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A Comprehensive Review on Nanoplex Nanotechnology Strategies

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ABSTRACT:
One strategy used to get around the problems with conventional medication delivery systems is the use of nanotechnology based on the creation and growth of nanostructures. The newest development in nanotechnology is the creation of Nanoplex.A polyelectrolyte with an oppositely charged drug nanoparticle forms a complex known as a nanoplex. Both cationic and anionic medicines combine with polyelectrolytes that have opposing charges to produce complexes. The yield of Nanoplex is higher and the complexation efficiency is better when compared to other nanostructures. Additionally, nanoplex are simpler to make. Using scanning electron microscopy, differential scanning calorimetry, X-ray diffraction, and dialysis investigations, the production yield, complexation efficiency, drug loading, particle size, and zeta potential of nanoplex formulation are all evaluated.Nanoplex have a wide range of uses in various domains, including cancer treatment, medication delivery to the brain, drug delivery via genes, and drug delivery via proteins and peptides.

Keywords: Nanotechnology, Nanoplex, Mechanism, Application, Evaluation.

I. INTRODUCTION:

The Latin-based origin of the word "Nano" is "dwarf" (Rangasamy et al., 2011). The field of study known as nanotechnology is concerned with molecular processes and the nano length scale (Kasar et al., 2018).Since several decades, the term "nanotechnology" has been most frequently used in the sciences of electronics, physics, engineering,pharmaceutical and biomedical disciplines, however, have not yet been thoroughly studied (Rangasamy et al., 2011).It has made a significant contribution to a number of medical specialties, including gene delivery, brain targeting, and the development of oral vaccines, as well as to the domains of cardiology, immunology, ophthalmology, oncology, endocrinology, and pneumology (Kadam et al., 2015).For better pharmaceutical applications, nanotechnology offers intelligent materials, systems, and devices (Bhattacharyya et al., 2009). This review will emphasis on a nanoplex.

Table 1: Types of Nanostructures

Type of Nanostructure	Description	References
Nanosuspension	Pharmaceutical nanosuspensions are stabilised, heterogeneous aqueous dispersions containing drug particles that are insoluble at the nanoscaledue to surfactants.	Jacob et al., 2020
Solid lipid nanoparticles	Solid lipid nanoparticles (SLN) are aqueous colloidal dispersions with solid biodegradable lipids as their matrix. SLN formulations have been developed and thoroughly characterised in-vitro and in-vivo for a variety of administration routes, including parenteral, oral, cutaneous, ocular, pulmonal, and rectal	Lingayat et al., 2017; Garud et al., 2012

Nanofibers	Fibres with a diameter between 50 and 500 nanometres are referred to as nanofibers. According to the National Science Foundation (NSF), nanofibers are materials with at least one dimension of 100 nanometres (nm) or less. In recent years, nanofibers have become a popular drug delivery technology in the healthcare industry for a number of disorders.	Kattamuri et al., 2012
Nanocomposites	Nanocomposites are multi-phase materials with at least one phase with diameters between 10 and 100 nm.Among other nanocomposites, polymer-based nanocomposite (PNCs) has emerged as a significant field of current study and development.	Pandey et al., 2017
Carbon nanotubes	Carbon nanotubes (CNTs) are beneficial in the disciplines of nanotechnology and medicines due to a variety of new features they possess. They exhibit a wide spectrum of electrical, thermal, and structural properties and are nanometres in diameter and several millimetres in length.CNTs are allotropes of carbon. They are tubular in shape, made of graphite.	Hirlekar et al., 2009
Nanopores	Due to their exceptional qualities in terms of thermal insulation, controllable material separation and release, and suitability as templates or fillers for chemistry and catalysis, materials with pore sizes in the nanometre range are of particular interest for a wide range of industrial applications.	Wanunu et al., 2012
Liposomes	In clinical settings, liposomal drugs have been shown to be most helpful when their average diameter is in the range of ultra filterable (b200 nm in diameter), when they are able to "passively" accumulate at sites of increased vasculature permeability, and when they are able to lessen the side effects of the encapsulated drugs compared to free drugs.	Allen et al., 2013
Polymeric nanoparticle	Solid colloidal particles having a diameter ranging from 1 nm to 1000 nm are called polymeric nanoparticles. Due to their distinct characteristics and behaviours brought on by their small size, polymeric nanoparticles (PNPs) have garnered a lot of attention in recent years.	Jawahar et al., 2012; Crucho et al., 2017
Polymeric micelles	Nanoscale drug delivery devices known	Ghezzi et al., 2021

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	as polymeric micelles have a core-shell structure that forms when amphiphilic block copolymers self-assemble in aqueous solution.Polymeric micelles, or aggregation colloids created in solution by the self-assembly of amphiphilic polymers, are an inventive way to solve a number of problems with medication administration, such as their low water solubility and poor permeability through biological barriers.	
Dendrimers	Dendrimers are distinctly shaped nanoparticles of dimensions about 1–15 nanometres. It has extremely flexible surface functionalization and are highly regarded pharmaceutical. They are branch-like macromolecules with a central core unit that exhibits excellent molecular homogeneity, a limited molecular weight dispersion, distinctive size and shape properties, and a highly functionalized terminal surface.	Mishra et al., 2011
Nanocapsules	The term "polymeric nanoparticles" refers to delivery systems with dimensions less than 1 µm, which are also known as "nanocapsules" or "nanospheres" according to their make-up.Nanospheres have a matrix organisation of polymer chains, and the drug molecules can be distributed, entrapped or dissolved in, adsorbed, or chemically bonded to the polymer matrix, whereas nanocapsules often have an oil core that leads to a vesicular or membrane-type structure.	Erdogar et al., 2018
Nanoplex	A drug nanoparticle compound with an electrostatically charged polyelectrolyte is known as a nanoplex. To create a nanoplex, a medication that is either cationic or anionic is made to react with a polyelectrolyte that has an opposing charge.	Kadam et al., 2015
Magnetic nanoparticles	A type of manufactured particulate materials with a particle size of less than 100 nm that can be controlled by external magnetic fields is known as magnetic nanoparticles. Dextran, a polymer, serves as the core of magnetic nanoparticles, which are then coated in an inorganic material like iron oxide.	Indira et al., 2010
Nanoemulsions	Thermodynamically stable, transparent (translucent) dispersions of oil and water with interfacial layers of surfactant and cosurfactant molecules	Indira et al., 2010

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	are known as nanoemulsions or submicron emulsions. Their droplets are smaller than 100 nm in size.	
Quantum dots	Quantum dots (QDs) are described as particles with physical dimensions smaller than the exciton Bohr radius and are nanometre-scale semiconductor crystals made of elements from groups II-VI or III-V.	Jamieson et al., 2007
Carbon allotrope graphene's	Pure carbon is used to make graphene, which has atoms arranged in a sheet that is one atom thick and has a regular hexagonal structure resembling that of graphite. It is a type of carbon known as an allotrope, and its crystal structure is made up of a single planar sheet of tightly packed, sp2-bonded carbon atoms. Consequently, graphene's can be thought of as the precursor to graphite, fullerene, and CNTs.	Bera et al., 2010

Nanoplex: An Innovative Development in Nanotechnology

A drug nanoparticle compound with an electrostatically charged polyelectrolyte is known as a nanoplex. To form a nanoplex, an opposingly charged polyelectrolyte and a cationic or anionic medication must react.The majority of potential medication candidates have low-saturation solubility in the aqueous phase. Because many medications have a low oral bioavailability, research is currently focused on making them more soluble.As a result, frequent dosing is necessary, which places a financial and pharmaceutical load on patients.Three main strategies can be used to increase bioavailability: (1) converting the API into a salt form that is extremely soluble, (2) creating crystalline nanoparticles (or nano API) of the API, and (3) delivering the API in its amorphous form (Ando, Radebaugh 2005).The simplest method for boosting a medicine's saturation solubility is to create a salt of the drug using a mild organic acidic or basic. However, salt production does not ensure an increase in saturation solubility (Rabinow et al., 2004).Due to the fact that the particles are reduced to nano size and behave in accordance with the Ostwald-Freundlich solubility principle, nano API formulations aren't restricted to for acidic or basic medications.

According to the Ostwald-Freundlich equation, the effect of nanoionization on saturation solubility is only felt at diameters much larger than 100 nm (Grant et al., 1995).It has been discovered that nanoscale API with diameters between 150 and 200 nm only have a 15% higher saturation solubility than their microscale counterparts. For the production of nano API with a size less than 100 nm, the current nano API formulation processes (such ashigh-pressure homogenization, wet milling) are unpromising. Consequently, improvements in nano API preparation methods are required to increase bioavailability.Making the API's amorphous form metastable is another tactic for boosting apparent solubility. The amorphous API dissolves into a highly supersaturated solution with an apparent solubility that is considerably higher than the saturation solubility of the crystalline equivalents.If the high supersaturation level can be maintained for a long enough time to allow for absorption, it will promote medication absorption throughout the gastrointestinal lumen and increase bioavailability. The important aspect of amorphous forms is that it has been demonstrated that high supersaturation levels result in increased bioavailability in vivo (Yang, Johnston, Williams 2010, Tam et al., 2008).

Mechanism of nanoplex formation:

To create an anionic or cationic drug solute, the water-insoluble medication must first dissolve in an acidic or basic solution. The drug-polyelectrolyte electrostatic interaction and charge neutralization are then triggered by the subsequent mixing of the ionized drug solution with a polyelectrolyte solution that is negatively charged. The drug solute undergoes a transformation that returns it to its minimally soluble state upon charge

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neutralization, which causes a loss of solubility. As a result, there is fast precipitation and the creation of the drug-polyelectrolyte complex at the nanoscale. The inability of the drug molecules to assemble into organized crystalline structures is due to a combination of fast precipitation and powerful electrostatic interactions between the drug and the polyelectrolyte.The result is the formation of an amorphous drug-polyelectrolyte nanoparticle combination (Cheow et al., 2012).

Advantage of nanoplex:

1. The process for making Nanoplex is easy because it simply requires the mixing of two solutions, one each of the medication and polyelectrolyte.
2. It is not necessary to use a lot of solvents during the preparation of nanoplex.
3. In comparison to other nanoformulations, the synthesis of nanoplex requires very less energy.
4. It takes a short period for nanoplexes to form.
5. For the preparation of Nanoplex, complex equipment is not required.

Evaluation of nanoplex:

- Complexation efficiency: This is described as the mass of a drug that, in relation to the drug that was first added, forms a complex with the polyelectrolyte. The optical density of the supernatant following the initial centrifugation of the nanoplex suspension is used to compute it (Cheow et al., 2012).
- Production yield:It is the proportion of the dry nanoplex generated after freeze-drying to the weight of the medication and polyelectrolyte initially used (Cheow et al., 2012).
- Drug loading: This represents the real drug content of the nanoplex powder. It is computed by combining 5 mg of the nanoplex powder with 20 ml of ethanol, centrifuging the mixture, and measuring the absorbance of the resulting solution (Cheow et al., 2012).
- Particle size analysis: A particle size analyzer is used to determine the nanoplex's particle size (Cheow et al., 2012).
- Zeta potential: A zetasizer is used to determine the nanoplex's zeta potential (Cheow et al., 2012).
- Differential scanning calorimetry (DSC):To ascertain how a medicine interacts with a polyelectrolyte, DSC is used. Their melting temperatures are also used to determine the interactions, and a DSC instrument is used to calculate the difference. Graphs are used to display the results (Cheow et al., 2012).
- Powder X-ray diffraction:A powder X-ray diffractometer is used to determine the patterns of samples' powder X-ray diffraction. This provides information regarding the sample's nature (Cheow et al., 2012).
- Scanning electron microscopy:Using a scanning electron microscope, the sample's surface morphology is examined (Cheow et al., 2012).
- Dissolution study:The dialysis bag method is used to assess the dissolution of the nanoplex to ascertain the drug release (Cheow et al., 2012).
- Saturation solubility study:The orbital flask shaker method is used to assess both the drug's and the formulation's solubility. Through the use of spectrophotometric analysis, the drug concentration is ascertained from the absorbance (Cheow et al., 2012).
- Stability study:By putting the nanoplex in an environmental stability chamber, it is tested for stability, and its drug content is measured (Cheow et al., 2012).

Applications of Nanoplex:

Enhancement of solubility and dissolution rate

Class II and IV medicines, which are poorly water-soluble, can be prepared as Nanoplex to improve their bioavailability by increasing their solubility and rate of dissolution. An increase in solubility lowers a drug's dosage required (Cheow et al., 2012).

Drug delivery to the brain

The most significant hurdle to the creation of a new medicine for the central nervous system is the blood-brain barrier (BBB). Endothelial cells with tight connections, enzymatic activity, and active efflux transport mechanisms, which are relatively impermeable, characterize the BBB. Through the action of enzymes or efflux pumps, it successfully blocks the entry of water-soluble molecules from the blood circulation into the CNS and can lower the concentration of lipid-soluble molecules in the brain.As a result, the BBB only allows the selective transit of chemicals required for proper brain function. A number of disorders, including HIV-1, AIDS, dementia, and cerebral ischemia, have been linked to nanoparticles, which have been proposed as non-viral gene delivery vectors and as having tremendous promise for therapeutic usage.The effectiveness and specificity

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of MMP-9-siRNA quantum dot (QD) complexes (nanoplex) in reducing the expression of the MMP-9 gene in the brain microvascular endothelial cells (BMVECs) that make up the BBB have been assessed. Adela Bonoiu et al. showed how to modulate MMP-9 activity in BMVECs and other MMP-9-producing cells using a unique nanoplex siRNA delivery technique.This application will stop neuroinflammation and protect the BBB (Bonoiu et al., 2009).

Nanoplex for gene delivery

Due to its biocompatibility, biodegradability, low cytotoxicity, absence of pathogenicity, and low immunogenicity, non-viral vector-mediated gene therapy is now one of the most alluring approaches used. Currently, research is concentrated on creating non-viral vectors made of cationic polymers, liposomes, and dendrimers.DNA's anionic character has been found to be usefully neutralized by cationic polymers, which effectively condenses DNA and makes it easier for DNA to enter cells. Plasmid DNA delivery formulations use an intriguing family of vectors called cationic polymers (Thomas et al., 2010).

Drug targeting in cancer treatment

For non-viral vectors, a wide variety of cationic lipids have been synthesized. A cationic lipid typically consists of three parts: a hydrophobic lipid anchor group that aids in the formation of the micellar structure and can interact with cell membranes; a linker group, such as an ester, an amido group, or a carbamate; and a positively charged head-group that is primarily made up of cationic amines.As the anchor group, cationic cholesterol derivatives might be chosen due to their strong transfection activity and low toxicity. In cationic cholesterol derivatives, the linker group regulates the conformational flexibility, level of stability, biodegradability, and effectiveness of gene transfection.When the nanoparticle/siRNA complex (nanoplex) is created in a NaCl solution, cationic nanoparticles made of OHChol (NP-OH) could deliver siRNA with a high transfection efficiency in vitro(Hattori et al., 2008).

Drug delivery of proteins and peptides

Numerous bioactive compounds and vaccines based on peptides and proteins have been discovered as a result of significant advancements in biotechnology and biochemistry. The development of appropriate carriers is still difficult since the gastrointestinal tract's epithelial barrier restricts the bioavailability of these compounds and makes them vulnerable to gastrointestinal breakdown by digestive enzymes. Proteins are a good choice for nanoplex formulation because they are charged molecules that form a complex with polyelectrolytes(Woitiski et al., 2007; Ranjan et al., 2010).

II. CONCLUSION:

The majority of medications taken orally have an amphiphilic character and are soluble in a mild acid or base. The straightforward complexation procedure can convert them into amorphous Nanoplex. A nanoplex can be created by simply combining two solutions under room temperature.It is also quick and free of solvents. It creates uniform-sized nanoparticles with good complexation efficiency, drug loading, and production yield while using little energy.

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