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Formulation and evaluation of Rosiglitazone nanosuspension

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ABSTRACT

The main aim of this study is to formulate and evaluate Rosiglitazone Nanosuspension. Nanosuspensions are colloidal dispersion 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 1micro meter in size. Rosiglitazone is an oral rapid and short –acting anti-diabetic drug from the sulfonylurea class. It is classified as a second generation sulfonylurea, which means that it undergoes enterohepatic circulation. Rosiglitazone Nanosuspension was prepared by precipitation technique. After preparation of Nanosuspension various characterisation studies were done such as drug content, % yield, FTIR, DSC, TEM, and Invitrodrug release.PVPK30, polaxomer are used as stabilizers. From the dissolution study F4 formulation which containts PVPK30 as stabilizer was considered as optimized formulation. It showed maximum drug release at 30min.FTIR and DSC studies revealed that good stability in dispersion.

INTRODUCTION

Oral drug delivery system

Oral dosage form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by oral route. Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration. Of drugs that are administered orally, solid dosage forms represent the preferred class of product.

Advantages

- Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms
- Ease of administration
- Solid dosage forms represent unit dosage forms in which one usual dose of the drug has been accurately placed
- Self medication
- Avoidance of pain
- Patient compliance

Disadvantages

- Action of drugs is slower
- Unpalantable drugs are difficult
- May cause nausea and vomiting

Importance of drug solubility

Solubility is one of the important parameter in Biopharmaceutical classification system (BCS), and dissolution rate is the most essential factor controlling the bioavailability of drugs. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. A compound with solubility of less than 1 part per 10,000 part of water is categorized as poorly water soluble drug (sanjeev K, et al. 2009).

However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism. The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form.

To overcome the problems associated with oral absorption and bioavailability issue, various strategies have been utilized including prodrug formation, complexation, microcapsulation, the use of surfactants, permeation enhancers, micronization, salt formation, self-emulsifying drug delivery system, solid dispersions, Nanosuspension.(Huda N.H. et al. 2011) One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate Nanosuspension.

Approaches for enhancement of solubility and dissolution rate

Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

dc/dt = AD (Cs-C)/h

Where, dC/dt = rate of dissolution

A = surface area available for dissolution

D =diffusion coefficient of the compound

Cs= solubility of the compound in the dissolution medium

C =concentration of drug in the medium at time t

h =thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

To increase the dissolution rate from equation the following approaches are available.

1. To increases the surface area available for dissolution by
   - Decreasing the particle size of drug.
   - Optimizing the wetting characteristics of compound surface.
2. To decrease the boundary layer thickness.
3. Ensure sink condition for dissolution.
4. Improving apparent solubility of drug under physiologically relevant conditions.

Methods for enhancement of bioavailability

(Pinnamaneni S, et al. 2002)

There are numerous techniques to enhance bioavailability, which involves:

Physical modification

Physical modification often aims to increase the surface area, solubility and wet ability of the powder particles and is therefore focused on particle size reduction or generation of amorphous states. The various approaches under this method are:

Particle size reduction

- Micronization
- Nanosuspension

Modifications of the crystal habit

- Polymorphs.
- Pseudo polymorphs (including solvates)

Complexation / solubilization

- Use of cyclodextrines
- Use of surfactants

Drug dispersion in carriers

- Solid dispersions
- Eutectic mixtures
- Solid solutions

Chemical modification

Chemical modification aim at altering the drug chemically by various methods in order to produce a water soluble compound. The widely used approaches under this category are:

- Formation of soluble prodrugs
- Formation of salts of the compound
- Preparation of covalent polymer drug conjugates.

NANOSUSPENSION

Nanosuspension is favoured for compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses. 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.(Banavath H, et al. 2010)

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

1micron = 1000 nm.

1 nm = 10^{-9} m = 10^{-7} cm = 10^{-6} mm.

Micron = 10^{-6} m= 10^{-4} cm = 10^{-3} mm 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.

Rationale for nanosuspension

- 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 lipidic
- Formulation 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 Nano suspensions are used as a formulation approach.
- Nano suspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose.(Mohanty S, et al.2010)

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 (.Nagare SK,et al.2012)

PREPARATION OF NANO SUSPENSION

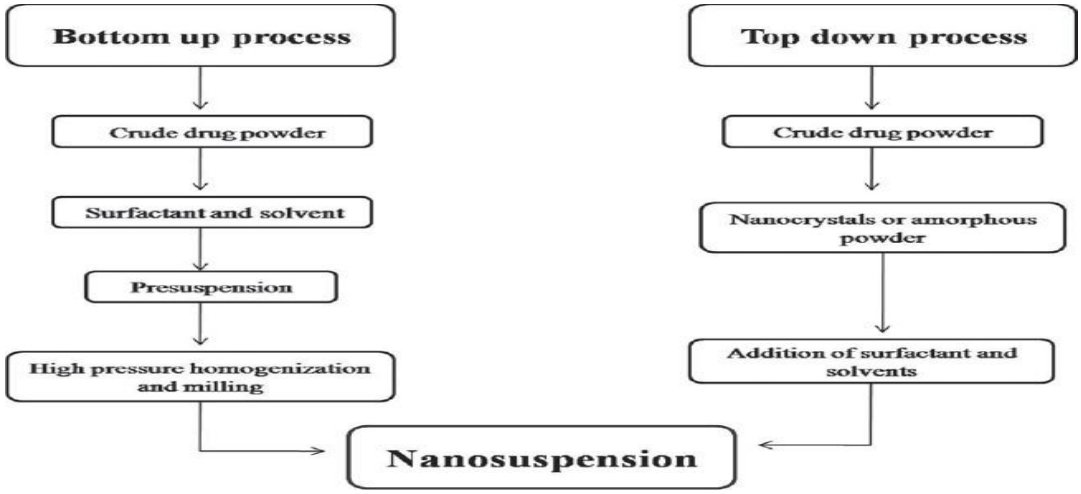

Figure no 1: Approaches for Preparation of Nano suspension

Precipitation method

Precipitation method is a general method used to prepare submicron particles of poorly soluble drugs.[Matteucci ME, et al.2007] In this method, drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid supersaturation of drug in the solution, and formation of ultrafine amorphous or crystalline drug. This method involves nuclei formation and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size. [Bodmeier R,et al.1998]

High-pressure homogenization

This technique involve the following three steps: First, drug powders are dispersed in a stabilizer solution to form pre suspension; after that, pre suspension is homogenized by high pressure homogenizer at a low pressure sometimes for pre milling; and finally homogenized at a high pressure for 10 to 25 cycles until the nano suspension

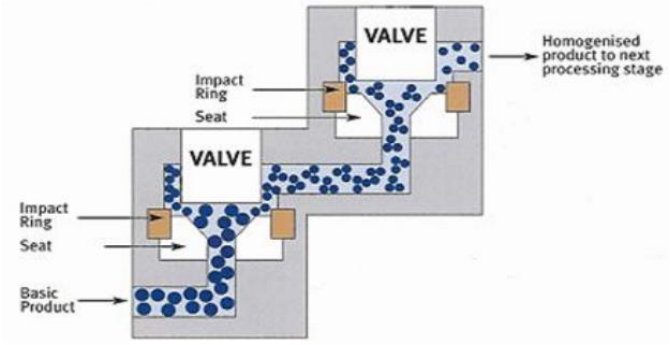

Figure no 2: High pressure homogenization

Homogenization in Aqueous Media (Dissocubes)

Dissocubes technology was developed by Muller in 1999. The instrument can be operated at pressure varying from 100 to 1 500 bars (2 800 – 21 300 psi) and up to 2 000 bars with volume capacity of 40 ml (for laboratory scale). For preparation of nanosuspension, it is essential to prepare a presuspension of the micronized drug in a surfactant solution using high-speed stirrer. According to Bernoulli's Law, the flow volume of liquid in a closed system per cross section is constant. The reduction in diameter from 3 cm to 25 µm 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 is 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 homogenizer and homogenization pressure. Preprocessing like micronization of drug and high-cost instruments increases the overall cost of dosage form. Various drugs like Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine And Dexamethasone were prepared as nanosuspensions using this method. [Nagaraju P,et al.2010]

Homogenization in Nonaqueous Media (Nanopure)

Nanopure is suspension homogenized in water-free medium. It is “deep-freeze” homogenization where the drug suspensions in non aqueous medium are homogenized at 0°C or sometimes below the freezing point. Because of very high boiling point and low vapor pressure of water, oils, and fatty acids, the drop of static pressure is not enough to begin cavitation in nanopure technology. Other homogenization technologies and patents on the homogenization processes are shown inTable 1(Keck CM,et al.2006)

Technology	Company	Patent number
Dissocubes	SkyePharma	US 5,858,410
Nanopure	PharmaSol	PCT/EP00/0635
Nanocrystal™	Élan Nanosystems	US 5,145,684
Nanomorph™	Soligs/Abbott	D 1963 7517
Nanoedge™	Baxter	US 6,884,436
Hydrosol	Novartis (prev. Sandoz)	GB 22 69 536 GB 22 00 048

Figure no 3:Homogenization technologies and patents on the homogenization processes

Media milling

Liversidge *et al*. had a patent on nanocrystal technology. In this technique, drugs are subjected to media milling for nanoparticle production. Effect of impaction between the milling media and drugs gives essential energy for disintegration of the microparticulate system into nanoparticles. In this process, the chamber of milling is charged with the milling media involving drug, stabilizer, and water or suitable buffer, which is rotated at a very high shear rate to generate suspension. Residues left behind in the finished product is a major problem of this method. [Patravale VB,et al.2004]

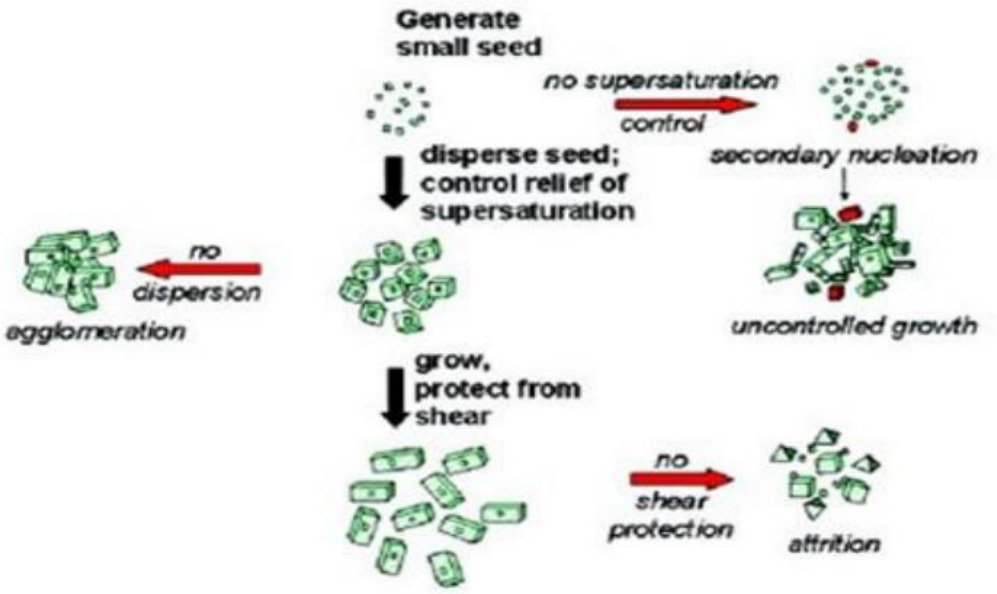

Figure no 4: Media milling process

Dry cogrinding

Since many years, nanosuspensions are prepared through wet grinding processes by using pearl ball mill. Nowadays, nanosuspensions can be prepared by dry milling methods. Stable nanosuspensions are prepared by using dry grinding of poorly soluble drug with soluble polymers and copolymers after dispersing in liquid medium. Itoh *et al*. have described the colloidal particles formation of many poorly water-soluble drugs like nifedipine, griseofulvin, and glibenclamide with sodium dodecyl sulfate and polyvinylpyrrolidone as stabilizer.
[Wongmekiat A, et al.2002]

Lipid emulsion/microemulsion template

Nanosuspensions are also obtained by just diluting the emulsion, formed by using a partially water-miscible solvent as the dispersed phase. The emulsion technique is applicable for drugs which are either partially water miscible or soluble in volatile organic solvents. Additionally, microemulsion templates can also produce nanosuspensions. Microemulsions are dispersions of two immiscible liquids like water and oil and stabilized thermodynamically by surfactant or cosurfactant. The drug is either loaded into preformed or internal phase of microemulsion and can be saturated by intimate mixing of drugs.[Patravale VB,et al.2004] Griseofulvin nanosuspension is prepared by the microemulsion technique by using water, butyl lactate, lecithin, and the sodium salt of taurodeoxycholate.[Trotta M,et al.2003]

Microprecipitation – High-pressure homogenization (Nanoedge)

Nanoedge is a combination of microprecipitation and high-pressure homogenization techniques. Method includes precipitation of friable materials followed by fragmentation under high shear and/or thermal energy.[Kipp JE.et al.2003] The preparation method of nanoedge is shown in Figure4.[Hintz RJ,et al.1989]

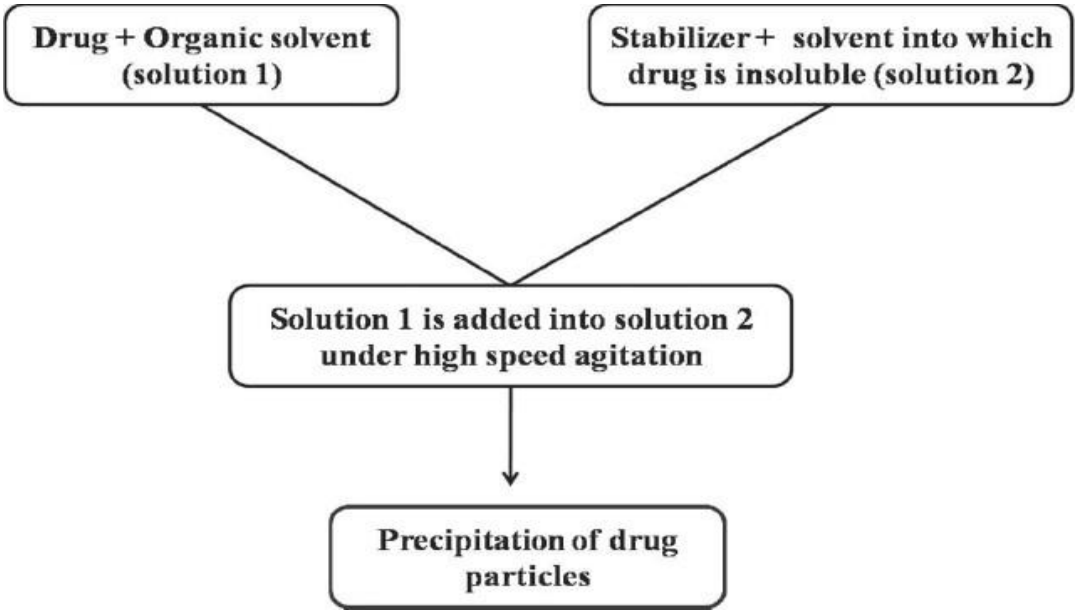

Figure no 5: Method for preparation of nanoedge

Melt emulsification method

Solid lipid nanoparticles are mainly prepared by melt emulsification method. Kipp and co workers firstly prepare nanosuspensions of ibuprofen by using melt emulsification method. It is a four-step procedure. Drug is first added to aqueous solution having stabilizer. The solution is heated at temperature higher than the melting point of the drug and then homogenized by high-speed homogenizer for the formation of emulsion. The temperature is maintained above the melting point of the drug during overall process. Finally, the emulsion is cooled to precipitate the particles. The particle size of nanosuspension mainly depends on parameters like drug concentration, concentration and type of stabilizers used, cooling temperature, and homogenization process. [Kipp JE, et al.2003]

Nanojet technology

This technique is also called opposite stream technology, uses a chamber where a stream of suspension is divided into two or more parts. Both streams are colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Dearns had prepared nanosuspensions of atovaquone using the microfluidization process. 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. [Dearns R,et al.2000]

Supercritical fluid methods

Various methods like rapid expansion of supercritical solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process are used to produce nanoparticles. In RESS technique, drug solution is expanded through a nozzle into supercritical fluid, resulting in precipitation of the drug as fine particles by loss of solvent power of the supercritical fluid. By using RESS method, Young *et al*. prepared cyclosporine nanoparticles having diameter of 400 to 700 nm. In the PCA method, the drug solution is atomized into the CO_2compressed chamber. As the removal of solvent occurs, the solution gets supersaturated and finally precipitation occurs. In supercritical antisolvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the drug solution becomes supersaturated.

PHARMACEUTICAL APPLICATIONS

Oral drug delivery

Poor solubility, incomplete dissolution, and insufficient efficacy are the major problem of oral drug administration. Due to smaller particle size

and much larger surface to volume ratio, oral nano suspensions are specially used to increase the absorption rate and bioavailability of poorly soluble drugs. [Boedeker BH,et al.1994] In case of azithromycin nanosuspensions, more than 65% drug was found to be dissolved in 5 hours as compared with 20% of micronized drugs.[Jia L,et al.2002] The nanosuspension have advantages like improved oral absorption, dose proportionality, and low intersubject variability. By using standard manufacturing techniques, drug nanosuspensions can be simply incorporated into various dosage forms like tablets, capsules, and fast melts. The nanosuspension of Ketoprofen was successfully incorporated into pellets for the sustained release of drug over the period of 24 hours. [Liversidge EM,et al.1996]

Parental drug delivery

The present approaches for parental delivery include micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes. But these methods have limitations like solubilization capacity, parental acceptability, high manufacturing cost, etc. To solve the above problems, the nanosuspension technology is used. Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, nanosuspensions increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have their superiority in reducing the median tumor burden.[Liversidge EM,et al.2003] Clofazimine nanosuspension showed an improvement in stability as well as efficacy above the liposomal clofazimine in *Mycobacterium avium*-infected female mice. Rainbow *et al*. showed that intravenous nanosuspension of itraconazole enhanced efficacy of antifungal activity in rats relative to the solution formulation.

Pulmonary drug delivery

For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Budesonide corticosteroid has been successfully prepared in the form of nanosuspension for pulmonary delivery.[HernandezTrejo N,et al.2007] Aqueous suspensions of the drug can be easily nebulized and given by pulmonary route as the particle size is very small. Different types of nebulizers are available for the administration of liquid formulations. Some of the drugs successfully tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc.[Heidi MM,et al.2009]

Ocular drug delivery

Nanosuspensions are used in ocular delivery of the drugs for sustained release. Liang and co-workers prepared cloricromene nanosuspension for ocular delivery using Eudragit. Experiment showed higher availability of drug in aqueous humor of rabbit eye. Thus, nanosuspension formulation offers a promising way of improving the shelf-life and bioavailability of drug after ophthalmic application.[Liang YC,et al.2008]

Targeted drug delivery

Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter *in vivo* behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly.[Kayser Oe,et al.2005] Kayser formulated an aphidicolin nanosuspension that improved the drug targeting to macrophages which were Leishmania infected. He stated that the drug in the form of nanosuspension had EC_{50} of 0.003 µg/ml, whereas the conventional form had 0.16 µg/ml. Scholer *et al*. described an enhanced drug targeting to brain in the treatment of toxoplasmic encephalitis using an atovaquone nanosuspension.[Scholer N,et al.2001]

MARKETTED PRODUCTS OF NANOSUSPENSIONS

Table no 1: marketed products of nanosuspensions

BRAND NAME	DRUG COMPOUND	INDICATION	COMPANY	NANOPARTICLE TECHNOLOGY
RAPAMUNE	**Sirolimus**	**immunosuppresant**	**Wyeth**	**Elan drug delivery nanocrystals**
EMEND	**Aprepitant**	**Antiemetic**	**Merck**	**Elan drug delivery nanocrystals**
TRICOR	**Fenofibrate**	**hypocholesteremic**	**Abbott**	**Elan drug delivery nanocrystals**
MEGACE ES	**Megestrol acetate**	**Appetite stimulant**	**PAR pharmaceutical**	**Elan drug delivery nanocrystals**
TRIGLIDE	**Fenofibrate**	**hypocholesteremic**	**First horizon pharmaceutical**	**Skyepharma iddp technology**