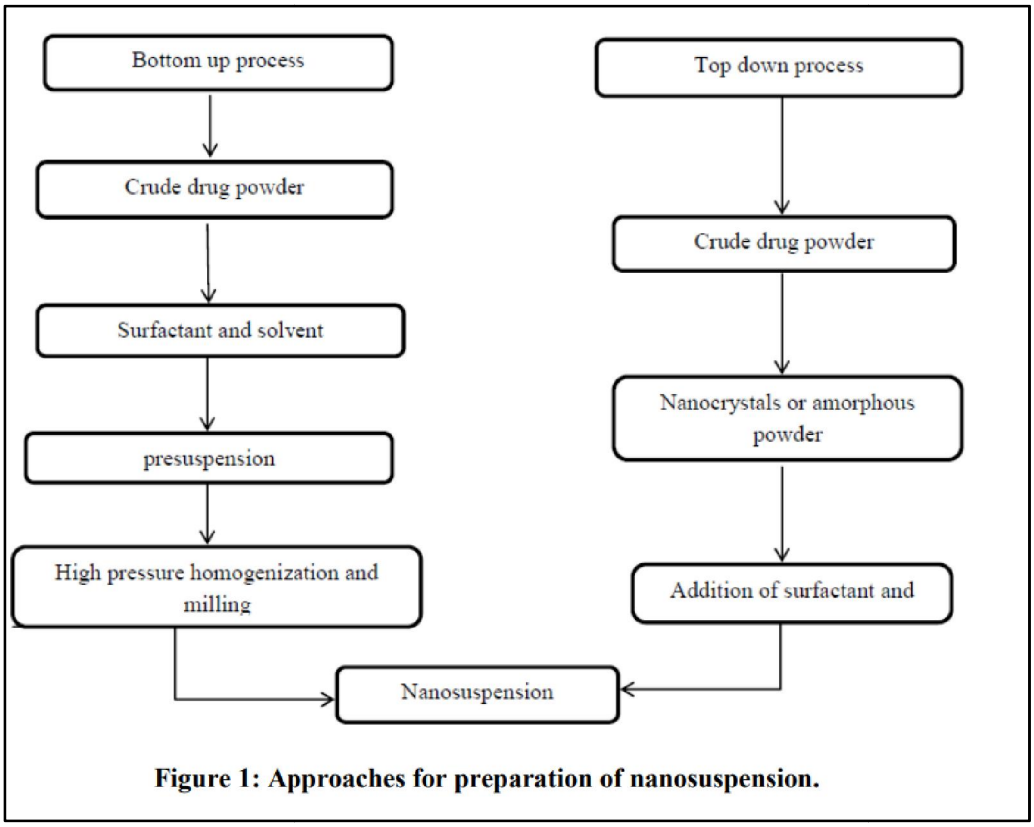

Figure 1: Approaches for preparation of nanosuspension.

Mainly there are two methods for preparation of Nanosuspensions. The conventional methods of precipitation (Hydrosols) are called 'Bottom up technology'. 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 non aqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege). [22-29]

1) Bottom-up technology
2) Top-down technology

2.1 Bottom-Up Technology

The term "Bottom-up technology" means that one starts from the molecular level, and goes via molecular association to the formation of a solid particle.That means that we are discussing classical precipitation techniques by reducing the solvent quality, for example, by pouring the solvent into a nonsolvent or changing the temperature or a combination of both. Precipitation is a classical technique in pharmaceutical chemistry and technology.[30-34]

Advantage

- Use of simple and low cost equipment.
- Higher saturation solubility is the advantage for precipitation compared to other methods of Nanosuspension preparation.

Disadvantages

- 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).
- The solvent needs to be miscible with at least one nonsolvent.
- Solvent residues need to be removed, thus increasing production costs.
- It is an Iittle bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction). In

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general, it is recommended that a second consecutive process has to be performed for particle preservation that is spray drying or lyophilisation.[35-37]

2.2 Top-Down Technology

The top down technologies include

- Media milling
- High pressure homogenization

Media 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 (PM100 and PM200; Retsch GmbH and Co., KG, Haan, Germany) is one example of an 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 ≥5 µm. [38-41]

Advantages

- Simple technology
- Low-cost process regarding the milling itself
- large- scale production possible to some extent (batch process).

Disadvantages

- Potential erosion from the milling material leading to product contamination.
- Duration of the process not being very production friendly.
- Potential growth of germs in the water phase when milling for a long time.
- Time and costs associated with the separation procedure of the milling material from the drug nanoparticle suspension, especially when producing parenteral sterile products.[38-41]

III. HIGH PRESSURE HOMOGENIZATION

3.1 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 center 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. This principle is employed in the APV Gaulin Micron LAB 40 Homogenizer (APV Homogenizer, Lóbeck, Germany) and the NS 1001L-Panda 2K high-pressure homogenizer (Nirosuavi. S.P.A., Parma, Italy).

To produce a Nanosuspension with a higher concentration of solids, it is preferred to start homogenization with very fine drug particles, which can be accomplished by pre-milling. 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.[42-45]

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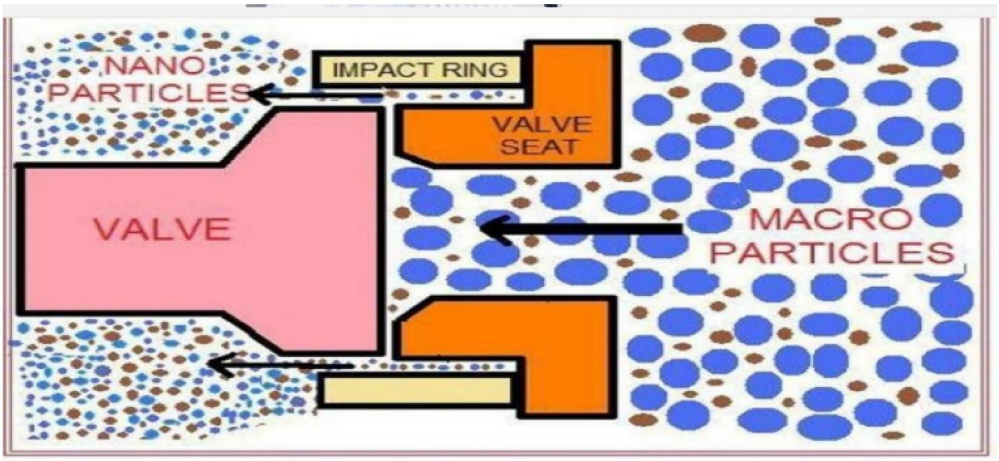

Figure No 2: Schematic representation of the high-pressure homogenization process.

3.2 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 800 C promoted disintegration, which cannot be used for thermolabile compounds. In nanopure technology, the drug suspensions in the non- aqueous media were homogenized at 00 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.[46,47]

3.3 Emulsion Diffusion Method

Apart from the use of emulsion as drug delivering vehicle they can also be used as templates to produce Nanosuspension. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscile solvent. Such solvents can be used as the dispersed phase of the emulsion. An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants with stirring to form an emulsion. The obtained emulsion was further homogenized by high pressure homogenization. After homogenization cycles the emulsion was diluted with water, homogenized by homogenizer to diffuse the organic solvent and convert the droplets into solidparticles. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the Nanosuspension by controlling the size of the emulsion optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally methanol, ethanol, ethyl acetate chloroform are used as a organic solvents .47-50

Advantages

- Use of specialized equipment is not necessary.
- Particle size can easily be controlled by controlling the size of the emulsion droplet.
- Ease of scale-up if formulation is optimized properly.

Disadvantages

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- Safety concerns because of the use of hazardous solvents in the process.
- Need for diultrafiltration for purification of the drug Nanosuspension, which may render the process costly.
- High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.[47-50]

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3.4 Micro Emulsion Template

This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the Nanosuspension which is stabilized by surfactants. Another method makes use of partially water-miscible solvents such as butyl lactate, benzyl alcohol and triacetin as the dispersed phase instead of hazardous solvents.48-51

Advantages

- Use of specialized equipment is not necessary.
- Particle size can easily be controlled by controlling the size of the emulsion droplet.
- Ease of scale-up if formulation is optimized properly.

Disadvantages

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- Need for diultrafiltration for purification of the drug Nanosuspension, which may render the process costly.
- High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.

IV. FORMULATION CONSIDERATION

4.1 Stabilizer

The main function of a stabilizer is 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 barrier. The type and amount of stabilize has a pronounced effect on the physical stability and in vivo behavior of Nanosuspension. Stabilizers that have been used so far are poloxomers, polysorbate, cellulosics, povidones, and lecithins. Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autoclavable nanosuspension.52

4.2 Organic Solvent

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, ispropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol, are preferent in the formulation over the conventional hazardous solvents, such as dichloromethane.52,53

4.3 Co-Surfactants

The choice of co-surfactant is critical when using micro emulsions to formulate Nanosuspensions. Since cosurfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected micro emulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassiumglycerrhizinate as cosurfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions.54

Other additives Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant.

4.4 Characterization of Nanosuspension1-54

- In-vitro evaluations
- Color, Odor, Taste
- Particle size distribution
- Particle charge (Zeta Potential)
- Crystal morphology
- Dissolution velocity and Saturation solubility
- Density

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- pH Value
- Droplet Size
- Viscosity Measurement
- Stability of Nanosuspension

In-vivo Biological Performance

- Evaluation for surface-modified Nanosuspension
- Surface hydrophilicity
- Adhesion properties
- Interaction with body proteins

V. PHARMACEUTICAL APPLICATION OF NANOSUSPENSION [55-58]

By means of making use of postproduction handling, Nanosuspensions are set up into different dose types. Nanosuspension raises dissolution rate and absorption of drug because of smaller particle dimension and bigger surface field [59-64] . By way of utilizing postproduction processing, Nanosuspensions are all set into various dosage types. Nanosuspension raises dissolution expense and absorption of drug as a result of smaller particle measurement and larger floor subject.

5.1 Oral Drug Delivery [66-69]

Negative solubility, incomplete solvency, deficient disintegration, and inadequate adequacy are the fundamental obstacle of oral medication organization. As an aftereffect of smaller particle dimension and far larger floor to volume ratio, oral Nanosuspensions are exceptionally used to develop the absorption price and bioavailability of ineffectively dissolvable medications [0] if there should arise an occurrence of azithromycin Nanosuspensions, more than sixty five% drug was observed to be broken down in 5 hours as when contrasted and 20% of micronized medicines [71] . The Nanosuspensionhave focal points like increased oral assimilation, measurements proportionality, and low intersubject variability. Via using typical fabricating strategies, drug Nanosuspensions will also be easily included into more than a few dosage forms like drugs, capsules, and rapid melts. The Nanosuspension of Ketoprofen used to be efficiently included .into pellets for the maintained unencumber of drug over the period of 24 hours

5.2 Parental Drug Delivery

The reward systems for parental delivery comprise micellar options, salt formation, solubilization using cosolvents, cyclodextrincomplexation, and extra recently vesicular programs akin to liposomes and niosomes. However these methods have barriers like solubilization ability, parental acceptability, high manufacturing fee, and so on. To resolve the above issues, the Nanosuspension science is used. Nanosuspensions are regulated through different parental courses comparable to intraarticular, intraperitoneal, intravenous, and many others. Additionally, Nanosuspensions expand the adequacy of parenterally managed medicinal drugs. Paclitaxel Nanosuspension was said to have their prevalence in decreasing the median tumor burden [73] ClofazimineNanosuspension showed an development in balance as good as efficacy above the liposomal clofazimine in Mycobacterium aviumcontaminated feminine mice [74-80] Rainbow et al. Showed that intravenous Nanosuspension of itraconazole improved viability of antifungal undertaking in rats relative to the answer formulation [81-85] .

5.3 Pulmonary Drug Supply

For pulmonary delivery, Nanosuspensions may also be nebulized by means of mechanical or ultrasonic nebulizers. Due to the nearness of numerous little particles all vaporized beads incorporate drug nanoparticles. Budesonide corticosteroid has been effectively prepared within the form of Nanosuspension for pulmonary supply [86-97] Aqueous suspensions of the drug can also be quite simply nebulized and given by way of pulmonary route because the particle dimension may be very small. Extraordinary forms of nebulizers are to be had for the administration of liquid formulations. One of the medications effectively tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc [86-92] .

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5.4 Ocular Drug Supply [93-97]

Nanosuspensions are utilized as a part of visual conveyance of the medications for supported free up. Liang and associates arranged cloricromeneNanosuspension for visual supply using Eudragit. Check affirmed better accessibility of medication in fluid humor of rabbit eye. Accordingly, Nanosuspension components offer a promising method of bettering the shelf-existence and bioavailability of drug after ophthalmic software [98].

5.5 Distinct Drug Delivery

Nanosuspensions are compatible for targeting precise organs considering that of their surface houses. Along with this, it is anything but difficult to modify in vivo conduct by altering the stabilizer [99-106]. The drug will probably be taken up by the mononuclear phagocytic method which allows area-particular delivery. This can be utilized for focusing on antifungal, antimycobacterial, or antileishmanial pharmaceuticals to macrophages if the pathogens continue intracellularly [107-112] Kayser formulated an aphidicolinNanosuspension that extended the drug concentrating on to macrophages that have been Leishmania infected. He acknowledged that the drug within the type of Nanosuspension had EC50 of zero.003 µg/ml, whereas the traditional form had 0.Sixteen µg/ml. Scholer et al. Described an superior drug concentrating on to brain within the treatment of toxoplasmic encephalitis making use of an atovaquoneNanosuspension [113-120]

Table 3: Available marketed drugs in the form of nanosuspension with their route of administration

Route	Drugs	Therapeuticclass	Company/author
Oralroute	Carbamazepine	Psycholytic	D.Douroumis
	Megestrolacetate	Steroidhormone	Par Pharmaceuticals
	Paliperidonepalmitate	Antischizophrenia	JohnsonandJohnson
	Insulin	Diabetes	BioSante
	Ketoprofen	Analgesic	RemonJ.P.
	Azithromycin	Antimicrobial	DianruiZhang
	Albendazole	Anthelminticdrug	MittapalliP.K.
	Tarazepide	SelectiveCCKa-antagonist	C.Jacobs
	Griseofulvin	Antifungal	BorisY.Shekunov
	Mitotane	AdrenalCortexHormones	MicheleTrotta
	Cilostazol	cagent	Jun-ichiJinno
	Aphidicolin	Antileishmanial	O.Kayser
	Buparvaquone	Antibiotic	MüllerR.H.
	Fenofibrate	Lipidlowering	SkyePharma
	Cytokineinhibitor	Crohn'sdisease	ElanNanosystems
	Emend	Anti-emetic	ElanNanosystems
	Rapamune	Immunosuppressant	ElanNanosystems
	Probucol	Lipidlowering	JyutaroShudo
	Danazol	Hormone	Rogers T. L.
Parental	Naproxen	Anti-inflammatory	AnchaleeAin-Ai
Intravenous	Loviride	Antivirotic	B.VanEerdenbrugh
	Clofazimine	Antimycobacterials	K.Peters
	Oridonin	Anticancer	LeiGao
	Ascorbylpalmitate	Antioxidant	VeerawatT.
	Dihydroartemisinin	Antimalarial	JirapornC.
	Omeprazole	Protonpumpinhibitor	JanMöschwitzer
	Thymectacin	Anticancer	ElanNanosystems
	Paclitaxel	Anticancer	AmericanBioscience
Ophthalmic	Hydrocortisone	Glucocorticoid	M.A.Kassem

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	Prednisolone		
	Hexadecadrol		
Pulmonary	Budesonide	Asthma	JerryZ.Yang
	Fluticasone		
Intrathecal	Busulfan	Anticancer	SkyePharma
Topical	Silver	Eczema	Nucryst

VI. CONCLUSION

Nanosuspensions are exceptional and commercially viable technique to remedy … the issues of hydrophobic medication. Akin to terrible solvency and poor bioavailability. For gigantic-scale construction of Nanosuspensions, media processing and high-weight homogenization science had been efficaciously used. Placing traits, like development of dissolution velocity, expanded saturation solubility, accelerated bioadhesivity, flexibility in surface change, and simplicity of postproduction preparing, have enlarged the utilizations of Nanosuspensions for quite a lot courses of organization. The utilizations of Nanosuspensions in oral and parental courses have been extremely good headquartered, despite the fact that purposes in pneumonic and visual conveyance must be assessed. However, their supply by means of buccal, nasal, and topical delivery is but to be accomplished

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