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A Novel Drug Delivery System: Nanosuspension

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Abstract: ***Over the past two years, Very innovative technology has been developed in pharmaceutical R&D business. Automation of technology like high - throughput screening is driving the drug invention process, combinatorial chemistry, and computer - aided medicine design. There are several medication candidates with very high effectiveness. Regrettably, most of these drug candidates are not easily soluble in water. The use of drug nano suspension is a universal formulation strategy it can be used to enhance the therapeutic effectiveness of these drugs in any mode of delivery. Colloidal dispersions of drug particles are called nano suspensions. immobilized by a surfactant that is submicron in size. A nano suspension is an extremely dilute dispersion of Oral, topical, parenteral and pulmonary delivery of solid drug particles in aqueous solution. Solid size distribution the particles of nano suspension particle are typically the particles are smaller than a micron in size, with an average particle size of 201 to 601 nanometers. The nano suspension made of a pure weakly a medication that dissolves in water suspended in dispersion the absence of a matrix component. This review article discusses the physicochemical characteristics of the drug. Nano suspension technology of production and potential clinically benefits.***

Keywords: Nanosuspension, Novel drug delivery system

1. Introduction

Drugs that dissolve poorly in water have been always a difficult problem for pharmaceutical researcher, and it is believed that more than 42% of the process in the drug discovery program leads to the development of new chemical compounds that do not dissolve well in water.[1] Medicines that are definitely insoluble in water present a variety of problems when prepared in traditional dosage form. The most important issues with non - dissolving drugs are their poor bioavailability and inconsistent absorption.[2] The issues is much greater for medication like itraconazole, which are classified under the BCS system.[3] Because they are insoluble in both aqueous and living solutions, and they have a log p value of two.[4] There is a disruption in the presentation of these medication rate - limiting (for classes 2nd and 3rd pharmaceuticals) and is influenced by the patient's eating/fasting status. Abnormal dissolution rates are associated with solubility as well as size of particles. As a result, the size of the particles also affects the rate of dissolutions increases.[5]

There are several techniques to address the challenges of poor solubility and bioavailability.[6] Micronization, solubilization use of co - solvents, enhanced oily solutions surfactant dispensers, salt formulations and rain technology are some of the strategies used.[7] Since these solubility enhancement strategies have some limitations, their value in solubility enhancement is restricted.[8] The colloid mill or jet mill improves micronization.[9] As surface area increases, drug dissolution rate increases but saturation solubility does not increase.[10]

Liposomes, emulsions, and micro - employing emulsions, solid - dispersion, and inclusion complexes are examples of other approaches.[11] Cyclodextrin has had moderate success but universality is lacking.[12] These methods are unsuitable for medications that do not dissolve in water and do not occur in every aquatic and biological environment. Consequently, there is a need for a new and easier strategy to deal with formulation issues to enhance and maximize drug efficacy with respect to bioavailability.[13]

The articles focus on work with nano suspensions and their ability to increase solubility. The challenges combined with the delivery of weakly soluble, as well as less water - soluble and lipid - soluble drug, and their foundation is their particular simplicity and they bring advantages over other suggestions. This review concentrates on several features of nano suspension and their potential as a viable drug delivery technology. The science and engineering of the nanoscale is known as nanotechnology, defined as 09–10 m.[14] Micronized drug microparticles Powder pharmaceuticals are translated into nanoparticles using bottom - up and top - down techniques as well as dissolution methods[15,.] Nano is a Greek word meaning "dwarf". Nano is a multiple of 09 - 10 or one billionth. Below are more nanoscale comparisons.[16]

0.1 nm = Diameter of one Hydrogen atom[17]
2.5 nm = Width of a DNA molecule.1micron = 1000nm.
1nm = 10 - 9m= 10 - 7cm = 10 - 6mm.
micron = 10 - 6m= 10 - 4cm = 10 - 3mm.

Nano Suspension is a colloidal dispersion of nano sized medicine particles that are generated using an appropriate technology and stabilized with a suitable stabilizer.[18] It is a colloidal dispersion of medicine particles immobilized on a sub - micron scale by surfactant. Nano suspension threading solves problems related with the water soluble distribution of poorly soluble and lipid soluble pharmaceuticals.[19] Nano suspensions unlike nanoparticles, which are polymeric colloidal drug carriers (Nano spheres and Nano capsules)

and solid - lipid nano particles (SLNs), which are lipidic medicine carriers.[20] Preferred Nano suspension preparation for substances with high log p values which are not dissolved in water yet dissolved in oil. Water - insoluble but oil - soluble drugs have been traditionally used. Although phage systems are built into liposomes and these lipid compositions are emulsion systems techniques are not suitable for all medication. Nano suspension is preferable in these circumstances. Instead of employing a lipidic system, Nano suspension is employed as a formulation strategy for medicine insoluble in both water and organic media. Approach to the most suitable is nano suspension formulation for chemicals with more log p values, melting points and unstable dosages.[21]

2. Methods of Preparation

There are mainly two approaches to prepare nano suspensions.[22] The traditional precipitation method (Hydrosols23) is called "nano technology". Nano technology innovation to precipitate crystals; the medicine is soluble in a solvent before being mixed with a non - solvent. Essential Benefits of precipitation this approach employs basic and lows cost equipment. The fundamental problem of this approach is that drug crystal formation must be controlled throughout the precipitation step. Surfactants are addition to inhibit the growth of micro particles.[23] The restriction of the medicine should be soluble and insoluble in at least one solvent in case the solvent fails during the precipitation process. Ahead, the precipitation approach does not apply to drugs that are weakly dissolved in both aqueous and non - aqueous media.[15] Method is called 'top down technology'. Evaporation and precipitation methods are recommended. Top down technologies attached media milling (nanocrystal), Water homogenization at high pressure (disocube), Non - media high pressure homogenization (nanopure), Simultaneous precipitation and high pressure homogenization (nanoage).[16] Other procedures for preparation are nanosuspension templates for emulsions and micro emulsion templates for emulsions.[22]

Media Milling (Nanocrystals or Nanosystems)

It was created by Liverseys et al (1992) using a patent - protected technique.[23] The technique was previously business owned by Nanosystems, although it was presently renamed to announce and was purchased by Drug Distribution. Using pearl mills or high shear media mills, this method forms nano suspensions.[24] The media mill is composed of three parts a milling chamber and shaft, and a recirculation chamber. Media, water, medicine and stabilizer on the milling chamber, and after the milling media or so, the beads are spun at a high shear rate. The milling method is complete at a regulated temperature.[25]

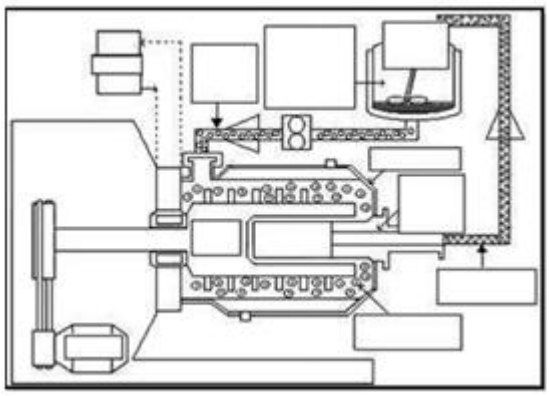

Figure 1: Schematic representation of the media milling process

The active component of the mill is a milling chamber filled with polymer medium. The mill may work in either batch or repeat mode. A crude solution including medicine, Water and stabilizer are supplied to the milling chamber, which is then nanocrystalline spread processing. Specific residence time for nanoscale sized dispersions with an average diameter of 200 nm 31–61 min.[24]

Principle

High shear and energy force produced is the basic principal of milling media which involve input medicine for converting microparticulate drugs into nanoparticles. Glass, zirconium oxide, or strongly cross - linked polystyrene resins are used as milling media. This process can be run in both batch and cyclic processes.[15] Amount of time necessary to obtaining dispersion with a unimodal diffusion profile and a mean diameter of approx 199 mm in batch mode is 31–61 min. Media milling techniques are possible.[23] Drug crystals, both micronized and non - micronized, are treated. One time formulation and technique are adjusted, batch - to - batch variation in dispersion quality is quite small.[20]

Advantages[16]

- Medicines that are not easy to dissolve in both aqueous and organic medium are subjected to media grinding.
- It is possible to fix both very thin and highly concentrated nanosuspensions. By adjusting the dosage of drug from 1mg/ml to 400mg/ml.
- Distribution of final nanosize objects in nanosize.

Disadvantages[16]

- When used for long - term treatments, ball - eroded materials can result in contaminated nanosuspensions.
- Media milling techniques take time.
- Some particles are micrometer in size.
- Due to the size and weight of the grinder, scaling is difficult.

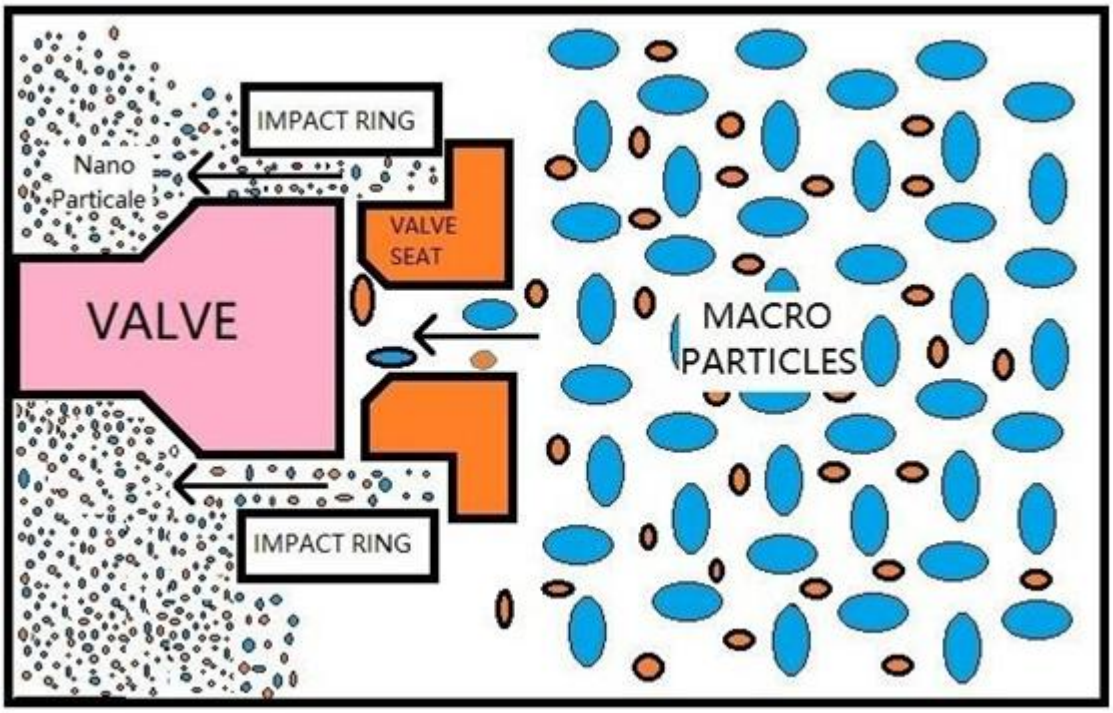

Figure: 2 Schematic representation of the high - pressure homogenization process

High pressure homogenizers (disocubes) [18]

R H Müller invented the disco cubes technique (Muller et al. 1998). The Disco Cubes patent was previously owned by medicine Delivery Services GmbH, but is now owned by Skypharma plc. Disco Cubes are designed with a piston - gap - type high - pressure homogenizer. Homogenizers in general use APV Micron Lab 40.[25] Other piston gap homogenizers, like as Avastin and Stansted, Stansted, UK, can be utilizing well used. Homogenizer with high pressure is composed of a high pressure plunger pump and an aftermarket relief valve. Plunger pump operation the relief is to

supply the needed amount of energy. The release valve is made using one fixed valve seat with one variable valve. These elements create a radial precision differential that is tunable. The force applied to the valve changes the position, resistance and therefore symmetry of the gap.[26] An outer impact ring creates a known external cross - section and protects the valve casing from flow damage (Jenke 1998). The device is present in both configurations which are discontinuous and continuous. The continuous version is ideal for fixing various homogenization process parameters. If the drug is too expensive, the discontinuous version or restricted availability is preferable. Equipment can be pressurized in variable between 100 and 1500 times. In some devices up to 2000 times the maximum pressure can be achieved. Overpressure homogenizers are present in sizes ranging from 41mL (for laboratory use) to a few 1000 L (for mass manufacture).[25]

For the manufacture of nano suspensions, it is best to start with micronized medicine. (particles size 24 m). Bridging the symmetry gap as a result, a jet milled medicine is used as raw materials for the manufacture of disco cubes. Before homogenization, it is important to create a precipitate micronized medicine in surfactant solution using high - speed stirrer. During the homogenization procedure the medicine solutions is forced through the homogenization gap to end the drug nano sizing process.[18]

Principle

The medicine particles are dispersed while homogenization. High shear force due to cavitation forces sand colliding particles to collide with one another. The medicine suspension encapsulated in a 3 mm diameter cylinder. Flows through a 25 m thin symmetry gap, resulting in a fast streaming velocity.[18]

The fluid's dynamic pressure rises as the homogenization interval decreases, Bernoulli's equation states. That boiling point of water at constant pressure and temperature is less than. As a result of this, the water begins to boil at ambient temperature, resulting in a gas bubble that closes the suspension gap (known as the cavitation) and returns to air pressure. Detonation force is powerful enough to shatter drug microparticles into nanoparticles. Furthermore, high - speed particle collisions aid in the nanosizing of pharmaceuticals. Additionally, viscosity enhancers are beneficial under certain circumstances to improve the effectiveness of nanosizing by increasing the powder density inside the dispersion region.[25]

Advantages[25]

- Low soluble medicine in both aqueous and organic media the nanosuspension can simply be made.
- Scalability and batch - to - batch variation (Grauetal2000).
- The nanoparticulate drug has a narrow size distribution in the finished product (Muller Bohm 1998).
- Allows for septic nanosuspension formulation for parenteral delivery.
- Dosage management for drugs ranging from one to four hundred milligram. Up to ML - 1, it remains incredibly thin and concentrated. Allows the production of

concentrated nanosuspension (Krause & Muller 2001).

Disadvantages[25]

- Prerequisites for Micronized Drug Particles
- Prerequisites for forming a suspension using a high - speed mixer before homogenization.

Emulsions as templates

In addition to using emulsions as a medicine delivery medium, they could be also used to create nanosuspensions as a template. Emulsions can be used as a template for pharmaceuticals which are partially dissolved in volatile water or organic solvent. As the dispersed state of an emulsion, such solvents can be employed. The technique involves the combination of solvents containing the medicine in a living solvent or an aqueous phase that includes suitable surfactants for making emulsions.[27] The living phase then evaporates under low - pressure, with the resulting drug particles immediately precipitating to produce the nanotechnology surfactant - stabilized suspension. Because a particle is created in adjusting the particle size of each emulsion droplet, nanosuspension is attainable by adjusting the size of the emulsion. The optimized surfactants structure improves the living phase absorption, and the medicine is finally put into the emulsion. Methylene chloride and chloroform were the most commonly used organic solvents.[27] Human safety concerns regarding environmental risks and waste solvents, however, Their use in general construction works is limitedIt is still possible to employ relatively safe solvents such as ethyl acetate and ethyl formate.[29]

Another approach employs solvents which are somewhat soluble in water dispersion; butyl lactate, benzyl alcohol and triacetin are some examples.[30] General approach produces emulsions and medicinal nanosuspensions only by dilution of the emulsion. The emulsion - based dilution of water promotes complete diffusion of the inner step in outer phase, which results in growth of the nano suspension in an instant. To be suitable for administration, the nanosuspension must be released from the internal phase and the surfactant must be released via diultrafiltration. However, if all of the chemicals employed in the manufacture of nano suspensions are present in appropriate amounts for the if you choose the conventional to separate the nano suspension, a simple centrifugation or ultracentrifugation process will suffice.[28]

Advantages[28]

- It is not necessary to use any special tools.
- The emulsion's size drop allows easy adjustment of the particle size.
- Ease of scaling if the formulation is tuned correctly.

Disadvantages[28]

- This process can’t be used to manufacture medicine that is less soluble in both aqueous and living media.
- Process safety risks stem from the use of toxic solvents.
- Drug purification nanosuspensions require diultrafiltration, which can be costly.
- As a comparison, a larger dosage of surfactant/stabilizer needed. For previously specified manufacturing processes.

Drug nanosuspensions made from emulsion templates that are poorly soluble in water has been effectively used for the low bioavailable anticancer medicine mitotane, in which the solubility rate is improved five times.[30]

Templates (microemulsions)

Microemulsions are two immiscible liquids, such as oil and water, dispersed that are thermodynamically stable and isotropically transparent, held together through an interface coating of surfactant and co - surfactant.[31] Their characteristics, including excellent drug solubility, long shelf life, simplicity of synthesis and low cost, make from one attractive medicine delivery vehicle.[32] Microemulsions have recently been reported as templates for the synthesis of solid lipid nano particles and polymer nanoparticles. Microemulsions can also be used to form nanosuspensions using the micro - emulsion structure.[33] For this reason, micro - emulsions of oil in water are recommended. As described previously, these microemulsions' internal phase can be either a slightly miscible liquid or a suitable organic solvent.[34]

New delivery system can be prepared ahead of time or loaded during the internal phase. By close mixing, the medicine can be soaked with a microemulsion. A previously known process is used to obtain the drug through the dilution of microemulsion nanosuspension. Co - surfactant concentration and ratio when ingesting effect surfactant in order to receive appropriate medivine loading, the size of the microemulsion should be on the internal stage and the globule tested and adjusted.[31] The resulting nanosuspension is to be liberated by the diultrafilament in order of the internal phase and surfactant to make it appropriate for administration. Therefore, if all materials are used to make the available in nanosuspension an acceptable concentration for the chosen administration route, to separate the nanosuspension, simple centrifugation or ultracentrifugation is sufficient. For emulsion templates, the benefits and drawbacks are similar. Only extra kilometer is required. Less energy is required for the production of nanosuspension based on microemulsion.[35]

3. Formulation Consideration

Stabilizer

The stabiliser is important in the development of the nanosuspension. When no sufficient stabilizer is present, the large surface strength of nanosized particles is capable of giving rise to drug crystal aggregation or aggregation. The primary role of a stabilizer is to completely moisten the medicine particles and to inhibit Ostwald's Ripening and Nanosuspension Stacks so that a physically stable formulation can be obtained by providing a stable or ionic barrier.[35] The drug - to - stabilization ratio ranges from 1: 20 to 20: 1 and should be assessed for each individual instance. Examples of stabilizers discovered so far are cellulosic, poloxamers, polysorbates, lecithin and povidone.[36]

Organic solvents

If the nanosuspension is to be made using an Emulsion or Microemulsion as a Model, living solvents may be necessary. Solvents that dissolve in water, such as ethanol

and isopropanol, as well as solvents that are partially soluble in water, In the manufacture of standard hazardous solvents such as dichloromethane, ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, and benzyl alcohol, ethyl acetate, ethyl formate, butyl lactate, triacetin, propy. Furthermore, when producing micro - emulsions using certain water nanosuspensions, miscible living solvents can be employed the inner phase. As a template, consider a micro emulsion.[36]

Co - surfactants

When working with fine emulsions, the selection of co - surfactant is crucial. Since co - surfactant may have adverse effects on behavior, the influence of the co - surfactant selected microemulsion composition and the intrinsic steps of medicine loading should be investigation. Despite the literature mentions dipotassium and bile salts glycyrrhizinate as co - surfactants, several soluble substances Co - surfactants such as transcutol, glycofurol, ethanol and isopropanol can be safely employed in the production of micro emulsions.[32]

Another additive

Depending on the salts, polyols, osmogen and cryoprotectant, nanosuspension additives such as buffers may be used. The method or quantity characteristics of the are also criteria for selection suitable of additive.[32]

Advantages of Nanosuspensions

Physical Long - term Stability

For Ostwald's ripening the formation of microparticles for crystal growth, causes physical instability in scattered systems. The other thinks are solubilization velocity, Small and big particle saturation solubility causes Ostwald ripening. Since all particles in the nanosuspension are of similar size, there is small variability in the drug particle saturation solubility. Due to the constant particle size, Ostwald ripening is completely absent in the nanosuspension, It is also in charge of the long - term physical stability of the nanosuspension.[37]

Applications of Nanosuspensions in Drug Delivery

Oral drug delivery

Among different delivery approaches, the oral approach is preferable method of medicine is administration. The effectiveness or performance of an oral dose of a medicine is usually affected by its solubility and absorption through the gastrointestinal system. The effectiveness or performance of an oral the solubility and absorption of a drug through the gastrointestinal tract usually determines its dosage. As a result, drug candidates with low water solubility and dissolution rates are considered to have sluggish and oral bioavailability is very diverse.[35]

Danazol is a gonadotropin inhibitor with low bioavailability, a significant increase in bioavailability was observed when the commercial danazol macrosuspension was delivered as a nanosuspension on Danocrine. The absolute bioavailability of the danazol nanosuspension is 81.9%, while the danazol of the danazol suspension is only 5.3% bioavailability.[38]

Parenteral drug delivery

In terms of formulation, the nano suspension fits practically all of them parameters of an optimal medicine delivery method for parenteral administration. Due to the fact that the drug particles are directly nanosized, practically all drugs can be processed by parenteral administration. As a result, considerable progress can be achieved in nano suspension. The dose of the drug tolerated by the parent, resulting in a decrease in the cost of treatment has also decreased, as has the clinical performances.[39]

Ocular drug delivery

Drugs with poor solubility in lacrimal secretion may also benefit from nanosuspension. The drug nanosuspension can be incorporated for a set amount of time to achieve sustained release. in a suitable hydrogel, mucoadhesive, or ocular insert foundation. The designed polymeric nanosuspension demonstrated superior in - vivo activity to the current marketing formulation and drug delivery ability for 24 hours.[40]

Pulmonary drug delivery

Drugs with low solubility in pulmonary secretions can be delivered via nanosuspension. Currently, such medications are administered using aerosols or dry powder inhalers. Both suspension aerosols and dry powder inhalers used in pharmaceuticals contain micron - sized particles.[41]

Targeted drug delivery

Because the surface characteristics and stabilizers of the nanosuspension can be easily modified in vivo, they can be employed for targeted delivery conduct.[41] Adaptability and simplicity of large - scale and commercial fabrication allow the creation of commercially viable nanotechnology solutions for targeted medicine delivery. Kaiser created aphidicolin as a nano suspension for medication development. Action directed toward Leishmania - infected macrophages, and aphidicolin was found to be very active at concentrations in the MG range.[42]

4. Conclusion

Low water solubility is becoming an obstacle for researchers working on different types of medicine delivery, leading to the use of pharmaceutical chemicals and innovative production processes for delivery. The use of medication nano suspension is a universal formulation strategy for improving therapeutic efficacy effectiveness of these pharmaceuticals regardless of the method of administration. Nearly every drug can be scaled down to the nanoscale range. For the large - scale fabrication of nano suspensions, industrial processes media milling and long pressure homogenization are two examples. effectively used. Emulsions and microemulsions as templates for ways of manufacturing progress Nevertheless, a straightforward approach to manufacturing is offered, although with limitations. Further research is still needed in this aspect.

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