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Review Article

Advancements and Future Directions in Nano-Enabled Drug Delivery Systems

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ABSTRACT

The collection of methods used to deliver a medication or pharmacologically active chemical to the target cell in order to treat a disease or other health concern is known as drug delivery. Oral, buccal, rectal, subcutaneous, intranasal, intramuscular, intravenous, pulmonary, and transdermal are the traditional drug delivery methods. These are widely used techniques to treat a variety of medical issues, but they have drawbacks, including sluggish absorption, enzymatic degradation, instability, uncontrolled release, risk of displacement, and discomfort and irritation as side effects, among many others. One of the most effective ways to deliver a medicine in a targeted and sustained manner is by incorporating it into a this nanocarrier overview discusses the uses of nanocarriers, including carbon nanotubes, solid nanoparticles, liposomes, dendrimers, polymeric nanoparticles, polymeric micelles, virus-like nanoparticles, and mesoporous silica nanoparticles. Nucleic acid-based drug delivery systems, cell-based drug delivery systems, self-nano emulsifying drug delivery systems, self-micro emulsifying drug delivery systems, chemical and physical stimuli-based drug delivery systems, nanoneedles, patches, ultrasound drug delivery, and microchip technology are some examples of innovative delivery systems that are designed to overcome the limitations of drug delivery. These systems are commonly referred to as smart drug delivery systems. The fundamentals of drug delivery, pharmacokinetic research, new developments, and potential directions for the drug delivery system are the main topics of this article.

INTRODUCTION

The Food and Drug Administration defines drugs as "intended for use in the diagnosis, cure,

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mitigation, treatment, or prevention of disease" and as "articles (other than food) intended to affect the structure or any function of the body of man or other animals." It is anticipated that the medications will be able to efficiently target the disease-causing cell at a precise therapeutic concentration. On the other hand, it is noted that stability, release rate, and the capacity to target cells and tissues specifically are uncontrollable and impossible to track.[1] Drug delivery methods include the use of microspheres, which are spherical particles with a diameter ranging from 1 to 1000 μm [2], and tubular vesicles, which have a persistent length longer than a microsphere [3]4Targeting moieties can help design focused nano delivery systems, improving anti-tumor outcomes and decreasing off-target effects. Additionally, this would necessitate using smaller dosages of the therapeutic drug.[4] Studying technical principles, material design, implementation strategies, and clinical application are all part of the drug delivery system design process. Diffusion, erosion, degradation, shear, swelling, binding kinetics, passive cell uptake, surface area, and active cell uptake are the main topics of engineering concepts. Two components of material the design are [5] According to Michael Faraday's explanation from 1857 [6], the history of nanoparticle study be with Roman glassmakers who created glasses called Lycurgus cups that contained nanosized metal particles. C. Maxwell and G. Eastman (1883) used silver nanoparticles, which are known to be halide photochemistry, to create photographic films in 1861.[7] The following can be accomplished with ease by using these methods: improve the transportation of both hydrophilic and hydrophobic medicines [12], making it simpler to deliver medication the size of macromolecules to intracellular locations [13].

3.Mechanism of targeted drug release:

A targeted drug delivery system is one that delivers pharmacokinetic medication at the place of action while avoiding the needless contact to prevent adverse effects with other healthy tissue(10) The process of targeted medication release involves three steps: The drug nanocarrier enters the cell through endocytosis, (i) connects with the target cell's receptors through multivalent receptor–ligand interactions, and (ii) releases the drug in the final phase. Through interactions with lipid membranes, targeted drug delivery can occur in the cytosol and cell membrane. [11]Unwanted effects on healthy cells result from non-targeted drug administration, such as chemotherapy drugs used to treat cancer. Targeted drug administration lowers the dosage and increases the consistency of the drug's effect.[12] There are two ways to release drugs: linker cleavage and carrier control, which are covered in more detail in this section.[13]

1) Linker cleavage

There are two kinds of linkers: cleavable and non-cleavable. In the right circumstances, cleavable linkers can readily break bonds. For example, endocytosis allows antibody–drug conjugates to enter the lysosome. Hydrolytic enzymes and a low pH environment within the lysosome facilitate cleavage. Non-cleavable link cleavage There is no chemical trigger that activates linkers. [14] Thiol groups cause disulfide bond breaking in the cytoplasm by electrochemical reactions or disulfide exchange reactions [15]. Hypoxic conditions, such as tumor microenvironments, are those in which tissue and cells have a reduced oxygen supply [l6] One of its advantages over other mechanisms is that it increases the frequency of release by repeatedly releasing a large number of drug units each reaction cascade8. The process of photochemistry uses a photocleavable linker, and light triggers this reaction.[17] Using a biological mechanism, the azo reaction cleaves the azo linker, activating the anti-inflammatory group

of azo-linked prodrugs of 5-aminosalicylic acid.[18]

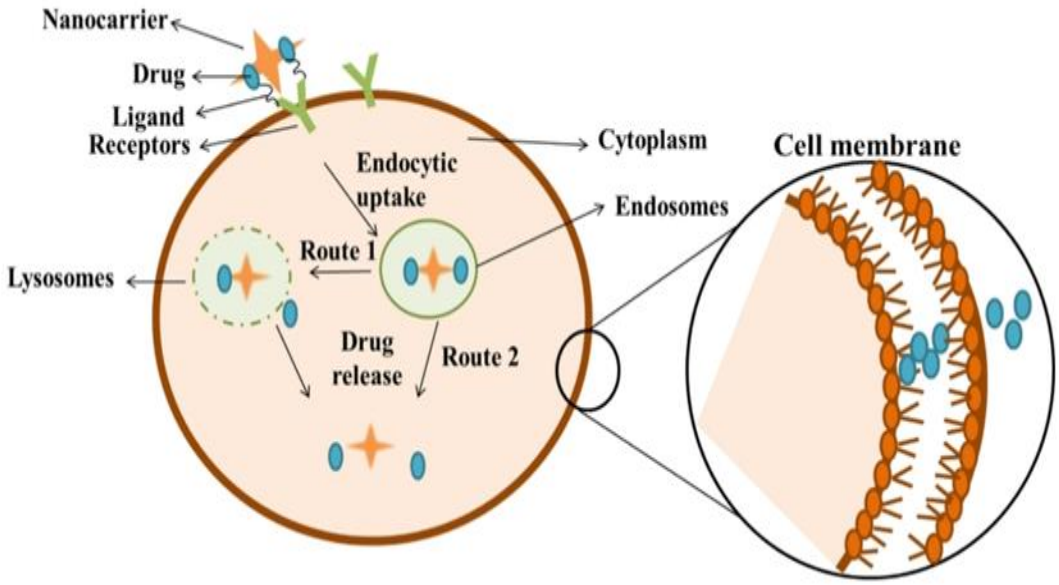

Fig. 1. Schematic illustration of target drug release system in cytosol and cell membrane. It shows that nanoparticles get linked to the receptors, then via endocytosis enters the cell and ultimately leads to up in release of drug

2) Control of carrier

Drugs can be loaded and released using non-covalent mechanisms. It can be carried out via encapsulation or interaction with the carrier, where the size, shape, and geometry of the particles play a crucial role in controlling the biological mechanism [19]. Drugs are placed into carriers and released through controlled diffusion mechanisms [20].

4. Pharmacokinetics:

Pharmacology is the study of the link between a patient's physiological condition (the response to the treatment) and the dosage of the drug administered to them. Pharmacokinetics is defined by a molecule's absorption, distribution, metabolism, and excretion; many of these processes are governed by the physicochemical characteristics of the molecule. Understanding these four crucial processes is aided by pharmacokinetics [21

1. absorption:

The transfer of the medication from the place of administration to the body's circulatory system is referred to as the "absorption step." There are five ways that a medication might enter the systemic circulation: transcellular absorption, paracellular absorption, transport protein-mediated absorption, endocytosis, and pinocytosis.[22]

2. distribution:

Dispersal The medicine travels from the systemic circulation to the tissue during the distribution stage. Nanocarriers facilitate target delivery and blood circulation prolongation.[23]

3.metabolism:

The process of drug metabolism, which might take place in the liver, gastrointestinal tract, kidneys,

lungs, or skin, involves the use of enzymes. Drug metabolism occurs in two stages, albeit in many instances, both phases take place at the same time for full metabolism.[24]

4.eliminations

Drug and metabolite elimination can happen in a number of ways, but the kidney is the most important. Kidney elimination entails glomerular filtration, active tubular secretion, and tubular reabsorption.[25]

5.Pharmacodynamic:

Pharmacodynamics is the process of applying quantitative tools to ascertain the kind and extent of pharmacological responses once they reach the site of action. The chemical interaction between a drug and its binding site is known as drug response. Drugs attach to macromolecules at binding sites, also referred to as receptors if they have functional action. Drug binding affects intracellular messengers or proteins and activates receptors.[26]

6.Classification of drug delivery systems based on routes

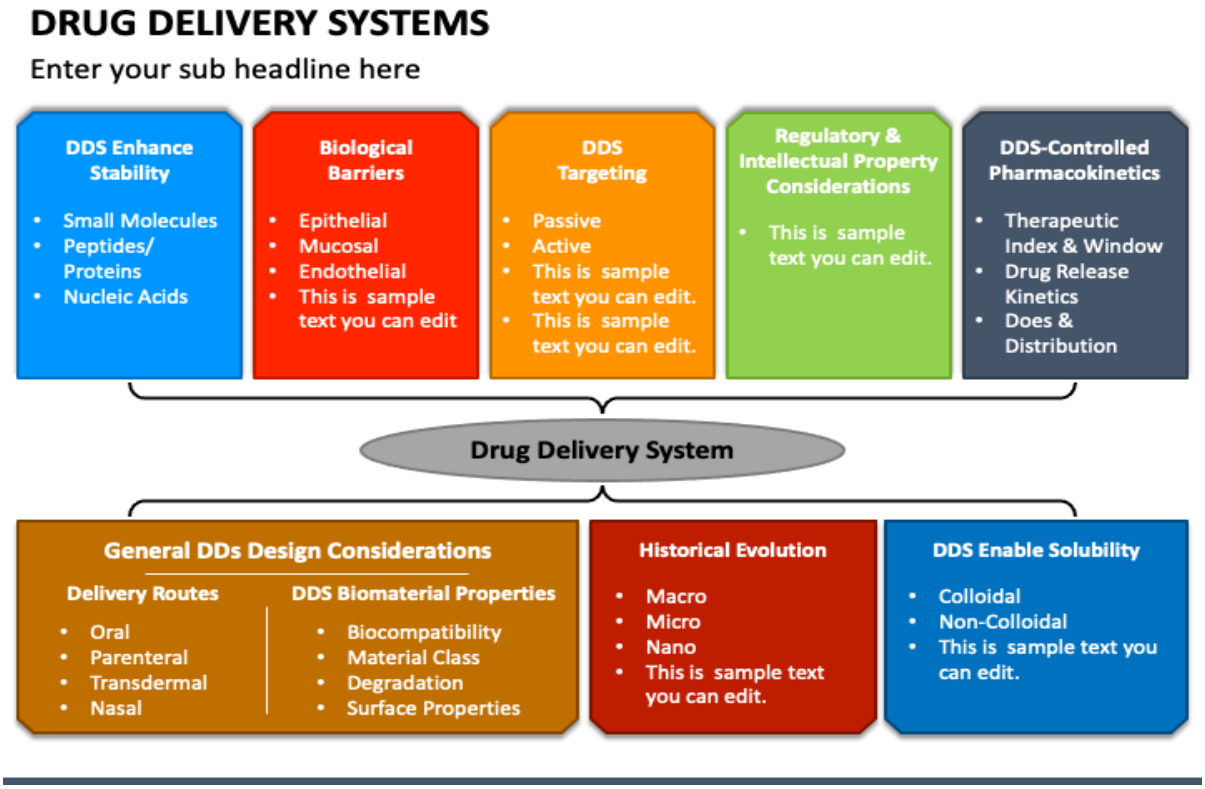

Fig No:-2 Drug Delivery System

7.Role of nanocarriers in drug delivery

1.Solid lipid nanoparticles:

Solid lipid nanoparticles (SLNs), which are made by melting solid lipids in water and adding an emulsifier to create a stable solution, range in size from 50 to 1000 nm [27]. Different targeted ligands and medications can be functionalized with dendrimers' surface. Furthermore, the distortion of the micelles is caused by the hydrophilic group's self-assembling nature with amphiphilic dendrimers [28].

2. Liposomes

Liposomes are servical vesicles that include an aqueous core surrounded by a lipid bilayer and can

transport bioactive substances like drugs [29] Because of their improved rheological characteristics and stability, the produced liposomal carriers were determined to be appropriate for topical administration. It is also discovered that the entrapment efficiency is high, which aids in achieving the therapeutic drug concentration of cyclosporine at the administration site. In the imiquimod-induced psoriatic plaque model, the cyclosporine-containing liposomal gel demonstrated significant effectiveness and decreased psoriatic cytokine levels. Therefore, it has been discovered that produced cyclosporine-loaded liposomal carriers are effective and can be used to treat psoriasis [30].

3.Dendrimer

A dendrimer is made up of several arms that branch off from the center and are made using sugar, nucleotides, and amino acids [31] Dendrimers are three-dimensional, highly branching, star-shaped macromolecules with diameters in the nanometer range (Fig. 3C). Three components make up the structure of dendrimers: (i) the multivalent surface, which has highly reactive sites; (ii) the outer shell, which is located directly beneath the multivalent surface and has a particular environment; and (iii) the core, which is the innermost part of the dendrimer and is greatly shielded by the branches of dendrimers of higher generation. [32]

4]. Polymeric nanoparticles

The spherical shell of polymeric micelles self-assembles in aqueous conditions utilizing amphiphilic di- or tri-bock copolymers.[33]

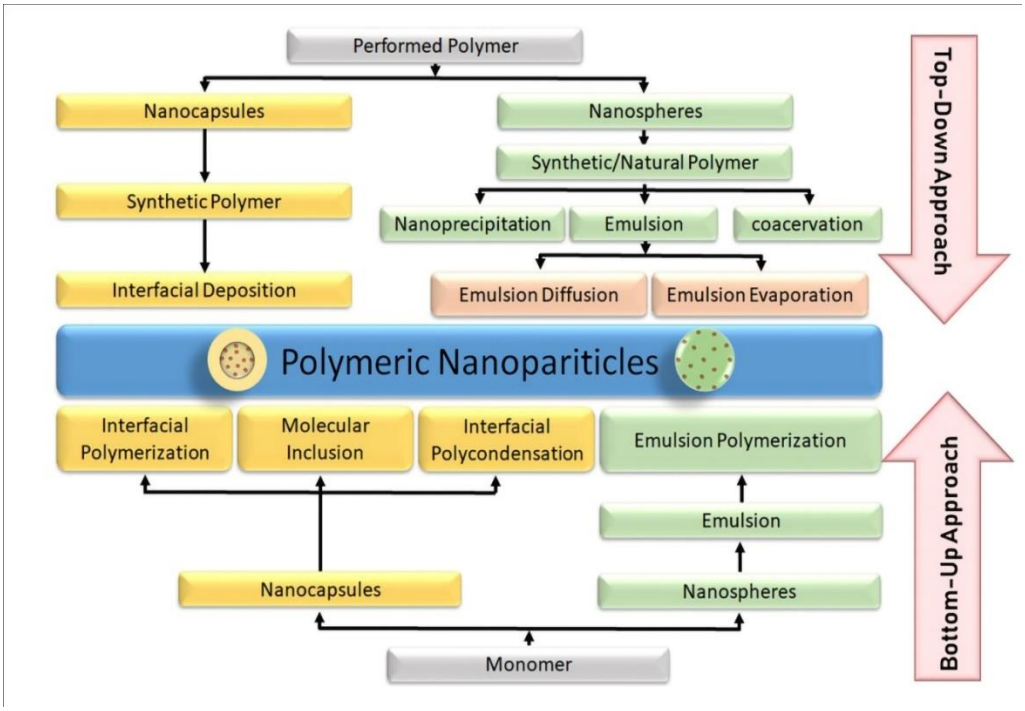

Fig No:-(3) Polymeric Nanoparticles

5] Carbon Nanotubes: -

A grapheme sheet is folded into a tube-like structure with a nanoscale diameter and a length that is thousands of times the diameter to create carbon nanotubes (CNTs) [34].

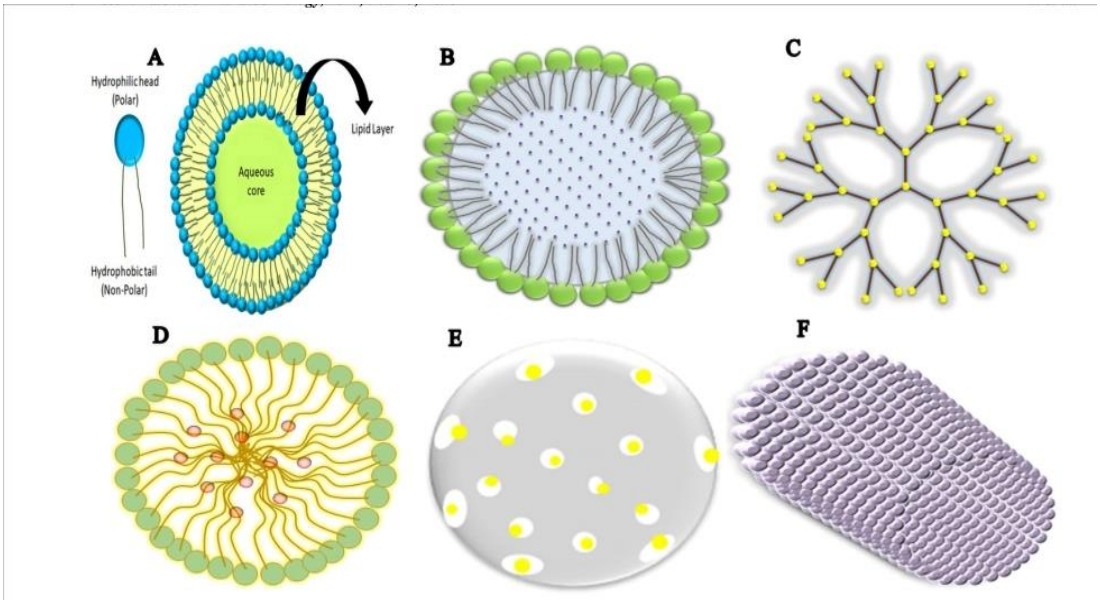

Fig. (4). Different types of nano-based drug delivery systems: A) Liposomes B) Solid-lipid nanoparticles C) Dendrimers D) Polymeric nanoparticles E) Mesoporous Silica nanoparticles F) Nanotubes

8. Smart drug delivery systems

Even while traditional drug administration methods are frequently employed to treat medical conditions, some drawbacks have raised demand for more sophisticated drug delivery systems, or "smart drug delivery systems." A smart medicine delivery system is one that offers spatiotemporal resolution and a regulated release rate. In these systems, endogenous stimuli like enzyme, pH, and retention effect, as well as external stimuli like electric fields, ultrasonic, and magnetic fields, cause drug release [35].

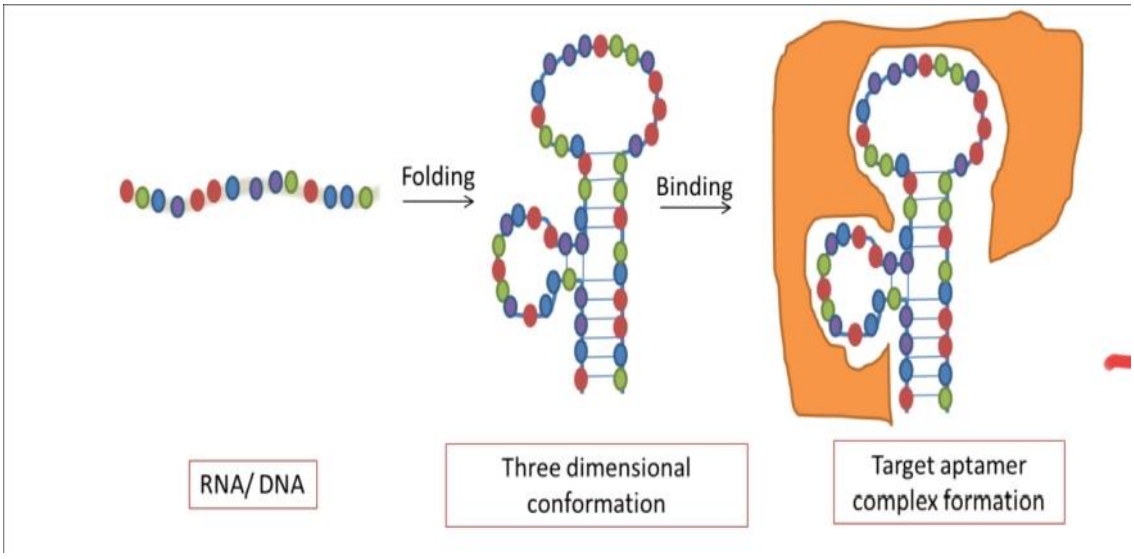

Fig. 5. Schematic representation of formation of aptamer from RNA or DNA which fold into three-dimensional conformation and then binding to the target resulting in target aptamer complex formation.

9.Nucleic acid-based drug delivery system

Since they are hydrophilic, negatively charged polymers that cannot pass through cells, are

enzymatically unstable, and might cause unintended biological reactions, nucleic acids are generally not thought to be a good choice for drug administration [37]. However, at low concentrations, the modified nucleic acid has demonstrated the capacity to activate the innate immune system [38].

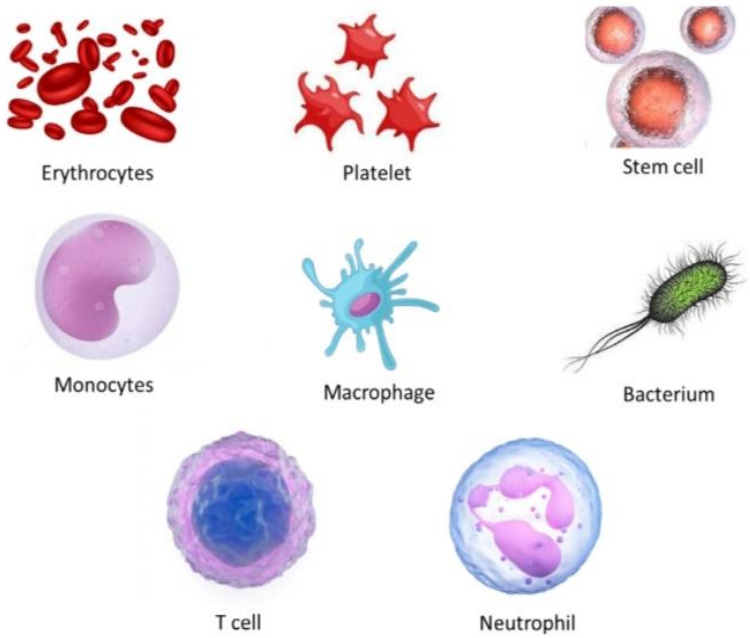

Fig. 6. Schematic representation for cell-based drug delivery system which is designed as an inspiration from erythrocytes, platelets, macrophages, leucocyte (monocytes and neutrophils), T cells, stem cell and bacterium

10.Ethics and regulatory affairs in nano-drug delivery system

Because certain studies indicate that nanomedicines may have negative health effects in addition to their many benefits, a regulatory body must be established for nanodrug delivery systems. This regulatory authority must focus on the drug's potential and non-possible risks while also taking ethical, legal, and societal effects into account. Ethical considerations must be made in addition to environmental ones, which results in the creation of stringent laws and regulations. One of the difficulties is the communication gap that exists between developed and less developed countries about risk assessment and management measures, which makes it difficult to create uniform norms. Another issue is the lack of understanding among scientists, the general public, regulatory agencies, and civil society, which results in insufficient risk assessment and management. [39]

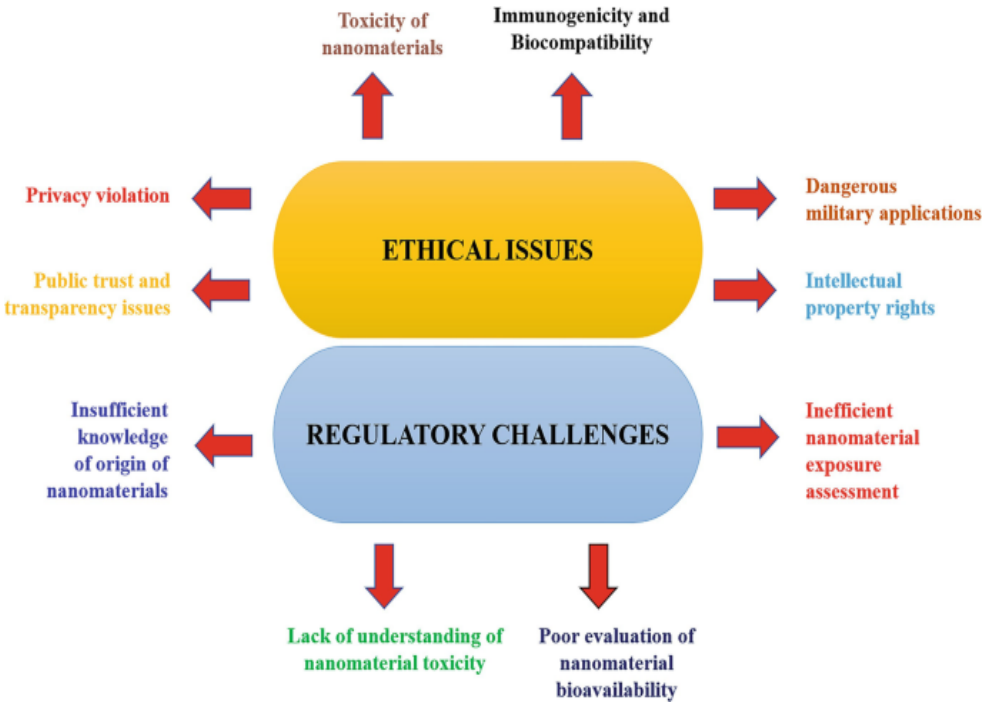

Fig no [7]. Ethics and regulatory affairs in nano-drug delivery system

11. Future scope

From the standard basic tablet with uncontrolled release to systems with increased bioavailability and fewer adverse effects, drug delivery methods have come a long way. Research into convenient, regulated, monitored, and targeted drug delivery methods is still ongoing. Future virus drug delivery systems, safety, symbiotic delivery systems, gender-sensitive delivery systems, affordability, more environmentally friendly drug delivery systems, and systems that address unmet clinical needs are some of the aspects that researchers must concentrate on. These factors are covered in more detail below.

1.Drug delivery for future viruses

Due to growing treatment resistance and barriers at the cellular and intracellular levels, viral infections are among the medical conditions that are difficult to treat. For instance, research is still ongoing to find an effective treatment for herpes zoster and herpes simplex virus. One example of the lack of a good therapeutic medicine is the Covid-19 pandemic that has been occurring all across the world. Remdesivir was thought to slow down patients' recuperation, although there are still a lot of contradicting reports [40].

2.Safety and efficacy of drug

In a different study, Lactobacillus acidophilus was microencapsulated in microbeads of alginate-gelatin and alginate-gelatin- sugars. The results indicated that the bacteria' survivability in the gastrointestinal tract and when added to yogurt was improved Metal-organic framework symbiosis was created and investigated for effective medication administration. According to the drug release profile, metal-organic frameworks had sustained release for seven days, while hydrogel release was finished in five days [41].

3.Symbiotic drug delivery

The use of bacteria to treat damaged human tissue is an example of symbiotic drug delivery, which is an effective method for targeted and regulated medication administration. In one trial, an anticancer medication was delivered by a

bacterium, which decreased toxicity and increased delivery effectiveness [42]. Alginate-gelatin and alginate-gelatin-fructose -saccharide microbeads were used to microencapsulate Lactobacillus acidophilus in a different study. The results indicated that the bacteria' survivability in the gastrointestinal tract and when added to yogurt was improved. [43]

4.Gender sensitive drug delivery.

The incidence and intensity of pharmaceutical side effects vary by gender [254]. Uneven pharmaceutical side effects may result from differences in physiological, hormonal, and genetic factors between the sexes. A stud looked into the detrimental effects of an antidiabetic medication based on gender differences. It was found that women were more likely than men to have 13 of the 17 system. organ class level abnormalities [44].

12.CONCLUSION

A drug delivery system is essential for treating a number of medical conditions. The fundamental process of drug release is when a drug-linked nanocarrier binds to a receptor, enters the cell by endocytosis, and then releases the drug into endosomes. Drug distribution can be targeted using encapsulation or a linker mechanism. After a medicine is provided, pharmacokinetics involves four fundamental steps: drug absorption, distribution, metabolism, and elimination. The advantages and disadvantages of the numerous traditional medication delivery methods are covered in this overview. Drug delivery systems have rapidly changed over time as a result of the application of cutting-edge technologies. The smart medication delivery system can address the drawbacks of the current or traditional drug delivery technologies. For the effective treatment of health issues, these intelligent drug delivery systems—such as those based on nucleic acids, cells, self-nano emulsifying, self-micro emulsifying, physical, and chemical stimuli—can increase the drug's bioavailability, stability, improved absorption, and controlled release. Recent developments in innovative drug delivery systems, including microchips, ultrasound-based delivery, nanoneedle patches, and many more, are being extensively researched with an eye toward the future to create regulated and targeted drug delivery systems. This study has outlined the seven main concerns that must be addressed in order to develop a viable and efficient medication delivery system and get past current obstacles in the treatment of medical conditions.

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