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Review Article

Review on nanoparticles technology and applications based on drug delivery

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ABSTRACT

This review is about nanocrystal technology and applications of nanocrystals based on drug delivery. Nanocrystal technology is applied to the drug molecules to access for good drug delivery as nano dimensioned carrier. Nanoparticle has at least one dimension smaller than 100 nanometers. The major properties of nanoparticles are increases dissolution velocity by surface area enlargement and increase in saturation solubility. Nanoparticle's productions are done with different methods such as precipitation method, Milling method, and homogenized method. Nanoparticles has got wide range of applications based on drug delivery such as gastrointestinal tract, brain, tumor cell targeting, respiratory tract, and gene delivery.

1. Introduction

A nanocrystal is a particle that composed of atoms in either a single or poly-crystalline arrangement with at least one dimension smaller than 100 nanometers, based on quantum dots. The size of nanocrystals recognized from larger crystals.

Nanotechnology is encountered all around our daily lives. The increasing field of biotechnology, where new tools are discovered to easily interact with proteins in ever smaller sizes are needed and categorized for cosmetic research and products where nanosized agents can provide a whole range of benefits. In all these fields the need for ever decreased size is common. The nano size of products, whether for medical use like mini robots to clean arteries, the food industry like nano encapsulated vitamins for functional food and the application of drugs for pharmaceutical uses, is an important factor both on the economical, as well as on the medical or pharmaceutical side. This article will focus on nanosized crystals in medical application. In drug delivery and clinical applications, the nanoparticles, where particles are reduced in size to below 1000 nm is one of the key factors for modern drug therapy, now and in the years to come.

At currently, 90% of all newer drug molecules are still in development process. Basically, the drug formulation development and dosage for treatment are considered based on BCS classification which gives the parameters of solubility and membrane permeability of drug molecules. So, the drug molecules are divided into 4 classes such as BCS class **I** (high solubility and high permeability), BCS class **II** (low solubility and high permeability), BCS class **III** (high solubility and low permeability), and BCS class IV (low solubility and low permeability). In which BCS class **II**, **III** and IV need of formulation tools, to increase the drug particles solubility and permeability should reduce the drug particle size. The drug particle size is reduced by using different size reducing technologies such as micronization, nanocrystal technology, cosolvents, etc. nanocrystals are one of size reducing technique, where particles are reduced to nano size. By reducing the drug particles to nano size

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leads to increase the surface area which finally increases the dissolution velocity of drug that results in better drug release and therapeutic action. This nano technique achieves the biopharmaceutics issues such as pharmacokinetic and pharmacodynamic issues which eventually solves the issues of bioactivity of drug core compound. [1–5]

2. Definition of Nanoparticle

Based on the size unit, in the pharmaceutical area nanoparticles should be defined as having a size between a few nanometers and 1000 nm (1 μm); micro particles therefore possess a size of 1–1000 μm.

2.1. What is Nanoparticles? [6]

Nanoparticles are solid colloidal particles which includes macromolecules such as active ingredients (drugs or biologically active molecules) with a size varying from 1 to 1000 nm., that is dissolved, entrapped, or encapsulated, or adsorbed.

2.2. Definition of Nano capsules

Nano capsules are in which the drug is confined to an aqueous or oily core surrounded by a shell-like wall. Alternatively, the drug can be covalently attached to the surface or into the matrix.

2.3. Properties of Nano Crystals

2.3.1. Increase of dissolution velocity by surface area enlargement [6–9]

The size reduction cause to an increased surface area and thus according to the Noyes-Whitney equation (Noyes and Whitney 1897) to an increased dissolution velocity. Therefore, micronization techniques is a acceptable approach to fortunately enhance the bioavailability of drugs. Here, the dissolution velocity is the rate limiting step.

2.3.2. Increase in saturation solubility [10–12]

The saturation solubility is a function of the particle size that is below a critical size of 1-2 μm., the particle size was decreased below 1000 nm which caused to an increased solubility. Therefore, the drug as nanocrystals possesses increased saturation solubility. This has got two advantages:

1. According to Noyes and Whitney (1897), the dissolution velocity was additionally enhanced because dc/dt is proportional to the concentration gradient (cs - cx)/h (cs - saturation solubility, cx - bulk concentration, h - diffusional distance).
2. The concentration gradient between the gut lumen and blood was increased, consequently the absorption by passive diffusion, this developments because of an increased saturation solubility.

2.4. Production of nano crystals [13,14]

There are different approaches to produce nanocrystals in the desired shape and size. Basically, three principles are categorized: milling, precipitation methods and homogenization methods, as well as a combination of the three methods.

2.5. Precipitation method

Precipitation method is the one of first method to build nanocrystals. The first most preparation was a hydrosol, which was developed by Sucker. The technology was basically used cause an ideal precipitation process which was called as "via humida paratum" (VHP). This VHP. Process was already explored in the old pharmacopeia for the formulation of ointments containing finely dispersed, precipitated drugs. The drug is dissolved in a solvent and subsequently added to a non-solvent, finally causing to the precipitation of finely dispersed drug nanocrystals. The nanocrystals are stabilized in order not to cross the range of micrometer. [15–17]

2.6. Milling method

An ideal Nanocrystals technology uses a bead or a pearl mill to develop particle size diminution. There are two basic milling principles. Either the milling medium is moved by an agitator, or the complete container is moved in a complex movement which cause to a movement of the milling media. When assumed that

76% of the volume of the milling chamber (maximum value at hexagonal packaging) are going to be filled with milling material, larger batches are difficult to produce when moving the complete container, so mills using agitators are used for large sized mill for large batches. The milling time depends on many factors such as the surfactant content, hardness of the drug, viscosity, temperature, energy input, size of the milling media. The milling time can be about 30 minutes to hours or several days. This technology is an important particle size reduction technology which is proven by four FDA-approved drugs using it. [18–21]

2.7. Homogenizing method

When producing nanocrystals using homogenization methods, there are three important technologies namely: Microfluidizer technology, Piston gap homogenization in water and in water mixtures or in nonaqueous media.

The Microfluidizer technology can generate small particles by a frontal collision of two fluid streams under pressures up to 1700 bar. This leads to particle collision, shear forces and also cavitation forces. It can be achieved with jet stream homogenizers such as the microfluidizer. The collision chamber can be designed in two shapes, being either Y-type or Z-type. Surfactants are required to stabilize

the desired particle size. Unfortunately, a relatively high number of cycles (50 to 100 passes) are necessary for a sufficient particle size reduction.[5,22–24]

2.8. Applications of nano cystals based on different drug delivery system[3,4,8,21]

2.8.1. Gastrointestinal tract

Other portals for drug absorptions are GI and skin. It is considered that kinetics of particles uptake in GI tract depends on the diffusion and approach through mucus are initial contact with enterocytes, cellular barriers, and post translocation events. Smaller the particle size, faster they could diffuse through GI secretion to reach the colonic enterocytes then following uptake by GI tract, nanoparticles will be translocated to the blood stream and distributed all over the body. Specific binding of ligand or receptors and nonspecific absorptive mechanism was approached by targeting strategies that improves the interaction of NPcs along with absorptive sites such as enterocytes and M-cells of Peyer's patches. The surface of enterocytes and M cells provides the cell-specific carbohydrates was provided by the surface of enterocytes and M cells, that cause to serve as binding sites to nanoparticles drug carriers with suitable ligands. Glycoproteins and lectines binds selectively to this kind off surface by specific receptor-mediated mechanism.

2.8.2. Brain

The brain is one of the least approachable organs for the drug delivery due to presence of the blood-brain barrier (BBB) which will controls the transport of endogenous and exogenous compounds, marked as providing the neuroprotective function. Drugs which has less lipophilicity, they tend to unable the crossing of BBB, so modified delivery is approached to brain by binding to the surface-modified poly (butyl cyanoacrylate) (PBCA) nanoparticles.

2.8.3. Tumor cell targeting

Anticancer drug has large volume of distribution, which is toxic to both normal and cancer cells. Therefore, precise drug release is approached into highly specified targets which involves miniaturizing the delivery system to become much smaller than their targets. By the use of nanotechnology, targeting the drug moiety to the site of action has become a reality achieves in personalized medicine which decreases the effect of drug on other sites while maximizing the therapeutic effect. Markable goal is achieved by small size of these particles, which will penetrate across different barriers through small capillaries into individual cells. NPcs will be prepared to entrap, encapsulate, or bind molecules improving the solubility, stability and absorption of several drugs, as well as avoiding the reticulo-endothelial system, thus protecting the drug from premature inactivation during its transport.

2.8.4. Respiratory tract

respiratory tract is mostly used entry passages for nanoparticles. Nanoparticles can prevent normal phagocytic defenses in respiratory tract and gain access to systemic circulation and get reached to CNS. Aerosol therapy of nanoparticles as drug carrier is gaining importance for delivering therapeutic compounds. Colloidal carrier (nano carrier system) in pulmonary drug delivery provides many advantages such as potential to get relatively uniform distribution of drug dose within the alveoli, improved stability of drug from its own aqueous solubility, sustain drug delivery which consequently decreases dosing frequency, improved patient compliance, reduce side effects, and potential of drug internalization by cells.

2.8.5. For gene delivery

Nanoparticles loaded with plasmid DNA can provides an efficient sustained release gene delivery system because of their rapid escape from the degradation of endo-lysosomal compartment to cytoplasmic compartment. Followed up by intracellular uptake and endo-lysosomal escape, nanoparticles can release DNA at a sustain rate which achieves in sustained gene expression. The gene delivery strategy can be applied to facilitate bone healing by categorizing PLGA nanoparticles involving therapeutic genes like bone morphogenic protein.

3. Conclusion

The above review is concluded as this study gives information about nanoparticle technology which useful for the drug formulations and dosage forms. Exploration of nanosized drug carriers for BCS class **II**, **III** and IV. Exploration of properties of nanoparticles such as enlargement of surface area which increases the dissolution velocity and solubility saturation. Exploration of production of nanoparticles with 3 methods such as precipitation method, milling method, and homogenization method. Nanoparticle gives the applications based on drug delivery such as gastrointestinal tract, brain, tumor cell targeting, respiratory tract and for gene therapy.

4. Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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