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Formulation Development Approaches of Sustained-Release Nanoparticles: Application in Drug Delivery System

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ABSTRACT

Materials of at least one dimension between approximately 1 to 100 nm and display dimension-based phenomena are known as Nanoparticles (NPs). Nanotechnology has demonstrated the ability to bridge the gap between biological and physical sciences by utilizing nanostructures and nanophases in several scientific fields, especially in nanomedicine and nano-based drug delivery systems, where such particles are of particular interest. Sustained-release behavior because of their potential to circulate for a long time, has better organ targeting and carries proteins, peptides, and genomes, biocompatible, biodegradable polymeric nanoparticles have received a lot of attention in recent years. NPs are prepared using a variety of techniques, including wet milling, high-pressure homogenization, Co-precipitation, evaporative precipitation, spray methods, emulsification/solvent evaporation, and emulsification/solvent diffusion. PLGA, cellulose derivatives, alginates, eudragits, chitosan, and other polymers can be used to make NPs. During the preparation of NPs, other excipients such as surfactants, stabilizers, and solvents are also used. Excipients used in NPs include tween 20, tween 80, sodium lauryl sulfate, glucose, trehalose, mannitol, and sorbitol. NPs improve the solubility and bioavailability of hydrophobic drug particles, regulate drug release, and maximize skin penetration. NPs have a wide range of therapeutic uses, including cancer treatment, respiratory disease, neurodegenerative disease, ocular disease, and pulmonary disease.

INTRODUCTION

Basics of Nanoparticles:

Nanotechnology is the branch of science that deals with the matter with dimensions of 10^{-9} = 1nm (nanometer)**[1]**. "Materials of at least one dimension between approximately 1 to 100 nm and display dimension-based phenomena are known as "Nanoparticles (NPs) or nanomaterials (NMs)" according to the USFDA**[2]**. NPs occur naturally and are often generated as a result of human activity. Because of their sub-microscopic size and other properties, nanotechnology is one of the most important branches with a broad range of applications in diverse fields such as medicine, agriculture, aerospace, food, and so on**[3]**. The study of nanostructured drug delivery systems enables the development of new technologies for the rapid absorption and controlled release of drug molecules in the brutal microenvironment of diseased tissues in living systems, resulting in a diverse set of usable nanoplatforms for biotechnology and nanomedicine applications**[4]**. The drug is dissolved, entrapped, encapsulated, or attached using a nanoparticle matrix. Depending on the method of preparation, nanoparticles, nanospheres, and nanocapsules can be formed. To develop nanomedicines, nanotechnology employs curative agents at the nanoscale stage. Nanoparticles also fueled the world of biomedicine, which includes nanobiotechnology, drug delivery, biosensors, and tissue engineering**[5]**.

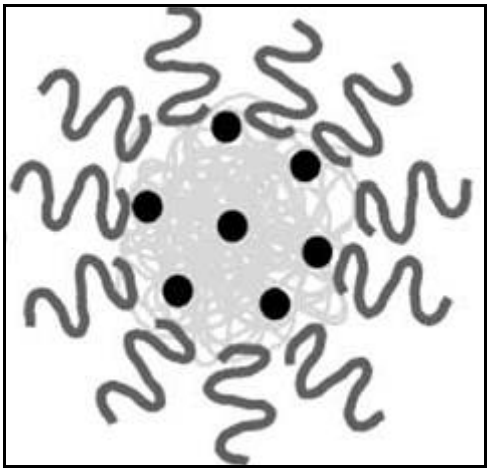

Figure No. 1: Matrix structure of polymeric nanoparticles

Nanotechnology has been shown to bridge the gap between biological and physical sciences by employing nanostructures and nanophases in a variety of scientific fields, especially in nanomedicine and nano-based drug delivery systems, where such particles are of particular

interest**[6]**. NP's are typically small nanospheres made up of materials designed at the atomic or molecular level. As a result, they can travel more naturally inside the human body than larger materials. Sustained-release biocompatible, biodegradable polymeric nanoparticles have gotten a lot of coverage in recent years because of their ability to circulate for a long time, have better organ targeting, and can transport proteins, peptides, and genomes**[7]**.

1. ADVANTAGES OF NANOPARTICLES [8-10]:

1) The matrix constituents used can easily modulate controlled release and particle degradation characteristics. Drug loading is extremely high, and medications can be inserted into structures without undergoing any chemical reactions; this is a crucial element in maintaining drug activity.

2) Due to the smaller particle size and surface area, NPs can withstand and regulate drug release. By ensuring adequate drug transportation of the drug molecule, drug dissemination throughout the body, and eventual clearance, NPs will mitigate side effects.

3) After parenteral administration, nanoparticle size and surface properties can be effectively controlled to accomplish both passive and active drug targeting.

4) The drug release profile of NPs can be regulated, and the drug degradation of the particle by the matrix constituents used in NP formulations can be minimized.

5) Oral, nasal, parenteral, intra-ocular, and other routes of administration are also possible for the nanoparticulate system.

6) Lipid-based NPs can bind to cell membranes and secrete their contents into the cytoplasm, making them a clever carrier mechanism for drug delivery.

7) Targeting ligands may be attached to the surface of NP's or magnetic guidance may be used to accomplish site-specific targeting.

8) NPs allow for easy drug administration through parental or mucosal routes. It also improves the solubility and bioavailability of medications that are poorly soluble and bioavailable.

2. LIMITATIONS OF NANOPARTICLES [11-13]:

1) particle-particle aggregation can occur due to the small size and large surface area of nanoparticles, rendering the physical processing of nanoparticles in liquid and dry forms challenging.

2) Furthermore, due to the small particle size and large surface area, drug loading and burst release are easily achieved.

3) Drug accumulation and permeation are restricted to the target location due to the heterogeneities in vascular permeability.

3. FORMULATION AND DEVELOPMENT APPROACHES OF SUSTAINED-RELEASE NANOPARTICLES:

The development of NPs can be done in a variety of ways which creates dry particles and liquid dispersions using these techniques. These techniques can be used to create nanostructures from atoms and then reduce the size of the microparticle to NPs.

a) High-pressure homogenization technique:

High-pressure homogenization is widely used to make NPs because it has a better capacity to reduce particle size than other processes. This technique reduces particle size bypassing drug suspensions in the micrometer scale through a very small nozzle at a very high-pressure range from 600 to 2000 bar. Since high-pressure homogenizers come in a range of sizes, they can be used for both large and small-scale production. Homogenization further eliminates nanoparticle contamination, which is one of the most important targets of the nanoparticle manufacturing method. The drawback to this method is that the strain used is so high that the crystal structure has been altered in some situations**[14]**.

b) Spray drying technique:

Spray drying is commonly used in the medicinal and biochemical industries, as well as in the food industry, due to its capacity for a large-scale embodiment of fragile drugs, use of gentle settings, unparalleled supply of machinery, and ease of automation to manufacturing crude medicine. In a conventional spray drying procedure, a solution containing the active pharmaceutical ingredient (API) and excipients is atomized through a nozzle into a chamber filled with a cryogenic liquid such as nitrogen, oxygen, or argon. The spraying process may

be performed under (spray-freezing into ice) or above the surface of the cryogenic material, depending on the position of the nozzle. The droplets quickly freeze due to the very low temperature. Following the spraying process, the frozen cryogenic solvent suspension is transferred to a lyophilizer, where it is dried into particulate powders**[15]**.

c) Ultrasonication:

Through the use of increased ultrasound in chemistry allows for the development of polymeric nanostructures flexibly and straightforwardly. The chemical effects of ultrasound that are important to material synthesis are caused by a process known as acoustic cavitation (the forming, expansion, and violent collapse of bubbles under the influence of a sound field), which can produce intense conditions within the collapsing bubbles, and this is where sonochemistry comes from. Homogenization, fragmentation, sonochemistry, degassing, and washing are only a few of the implementations. Ultrasonic processors are used as homogenizers to reduce small particles in a fluid and improve accuracy and consistency. In the first step, an erratic interfacial wave system forms at the oil-water interface, resulting in the ejection of large oil beads into the water, whilst in the second stage, cavitation stun floods occur in the surrounding area of the course oil beads, disrupting them into far better drops**[16]**.

d) Ionotropic gelation technique:

This method is used to formulate chitosan NP's that are encapsulated with active drug molecules or biomaterials. This approach involves the use of tripolyphosphate (TPP) as a negative-charged counterion that forms a complex with the positively charged chitosan polymer, resulting in drug-encapsulated NPs. Biological molecules such as albumins, toxins, and anticancer agents could be encapsulated using this process**[17]**.

e) Emulsification/solvent evaporation:

A single emulsion or multiple emulsion methods are used to mask the drug in the polymeric material. The preference of scheme is determined by the medication's hydrophilicity and hydrophobicity, which would result in greater drug incorporation into polymeric nanoparticles. The emulsion solvent evaporation methods include o/w, w/o/w, s/o/w, o/o/w, and o/o/w, among others. This is a two-step approach used for the synthesis of microspheres and NPs. Emulsification of the polymeric solution in the aqueous or organic phase is done first, followed by evaporation of the polymeric solution. This whole process causes the

polymers to precipitate, resulting in the formation of NPs. When the polymer precipitates as nanospheres, the drug can be distributed in a polymeric matrix structure. It evaporates the organic solvent in the device with constant stirring and, on occasion, by raising the temperature under decreased pressure**[18]**.

f) Wet milling method:

Wet milling is an attrition-based procedure that disperses the drug in an aqueous-based surfactant solution first. The resultant suspension is wetly milled in the presence of milling media using a pearl mill and ultimately the particle size of the material gets reduced to nanosized**[19]**.

g) Co-precipitation technique:

These reactions include the formation of nucleation, cursing, and agglomeration all at the same time. The second method is Ostwald's ripening or aggregation, which influences the morphology, scale, and other properties of the materials. It is a very simple and quick process that allows for fast regulation of particle size, surface charge, and overall particle homogeneity. The process can also be run at lower temperatures, making it an energy-efficient process**[20]**.

4. VARIOUS POLYMERS AND EXCIPIENTS USED IN THE DEVELOPMENT OF SUSTAINED-RELEASE NANOPARTICLES:

1) Eudragit polymers:

Polymethacrylates are known as Eudragit in industries all over the world. It can achieve the correct drug-release profile at the right time, right location, and also over the desired period, if necessary, thanks to the versatility of combining with distinct polymers. Eudragit Retard polymer nanoparticle suspensions have been studied as a carrier mechanism for ophthalmic release of nonsteroidal anti-inflammatory drugs including ibuprofen and flurbiprofen in this region. Ibuprofen, flurbiprofen, cloriocromene, piroxicam, methylprednisolone, and amphotericin B24 have all been studied thoroughly in polymeric nanosuspensions made from Eudragit® RL 100 and RS 100**[21]**.

2) Chitosan polymers:

Chitosan is a polymer found naturally in marine animals that must be extracted with proper procedure to use in drug delivery. It has mucoadhesive, disintegrating, sustained release, antioxidant properties, and widely used in nanoparticulate drug delivery techniques. Chitosan NPs are used in buccal, multiple epithelia, including buccal, intestine, nasal, ears, and pulmonary epithelial regions. With continuous and extended drug release profiling, the mucoadhesive NPs of chitosan has a good affinity with the mucous membrane of the oral or ocular cavity**[22]**.

3) Poly (Lactic-Co-Glycolic Acid) (PLGA polymer):

Because of its biodegradability and biocompatibility, it has been approved by the US Food and Drug Administration (FDA). Since it undergoes hydrolysis in the body to create the initial monomers, lactic acid, and glycolic acid, PLGA has proven to be an effective biodegradable polymer. The use of biodegradable polymeric NPs for drug delivery is gaining attraction and has demonstrated promising therapeutic results. Biodegradable polymers like poly(D, L-lactic acid), poly(D, L-lactic-co-glycolic acid), and poly(3-caprolactone), as well as their co-polymers deblocked or multiblock with PEG, have been used to shape core–shell-shaped NPs to encapsulate several therapeutic compounds**[23]**.

4) Polycaprolactone (PCL):

PCL (polycaprolactone) is a biodegradable polyester with a very low melting point of 60°C and a glass transition temperature of -60°C. Controlled-release microspheres and NP's have also been studied in the brain, but not as thoroughly as PLGA**[23]**. Chitosan decorated PCL NP's have been used for improved ocular delivery of dorzolamide **[24]**. PCL is an aliphatic polyester polymer that is semi-crystalline and bioresorbable. In certain cases, PCL is considered to have a very slow degradation period of up to four years. PCL has been observed in a variety of tissue types and has a tradition of drug delivery and tissue engineering studies in other parts of the body**[25]**.

5) Cellulose derivatives:

Ethylcellulose is a hydrophobic medium that is used for several purposes, including sustained and controlled release and taste masking. The addition of a water-soluble or water-swellable polymer, such as methylcellulose, will regulate and accelerate drug release to some

degree**[26]**. Furthermore, the incorporation of the active principle in a faster dissolving hydrophilic excipient, such as ethyl/methylcellulose blends, improves the bioavailability of poorly water-soluble compounds. Cellulose derivatives have been widely used in the formulation of sustained-release drug delivery systems **[27]**. Repaglinide-loaded sustained-release NP's were developed by using ethyl cellulose as a rate-controlling polymer using a high-pressure homogenization technique. The developed nanoparticles showed nearly 18 % drug release throughout 12 hours non-Fickian diffusion mechanism **[28]**.

6) Alginate:

Alginate is a biopolymer that is extensively used in drug delivery applications as a sustained-release polymer. This polymer has an anionic structure due to the inclusion of the carboxyl group, and it is also used in mucoadhesive and bioadhesive drug delivery applications**[29]**.

7) Other excipients used in NP's preparation:

Different excipients like surfactants, stabilizers, cryoprotectants, solvents are used in the preparation of NPs. Tween 80, Tween 20, sodium lauryl sulfate (SLS), and PVA are the most widely used surfactants. Surfactants are used to keep the particles from clumping together. As an organic phase, cyclohexane, n-pentane, and toluene are used, as well as water-soluble solvents like propylene carbonate are widely accepted. Polyvinylpyrrolidone or hydroxyethylcellulose are used as stabilizers. Cryoprotectants are used to increase the NP's integrity e.g. Glucose, trehalose, mannitol, and sorbitol**[30]**.

5. DRUG DELIVERY APPLICATIONS OF NANOPARTICLES [31-35]:

1) To treat brain cancers, Alzheimer's disease, prion disease, and other neurological diseases, nanoparticles are used as drug delivery vehicles to transport medications and therapeutic peptides over the blood-brain barrier.

2) Nanoparticulate drug delivery systems have been studied as an innovative approach to improve drug and therapeutic agents through the ocular route of administration.

3) Because of their capacity to encapsulate different molecules, adsorption of drugs to nanostructures, and regulated distribution to selected tissues and organ systems, nanoparticles have gained attention in recent years.

4) Tissue repair and reconstruction, implant coatings, tissue regeneration scaffolds, structural implant materials, bone repair, bioresorbable materials, certain implantable devices (sensory aids, eye implants, etc.), surgical aids, operating equipment, and smart instruments all benefit from nanotechnology.

5) NPs aids in the improvement of solubility and bioavailability, the reduction of toxicity, the enhancement of release, and the development of improved drug formulation opportunities.

6) Targeting ligands may be attached to the surface of NP's or magnetic guidance may be used to accomplish site-specific targeting in case of colon cancer, brain cancer, lung cancers.

7) NPs monitor and maintain release profile during shipment and at the site of localization, modifying drug delivery and eventual clearance to improve clinical effectiveness and reduce side effects.

8) NPs both polymer-based and non-polymer-based, as well as liposomes that enhance the efficacy of the antimicrobial agents, are all used in the treatment of infectious diseases. Ciprofloxacin is a broad-spectrum antibiotic used to treat diseases of the lungs. Lipoquin, ciprofloxacin's liposome formulation, is intended to be inhaled for up to 24 hours after prolonged exposure, removing the high-dose antibiotic's systemic effects.

6. CONCLUSION:

The use of NPs in medicine, especially drug delivery, is expected to grow rapidly. The ability of nanoparticulate systems to transform poorly soluble, poorly absorbing, and labile biologically active substances into promising deliverable drugs has huge potential. Even though nanoparticle-based delivery systems increase targeted therapy efficacy, minimize side effects, and improve bioavailability, we also know relatively little about nanoparticle metabolism, clearance, and toxicity.

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