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Review

A Review of Next-Generation Drug Delivery Systems And Technologies

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Abstract

Recent drug delivery systems (DDS) are formulated using advanced technology to accelerate systemic drug delivery to the specific target site, maximizing therapeutic efficacy and minimizing off-target accumulation in the body [2].

As a result, they play an important role in disease management and treatment. This is especially true for most life-threatening diseases requiring therapeutic agents with numerous side effects, thus requiring accurate tissue targeting to minimize systemic exposure.

Delivery strategies have greatly helped convert promising therapeutics into successful therapies. As the therapeutic landscape evolved, delivery strategies and technologies quickly adapted to changing drug delivery needs. A few decades ago, small-molecule drugs were the primary class of therapeutic [13].

Drug delivery technologies have enabled the development of many pharmaceutical products that improve patient health by enhancing the delivery of a therapeutic to its target site, minimizing off-target accumulation, facilitating patient compliance, and enabling entirely new medical treatments [17].

The components of the drug account for its physicochemical properties and are responsible for the changes it influences in the body. It, improves the drug solubility, target site accumulation, efficacy, pharmacological activity, pharmacokinetic properties, patient acceptance, and compliance, and reduces drug toxicity [2].

Innovation in delivery technologies and strategies has been catalyzed by the identification of unique delivery challenges associated with each class of therapeutics. As the therapeutic landscape evolved, delivery strategies and technologies quickly adapted to reflect changing drug delivery needs.

Keywords: Drug Delivery systems, Drug Delivery technologies, Nanocarriers, RBC Membrane, ingestible injectables, NGS, Artificial intelligence, 3D printing.

INTRODUCTION

Drug delivery technologies have enabled the development of many pharmaceutical products that improve patient health by enhancing the delivery of a therapeutic to its target site, minimizing off-target accumulation, and facilitating patient compliance. Delivery strategies have greatly helped convert promising therapeutics into successful therapies. A few decades ago, small molecules of drugs were the primary class of therapeutics. Because the delivery of small molecules is largely dictated by their physicochemical properties, which heavily influence

the bio availabilities of the drugs, delivery efforts first focused on improving the solubility of the drugs, controlling their release, broadening their activity, and adjusting their pharmacokinetics

Next-generation technologies are defined as ensuring novel treatments effectively reach and optimize the design, properties, analysis, formulations, and delivery of new medicines and therapies. It turns promising molecules into medicines of the future. They will be used to develop more effective treatments, identify new drug targets, streamline clinical trials, and plan sales strategies [2].

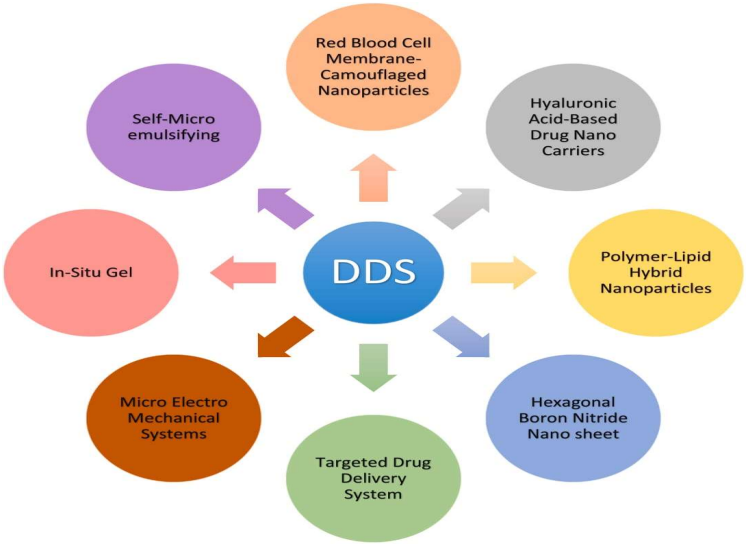

Fig 1: schematic diagram of different delivery systems[19,41]

The challenges of next-generation drug delivery technologies for all drugs, the goal of delivery is to maximize therapeutic efficacy by transporting and releasing the drug (passively or actively) to the target site in the body and minimizing off-target accumulation of the drug. This can be achieved by controlling drug pharmacokinetics, reducing drug toxicity, increasing drug accumulation at the target site, and improving patient acceptance and compliance. Innovation in delivery technologies and strategies has been catalyzed by the identification of unique delivery challenges associated with each class of therapeutics [4].

ADVANTAGES

Ease of administration, safety, and Efficacy
Require less frequent dosing
More patient convenienceEase of administration, safety, and Efficacy
Require less frequent dosing
More patient convenience
Increased drug efficacy
Reduced side effects

DISADVANTAGES

Poor absorption and solubility
In vivo instability
Poor bioavailability

NEXT-GENERATION – NOVEL TECHNOLOGIES

Artificial intelligence and machine learning
3D printing
Digital apps- mobile
Data Analytics
Genomics

NEXT-GENERATION- NOVEL METHODOLOGIES

Next-generation sequencing
Ingestible injectables

NEXT GENERATION SEQUENCING

NGS technology refers to non-sanger-based DNA sequencing methods that have replaced conventional sequencing methods. NGS has been widely used for disease diagnosis, prognosis, therapeutic decisions, and follow-upof the patient. Next-generation sequencing (NGS) is a massively parallel sequencing technology that offers ultra-high throughput, scalability, and speed. The technology is used to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA [11].

STEPS OF NEXT-GENERATION SEQUENCING

STEP 1- NUCLEIC ACID EXTRACTION AND ISOLATION

Nucleic acid extraction and isolation is a vital first step in next-generation sequencing. This is regardless of whether you are sequencing total RNA, genomic DNA, or various RNA types. The extraction method that's used will depend on the starting material. It is crucial to choose an extraction protocol that's optimized to yield the maximum amount and highest purity of nucleic from the respective sample type. The yield, quality, and integrity of isolated nucleic acid are critical for successful sequencing and must be assessed before proceeding to the next step.

STEP 2- LIBRARY PREPARATION

Library preparation involves preparing DNA or RNA samples so they can be processed and read by sequencers. This is done by fragmenting the samples to yield a pool of appropriately sized targets, and then adding specialized adapters at both ends, which will later interact with The NGS platform. These prepared, ready-to-sequence samples are called "libraries". A library represents a collection of molecules that can be sequenced. The exact library preparation procedure may differ depending on the reagents and methods used. Prepared NGS libraries must contain DNA fragments of desired lengths with adapters at both ends.

STEP 3- CLONAL AMPLIFICATION AND SEQUENCING

Clonal amplification involves amplifying DNA fragments to be sequenced by binding to ion surfaces, beads, or flow cells. This helps develop strong fluorescent signals that can be detected by the sequencers.
Sequencing by synthesis (SBS) is the next step after clonal amplification. In this step, the library is loaded onto the sequencer, which then 'reads' or detects the nucleotides one by one.

STEP 4 – DATA ANALYSIS USING BIOINFORMATICS

This final step involves three stages – processing, analysis, and interpretation of the raw sequencing data generated. A variety of bioinformatics tools are used to process, analyze, and interpret the raw sequencing data and convert it into meaningful information. The extract tools used as well as how the data is processed and analyzed depends on the applications and goals of the NGS assay.

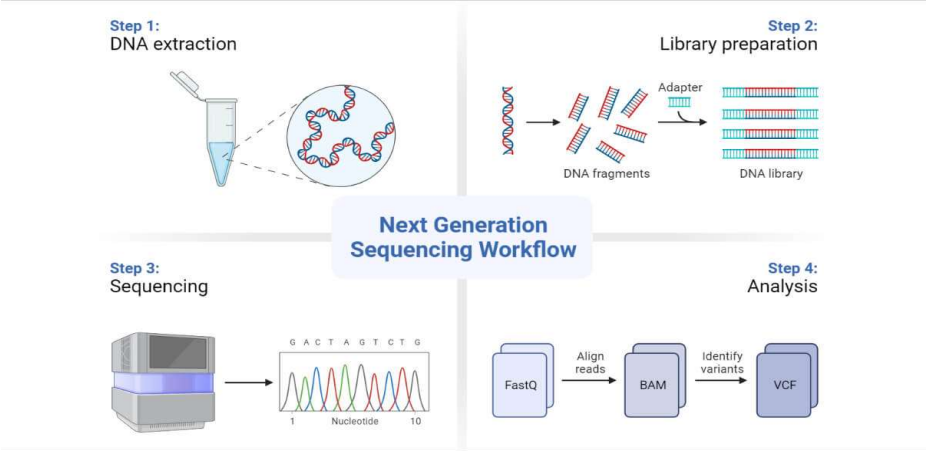

Fig 2: schematic diagram of next-generation sequencing

The importance of NGS has become an important technology that provides deeper insides into the human genome. its speed, accuracy, and affordability, NGS enables a wide variety of applications. It includes whole genome sequencing, chip sequencing, exome sequencing, and transcriptome sequencing.

APPLICATIONS OF NGS

Rapidly sequence the whole genome

Deeply sequence target regions
Utilise RNA sequencing to discover novel RNA variants and splice sites or quantify mRNAs for gene expression analysis
Analyze epigenetic factors such as genome-wide DNA methylation and DNA-protein interactions.
Sequence cancer samples to study rare somatic variants, tumor subclones, and more
Study the human microbiome
Identify novel pathogens.

ADVANTAGES
Low price
High Throughput and fast speed
Greater sensitivity and massively parallel sequencing
More flexibility

DISADVANTAGES
Need for specialized software
High infrastructure cost and high sequencing errors [12].

INGESTIBLE INJECTABLES

It is another emerging technology to enable oral delivery of biologics. The patient takes a pill after swallowing activates to inject the biologic into the GI mucosa using microneedles or liquid jets. The oral administration of therapeutic macromolecules has been an extensive field. The ingestible capsule is named a " luminal unfolding microneedle injector". The device is roughly the size of a pen cap, measuring 9mm (35 inches) in diameter and 30mm (1.2 inches) in length. A leopard-tortoise-inspired oral insulin capsule containing a compressed insulin milepostis also called a self-orienting millimeter-scale applicator (SOMA) [3].

SMART INGESTIBLE DEVICES
Self-orienting millimeter-scale applicator
Luminal unfolding microneedle injector (LUMI)
Liquid-injecting SOMA (L-SOMA)
Magnetic-controlled microneedle robotic (MMR) [20].

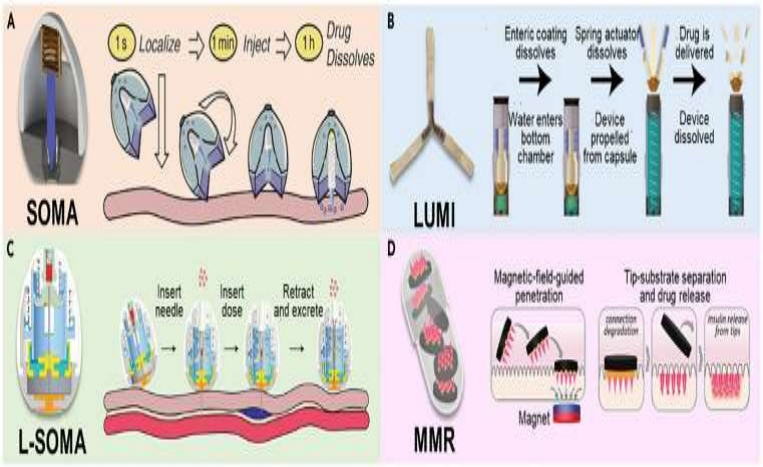

Fig 3: Schematic illustration of four smart ingestible devices

SELF-ORIENTING MILLIMETER-SCALE APPLICATOR

The SOMA autonomously inserts drug-loaded million posts into the stomach lining. the SOMA reliably proposes an actuation mechanism to insert active pharmaceutical ingredients (API) into the mucosa rather than the lumen. The SOMA's small form factor prevents obstruction in the lower GI tract and allows for easy ingestion. The self-orienting shape is similar to that of the tortoise to ensure that the millipost would not misfire into the lumen if a patient leaned over during actuation.

The SOMA reliably positions an actuation mechanism to insert active pharmaceutical ingredients into the mucosa rather than the lumen. The SOMA's small factor prevents obstruction in the lower GI tract and allows easy ingestion. It is smaller in volume than the U.S. Food and Drug Administration

(FDA) approved daily dosed osmotic-controlled release oral delivery system (Ø 9 mm × 15 mm), a non-degradable drug delivery capsule.

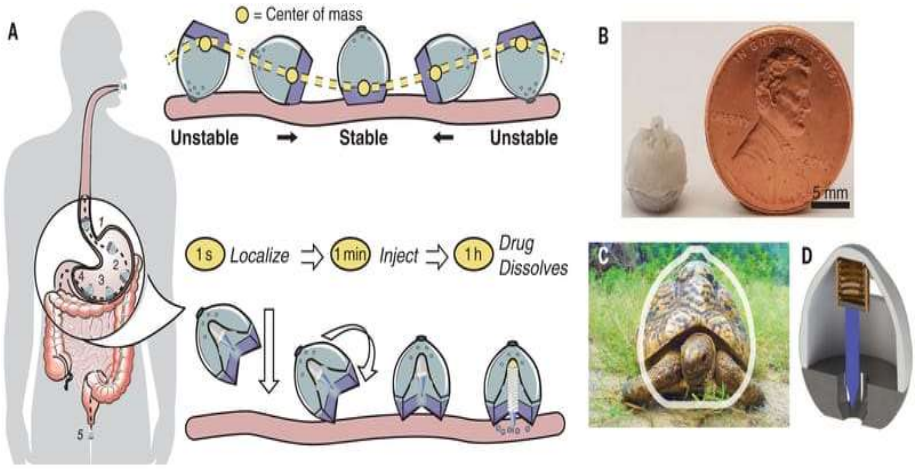

Fig 4: Mechanical API localization and injection for oral gastric delivery

The SOMA localizes to the stomach lining, orients its injection mechanism towards the tissue wall, and injects a drug through the mucosa. (B) A fabricated SOMA. (C) A comparison between the shape of the leopard tortoise and that of the SOMA. The SOMA quickly orients and reaches its preferred orientation. (D) The SOMA uses a compressed spring fixed in caramelized sucrose (brown) to provide a force for drug-loaded millipost (blue) insertion. After actuation, the spring remains encapsulated within the device.

LUMINAL UNFOLDING MICRONEEDLE INJECTOR(LUMI)

An injectable capsule named the "luminal unfolding microneedle injector " or LUMI. The device is roughly the size of a pen cap, measuring 9 mm (.35 inches) In diameter and 30 mm (1.2 inches) in length.

The capsule protects the LUMI during the acidic journey through the stomach and ejects the LUMI when it reaches the small intestine. Three spring-loaded arms extended, pushing a cluster of 1-mm long microneedles into the tissue wall of the small intestine. These microneedles dissolve, releasing the medication. The drug is then carried into the bloodstream. Finally, the device broke into species after the delivery of the drug and was safely excreted from the body. This prevents blockages in the intestine.

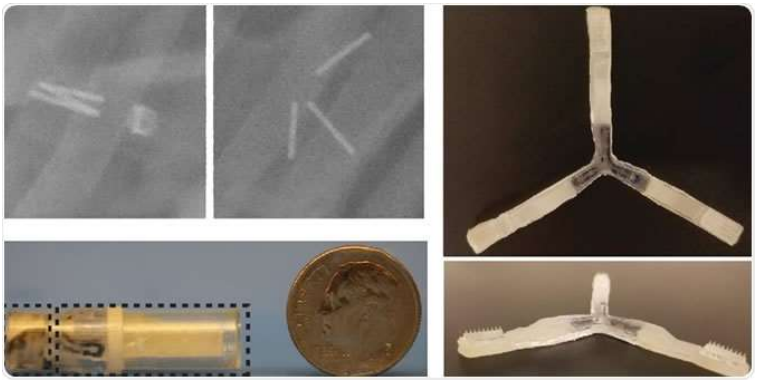

Fig 5: Schematic representation of LUMI

LIQUID-INJECTING SOMA (L- SOMA)

A new version of SOMA in nature biotechnology by redesigning the actuation and delivery systems. The new pill, called liquid-injecting SOMA (L-SOMA), upgraded the drug loading capacity to 4mg and enabled liquid formulations of bioavailable drugs into gastric submucosa. overall, based on the L-SOMA macromolecules drug delivery system, maximum drug plasma concentrations similar to standard subcutaneous injections could be achieved in 30 minutes, and absolute bioavailability of up to 80 percent could be achieved in a few hours.

MAGNETIC-CONTROLLED MICRONEEDLE ROBOTIC(MMR)

The magnetic-controlled microneedle robotic (MMR) could be taken orally with the aid of commercial enteric capsules, and it could be released as it entered the small intestine. With the presence of its polarised magnetic substrate, the tips of the MMR could be reoriented to the wall of the small intestine, overcoming obstacles, inserting into the tissue, and delivering encapsulated bioactive substances under a specific magnetic field.

In addition, after the degradation of the separable connections, the tips could be left in the tissue and continuously release drugs; the magnetic substrate could be safe [22].

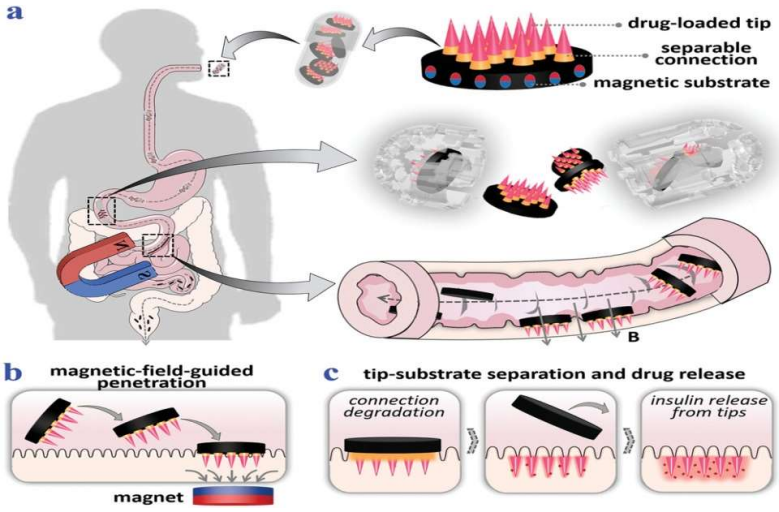

Fig 6: schematic representation of MMR [21**]**

ADVANTAGES

Pain-free
More accurate, efficient diagnosis and treatment
Removing invasive or costly procedures such as endoscopy or colonoscopy
Reducing the chances of infection

DISADVANTAGES

High cost
Biocompatibility issues
Potential adverse reactions
The danger of device failure

RBC MEMBRANE – CAMOUFLAGED NANOPARTICLES DRUG DELIVERY SYSTEM

RBC membrane camouflaged nanoparticles are a new class of drug delivery systems. Engineered RBCs have been investigated and found to be excellent carriers. It hasa variety of bioactive chemicals, including enzymes, medications, proteins, and macromolecules. Because of their abundance, red blood cell membranes serve as a "camouflage," allowing nanoparticles to combine the benefits of native red blood cell membranes with those of the nanoparticles. Several strategies have been developed to load therapeutic agents onto RBCs without compromising the structure and the physiological function of RBCs. When injected, the coated nanoparticles will mimic RBCs and interact with the environment to establish long systemic circulation. Sonication is the most common method for creating RBC camouflaged nanoparticles. Other methods of RBC fusion with nanoparticles include in-situ polymerization, microfluidic electroporation, and extrusion [12]. However, advantages and disadvantages in terms of synthesis, scale-up challenges, reproducibility, and the nature of the final product. Before the fusion, the RBC membrane-derived vesicle is obtained through hypotonic treatment (dialysis, hemolysis, or dilutions) of fresh whole blood from an organism. The hypotonic treatment will help to remove unwanted cells and plasma. The use of RBCM-NP drug delivery systems is extremely promising and offers numerous benefits due to their low immunogenicity and ability to maintain long systemic circulation (a lifespan of 120 days). Furthermore, because of the large number of cell membranes, RBC vesicles are inherently biocompatible and biodegradable, and can easily achieve high load capacity, resulting in higher accumulation at the target site [12].

METHODS FOR RBCM-NPs

- ✓ Co-extrusion method
- ✓ Microfluidic electroporation method
- ✓ Cell membrane- templated polymerization
- ✓ In-vitro verification of RBCM-NPs

The importance of using RBCM-NPs has numerous benefits due to their low immunogenicity and ability to maintain long systemic circulation. Remarkably, erythrocyte membrane-coated nanoparticle formulations have been extensively applied in anticancer research, cardiovascular diseases, and encephalopathy [13].

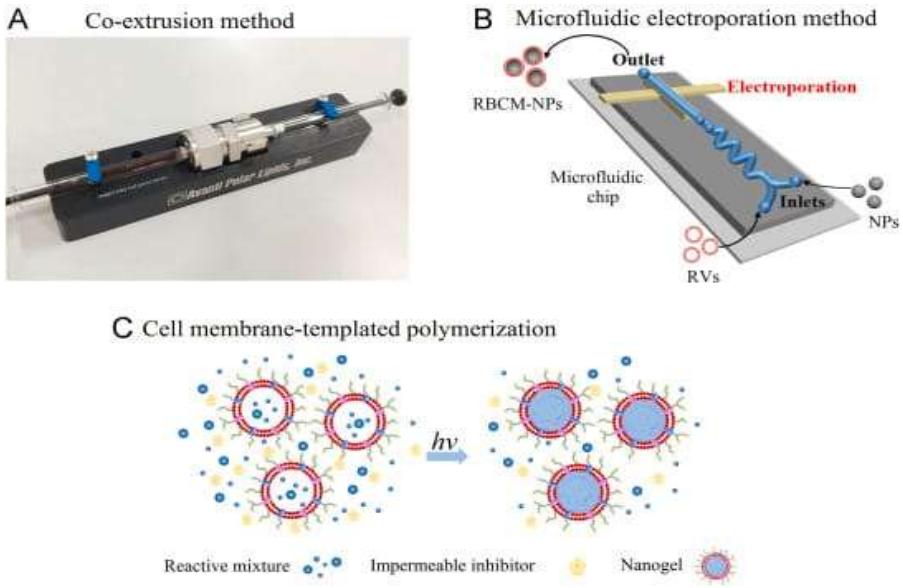

Fig 7: Schematic of RBCM-NPs preparation by three different methods. (A) co-extrusion method; (B) microfluidic electroporation method; (C) cell membrane- templated polymerization.

CO-EXTRUSION METHOD

Prepared nanoparticles are usually fused with obtained RVs through mechanical extrusion. the principle for the coating process is the interfacial interactions. Depending on the prepared nanoparticles' size, the mixture is repeatedly extruded through different-sized porous membranes before bath sonication for several minutes.The mechanical force promotes the nanoparticles to pass through the lipid bilayer, generating vesicle-particle fusion. In particular, the RBCM phospholipid bilayer structure should be as complete as possible throughout the preparation process to minimize membrane protein loss and damage [7].

MICROFLUIDIC ELECTROPORATION METHOD

Biomimetic membrane-coated Nano-particles in the biomedical field and microfluidic electroporation have also been demonstrated to effectively promote RBCM-NP synthesis—mixed Fe3O4 magnetic nanoparticles (MNs) and RVs in a microfluidic device. The microfluidic chip for electroporation consists of five sections: two inlets for the RVs and nanoparticles, respectively, a Y-shaped merging channel, an S-shaped mixing channel, an electroporation zone, and an outlet [7].

CELL MEMBRANE-TEMPLATED POLYMERISATION

The majority of existing cell membranes covering nanoparticles are prepared via a nanoparticle-templated coating route, such as the co-extrusion method, and microfluidic electroporation method, wherein the nanoparticle core is pre-synthesized then the outer layer is coated with cell membranes. In this process, the interfacial interactions between the membranes and the cores may hinder the application of some non-compliant nanomaterials. This led us to cell-derived vesicles.

After the addition of the macromolecular inhibitor, ultraviolet (UV) irradiation-induced gelation, has resulted in the formation of cell membrane-coated hydrogel, termed nanogels. The cell membrane-templated coating method will likely apply to coating various nanostructures aside from nanogels.

IN VITRO VERIFICATION OF RBCM-NPs

In vitro evaluation of these cellular vectors is necessary as the chemical structures and surface proteins of the RBCMs play a vital role in their immune escape and circulation. The main characterization parameters are as follows:

1. Surface morphology
2. Verification of surface proteins
3. Fluorescence colocalization
4. UV- vis absorption spectra

Together, these in vitro characterizations verify the ideal state of RBC separation into vesicles and integration with nanoparticles.

ADVANTAGES

Improving nanoparticle stability
Enhancing in-vitro storage time
Discouraging aggregation
Escaping the immune system and achieving long-term circulation
Avoiding some intrinsic Nanoparticle toxicities
Marked inherent biocompatibility and biodegradability

DISADVANTAGES

Complex issues of regulation may arise also:
Protein identification
Protein purification
Protein conjugation may be bypassed [12].

PROTEIN AND GENES

Proteins and genes of therapeutic interests in conjunction with different delivery systems are growing toward new heights. Next-generation delivery systems may provide a more efficient platform for the delivery of proteins and genes. The therapeutic protein is used to describe medicines that are genetically engineered versions of naturally occurring human protein. Gene is used for direct transfer when the foreign DNA is directly introduced into the plant genome.[1]

EXTRACELLULAR VESICLES

Extracellular vesicles can be loaded with therapeutic drugs, including nucleic acids and chemotherapeutic drugs. They are a promising delivery agent for carrying exogenous drugs due to their low immunogenicity and good biocompatibility [5].

NEXT-GENERATION – NOVEL TECHNOLOGIES

Artificial intelligence and machine learning
3D printing
Digital apps- mobile
Data Analytics
Genomics

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Artificial intelligence(AI) has emerged as a powerful tool that harnesses anthropomorphic knowledge and provides expedited solutions to complex challenges. Remarkable advancements in AI technology and machine learning present a transformative opportunity in the drug discovery, formulation, and testing of pharmaceutical dosage forms.

AI potential to revolutionize the drug discovery process, and improve efficiency, accuracy, and speed algorithms can analyze and optimize drug candidates by considering various factors, including efficacy, safety, and pharmacokinetics.

Machine learning algorithms assist in experimental design and can predict the pharmacokinetics and toxicity of drug candidates. this capability enables the prioritization and optimization of lead compounds, reducing the extensive and costly animal testing [7, 8].

AI FOR DRUG DEVELOPMENT AND RESEARCH

AI can be used to enhance nanosystem design and expand the present drug testing modeling system. increase the accuracy of parameters and factor selection in drug design, drug discovery, and drug repurposing methods is also useful for the drug discovery process along the drug repurposing method it also helps to better

understand the mechanism of membrane interaction with the modeled human environment by studying drug permeation, simulation, human cell targets, etc.studying drug permeation, simulation, human cell targets, etc [14].

CHALLENGES

The potential benefits of AI in drug discovery, there as several challenges and limitations that must be considered. One of the key challenges is the availability of suitable data. AI-based approaches typically require a large volume of information for training purposes [14]. In many cases, the amount of data accessible may be limited, or the data may be of low quality or inconsistent, which can affect the accuracy and reliability of the results. This can increase the quantity and diversity of data available for training ML algorithms, improving accuracy and reliability. Another approach is the use of explainable AI methods, which can provide interpretable and transparent explanations for the predictions made by ML algorithms. The integration of AI with traditional experimental methods can also enhance the drug discovery process. By combining the predictive power of AI with the expertise and experience of humans. It is possible to optimize the drug discovery process and accelerate the development of new medication [15].

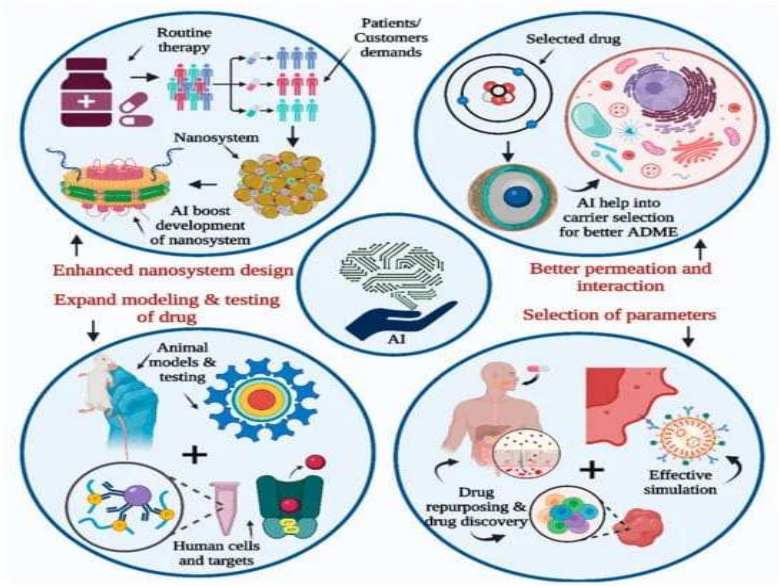

Fig 8: Schematic Diagram of AI for drug developments

ADVANTAGES

Reduces time
Reduces the cost of drug
Early detection and diagnosis of diseases
It can analyze the adverse effects and other health risks of the medication
AI programs like various artificial surgery simulators (GI simulation, heart simulation, brain simulation)
Error minimization

DISADVANTAGES

Expensive
No replicating humans
AI in healthcare has the potential for ethical and privacy concerns
Heavily on patient data, including sensitive medical information
To ensure that this data is collected stored and used in a secure and privacy-consumer manner,

APPLICATIONS

The application of these methods is that the AI can establish a link between the chemical structure of compounds and their biological activity. Drug delivery aims to potentiate the therapeutic effect of medicinal drugs by physicochemical features. they are overcoming the inherent instability of biologics, which impairs their pharmacokinetics [9].

3D PRINTING TECHNOLOGY

It is also called additive manufacturing technology. it allows the fabrication of personalized drug delivery that uses different materials. It is an alternative to injection molding technology [6].

TYPES OF 3D PRINTING

Selective laser sintering (SLS)
Fused deposition modeling (FDM)
Stereolithography(SLA)
Inkjet printing
Hot melt extrusion
Extrusion 3D printing

SELECTIVE LASER SINTERING

SLS uses laser energy to heat and fuse powder particles, resulting in a solidified 3D product. the spreading platform, powder bed, and laser system are three components. It's - a step, quick production method that doesn't require any solvents. due to the laser precision, it's also high-resolution objects.

SLS is a quick manufacturing process based on the use of powder-coated metal additives, a process generally used for rapid prototyping. A continuous laser beam is used as a heating source for scanning and aligning particles in predetermined sizes and shapes of the layers [14].

ADVANTAGES

Enhanced productivity
Enhances safety, potency, and accessibility of medicines
Faster production and high repeatability
No limits on its spatial configuration, and simple, cost-effective manufacturing

DISADVANTAGES

High-volume production and machinery cost
Restricted build size and copy-right issues
High power consumption
Poor surface finish
The large physical size of the unit

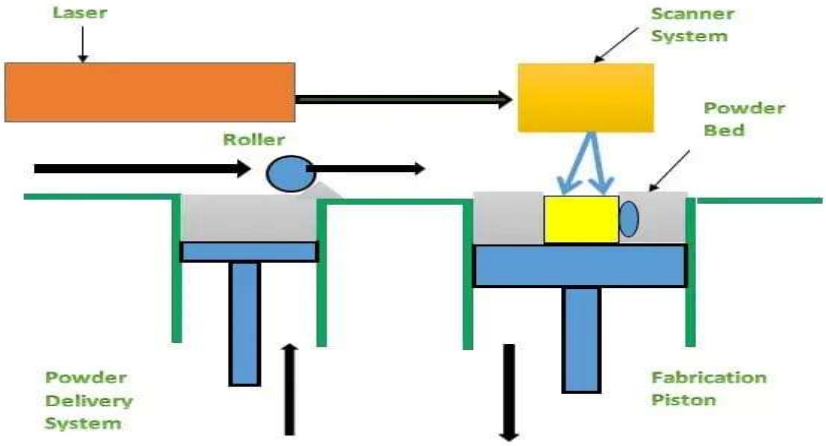

Fig 9: Schematic diagram of selective laser sintering in 3D printing

APPLICATIONS

Bio-printing of tissues and organs
Unique dosage forms
Personalised drug dosing
Complex drug release profile
Customized implants
Rapid prototyping [9]

FUSED DEPOSITION MODELLING

Fused deposition modeling printers are much more common and inexpensive than the selective laser sintering type. A fused deposition modeling printer uses a print head similar to an inkjet printer. Depending on the complexity and cost of a fused deposition modeling printer, it may have enhanced features such as multiple print heads.it is used in traditional injection molding or machining, so they have similar stability, durability, and mechanical properties.

STEREOLITHOGRAPHY

Charles Hull discovered this technique in 1998 as the first printing technique of a 3D system. During the printing process, photopolymer material like resin or acrylate was used which can cured by UV laser. The platform is lowered by a distance equal to the layer thickness (typically 0.003-0.002 inch), and the resultant layer is formed on top of the previously completed layers [10, 20].

INKJET PRINTING

This approach to personalized medicine originates from the same technique of computer-operated inkjet printing. The two printing types employed under inkjet printing are thermal inkjet printers and piezoelectric inkjet printers. Printing-based inkjet systems encompass two types of techniques: continuous inkjet and drop-on-demand printing.

HOT MELT EXTRUSION

Hot melt extrusion is the process of melting polymer and drug at high temperature and the pressure is applied in the instrument continuously for blending. HME is used to prepare sold solutions for drug delivery systems such as pellets and granules, it can reduce the number of processing steps in dosage form manufacturing and can be automated as a continuous process to give better drug homogeneity, and capabilities of sustained, modified, and target release.

EXTRUSION 3D PRINTING

Extrusion is the most common and the simplest 3D printing technique. It is used in almost every environment. The main printing material is plastic filament. The filament is heated and melted in the printing head for the 3D printer [1, 20].

CHALLENGES

It shows promising results in drug delivery applications. It Faces many challenges such as optimization processes, Improving the performance of the device for versatile use, Selection of appropriate excipients, post-treatment Methods, etc., to improve the performance of 3D printed Products and expand the application range in novel drug delivery systems [16, 17].

DIGITAL APPS- MOBILE

Mobile apps can offer users (patients or health consumers) tools to facilitate their engagement in the treatment and well-being. Digital technologies are increasingly relevant resources for health services because they can improve the quality, efficiency, and safety of health care. In recent has been a significant increase in the quality and quantity of mobile health professionals and app developers [24].

DATA ANALYTICS

Data analytics helps pharmaceutical companies swiftly identify appropriate clinical trial participants through a structured analysis of patient information, including demographic data, genetic makeup, medical histories, personality attributes, and more [25].

GENOMICS

Genomics, particularly high-throughput sequencing and characterization of expressed human genes, has created new opportunities for drug discovery. Knowledge of all the human genes and their functions may allow effective preventive measures, and change drug research strategy and drug discovery development processes.

SUMMARY AND CONCLUSION

NGS technologies have transformed genomics research and have significant potential in the field of toxicology. Ingestible injections deliver macromolecules, and therapeutic cells (stem cells, probiotics, etc.) precisely to target sites avoiding damage by physiological environments. Artificial intelligence plays a significant role in data and information storage and management such as patient medical histories, medicine stocks, sale records of interpretation of MRI, Radiation technology, and CT diagnosis to simplify health care measures. 3D

printing in pharmaceuticals plays a critical role in health care in providing on-demand design of drugs of flexible formulations with personalized dosages, and multi-drug combinations.

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