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REVIEW ARTICLE

Bioengineering Marvels in Pharmaceutical Delivery: Pioneering Strategies for Future Therapeutics

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Abstract: Many bacterial species have been considered as possible pharmacological biofactories for pharmaceuticals. Multiple hosts might now be used for bioproducts due to the development of biology combined with bioengineering technologies for genome modification.

This review highlighted the drug delivery *via* various bioengineering tools for the targeted drug delivery using biochips, bacterial species, and many more. Bioengineering technologies are equally important for growing or enhancing metabolites that are linked to their increased strength and improvement of their bioactivities. There are various techniques such as biochips using microrobots, oral drug delivery through diatomic nanoparticles as a microcapsule, treatment *via* bacterial gene and bacterial organelle *i.e.*, encapsulin, microfluidic chips for precision medicine, and other smart tactics that the pharmaceutical business is now employing.

In conclusion, the approval from the drug development authority on the most recent investigation and expansion of synthetic biology, animal, plant, and bacterial-based manufacturing techniques, as well as molecular bioengineered approaches, has led to the widespread acceptance of bioengineered tools for the creation of pharmaceuticals.

Keywords: Bioengineering, drug delivery, encapsulin, biochips, microrobots, diatomite NPs.

1. INTRODUCTION

The majority of the bacterial species have been extensively used as prospective pharmaceutical drug biofactories. The use of many hosts for bioproducts expanded the integration of developmental biology and bioengineering technologies for genome manipulation. The most useful recombinant proteins are those produced by bioengineering techniques and are known as biopharmaceuticals. They come from bioresources, including microbial, botanical, animal, or genetically altered tissues and organisms. To increase or grow metabolites, which are entangled in their enhanced durability and augment their bioactivities, bioengineering tools are equally vital which accelerates cutting-edge opportunities in the pharmaceutical industries. To advance intrinsically transformed or altered hosts with novel properties, bioengineering technologies have now included a variety of procedures for isolating and identifying the essential genes from a wide range of microorganisms into the host plant genetic material [1-3].

Modern bioengineering tools with cutting-edge technologies mandate genetic variation in plants, animals, and microbes to increase the importance of their pharmaceuticals. Metabolic bioengineering might be employed as a concentration and useful management of metabolic pathways in a biosystem by using the enzymatic and regulatory activities of the cells through biotechnology interaction *via* recombinant DNA (rDNA) technology. The primary objective of bioengineering instruments is the bio-advancement of affordable and productive techniques. Therefore, the enlarged metabolic actions may be carried out more skillfully by utilizing bioengineering equipment and approaches from the biotechnological aspect, as well as other recombinant molecular procedures [4, 5]. For instance, nanotools for studying biological organizations, *in-vitro* organs "on-a-chip" for disease models, nanoparticles (NPs) for targeted drug delivery, and molecular sensors that can be turned on and off with light are certain illustrations of the bioengineering tools that many researchers use to better understand proteins, tissue, cells, and organs [6]. Many tools and database packages are available that use cutting-edge technology to accomplish a wide range of systems biology goals through modeling and simulation. The engineering techniques for biopharmaceuticals are made simpler with the help of these instruments, which are constantly being produced, as shown in Fig. (**1**).

The treatment using recombinant cell therapy, proteins, gene therapy, and antibody therapy are the most advantageous biopharmaceutical forms. Because they demonstrate

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biological action and carry out specific tasks by simulating the pathophysiology of a disease, biopharmaceuticals are adept at treating diseases safely and effectively. Antigens, immunosera, vaccines, blood, cell therapies, monoclonal antibodies, hormones, enzymes, cytokines, allergens, gene remedies, and other bioproducts made from rDNA are just a few examples of the many different biopharmaceuticals that are currently used widely as beneficial agents [7]. Also, a growing mandate for bioanalytical capabilities towards evaluating therapeutic pharmacology, immunogenicity, and safety is created by the complexity of biopharmaceuticals, which is increasing as technology develops. Moreover, an increasing number of biosimilar methods are acknowledged by regulatory bodies, harmonized among the industry, and are based on strong science to determine how well they work with their respective originators [8, 9].

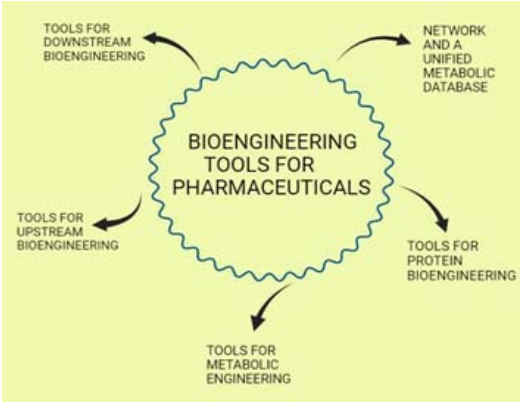

Fig. (1). Various types of bioengineering tools for pharmaceuticals. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. TARGETED DRUG DELIVERY USING MICRO-ROBOTS ON A BIOCHIP PLATFORM

When treating patients with antibiotics, targeted drug administration has a significant advantage over off-target delivery and overuse, which are known to cause systemic toxicity and resistance. By using remote actuation and on-site medication release, drug delivery devices like drug-loaded microrobots might help localize antibiotics to a difficult-to-reach spot that needs treatment [10]. Traditional medication delivery methods rely on repeated doses of high drug concentrations administered systemically. This strategy is justified by the idea that a high medication concentration in the bloodstream will ultimately have an impact on the targeted spot. This kind of therapy is troublesome when using antibiotics since it leads to elevated degrees of resistance and offsite harm due to overuse [11-13]. Upcoming materials-based technologies that improve therapeutic effects and regulate drug flaws are anticipated for targeted drug distribution. Drug-loaded microrobots provide remote access to difficult--to-reach areas and are non-invasive, which may obviate the requirement for systemic therapeutic drug delivery.

Future microrobots for targeted medication delivery have to be soft, steerable, and capable of navigating biological obstacles to successfully deliver therapeutic cargo [13-15]. Hydrogel-based microrobots appear to have potential as drug delivery devices due to their flexible mechanical and physical properties that allow cargo retention and structural stability, as shown in Fig. (**2**). Also, proof of concept testing *in-vitro* is necessary for the future *in-vivo* placement of microrobots for localized or targeted medication administration. To achieve this, a biochip platform was created that served as a model for the Targeted Drug Delivery System (T-DDS) and allowed loaded-drug microrobots to be activated towards a biofilm infection to locally release antibiotics [16]. Moreover, to treat the infection model, tetracycline was loaded onto a tet-microrobot that was intended to provide an inhibitive concentration of the medication locally at the target biofilm area. In subsequent research, the tetracycline-loaded microrobot was put into a cardiovascular-diseased model and magnetically driven toward the targeted area. Microrobot-targeted drug delivery was tracked over time for both bacterial prophylaxis and medical treatment.

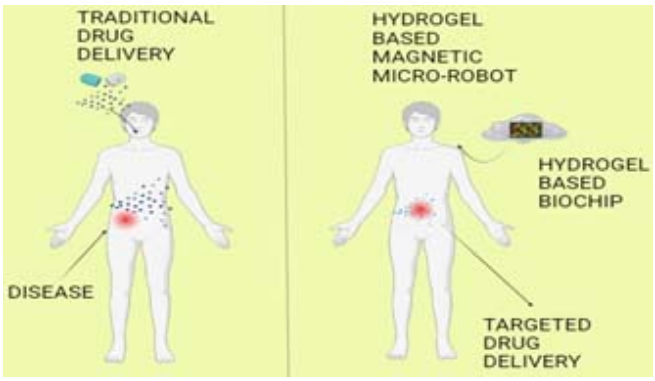

Fig. (2). Pictorial representation of successful targeted drug delivery of hydrogel-based magnetic micro-robot over traditional drug delivery. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The outcomes provide a visual proof-of-concept demonstration of tet-microrobots using hydrogel as a platform for targeted medication administration with minimal off-target consequences. This result was obtained using computer vision-based time-course evaluations of gel-encapsulated bacterial cultures in treated and untreated infection models. In comparison to the unrestrained expansion shown in the off--target model of infection, the results of the preventive treatment condition demonstrated that the target Tet-microrobot-treated infection had less bacterial development. These findings provide a clinical instance of early diagnosis and infection prevention therapy. This instance supports the use of tailored antibiotic medication administration, for example, to reduce the risk of infection downstream after oral surgery [17, 18]. Another illustration of treatment was the introduction of a tet-microrobot after initial culture development. This requirement for treatment provides a focused, therapeutic approach to a persistent illness, which is consistent with the usual recommendation of antibiotics [19]. Further study of these findings supports the necessity for antibiotics to be delivered *via* tailored drug delivery systems. Al-

though simplified in terms of complexity and physiological representation, the comparison of bacterial growth in off-target cultures under therapeutic and preventative conditions addresses the off-target side effects associated with conventional antibiotic therapy [11, 12, 20]. It is possible that the off--target administration of tetracycline to the off-target prophylactic culture occurred before the culture began to develop exponentially because of the modest delay in the growth of the culture. The fact that the target culture recovered by the next time point, in contrast to the target prophylactic culture, shows that nearly all of the loaded tetracycline nevertheless had the intended effect on the target culture. The steady expansion of the therapeutic off-target colony serves as a piece of evidence.

The researchers observed the next phase in the development of hydrogel-based, biomedical microrobots are targeted medication delivery using microrobots on an on-a-chip platform. The potential exists for targeted antibiotic delivery materials. It was found that the agar-based microrobots could transport and distribute antibiotics into the surrounding environment. Additionally, inhibitive, tolerant, and susceptive dosages of tetracycline may be added to gel-encapsulated bacteria to treat them as an infection model. For standardized microrobot testing, tet-microrobots could deliver efficient amounts of antibacterial agents for preventative and therapeutic purposes to deliver efficient amounts of antibacterial agents for preventative and therapeutic purpose and to avert the growth of bacteria in an intended area while limiting undesirable consequences in fluidically connected models of infection. By targeting moieties and controlling drug release in response to certain stimuli, hydrogel-based, magnetic micro-robots can be constructed in the future [21, 22]. This platform may also be utilized to replicate cooperative microrobot actions for reliable target engagement of infection-resistant models. Hence, with the use of untethered, mobile drug delivery materials, the long-term aim of this characterization is to provide healing access and efficient medicinal administration to ailment locations of notice that are otherwise inaccessible [23].

3. DIATOMITE-BASED VECTOR DRUG DELIVERY BY SURFACE BIOENGINEERING

New naturally occurring porous materials for biomedical applications have also been introduced in recent years to address the shortcomings of synthetic porous materials, leading to the suggestion that diatomite is a workable replacement for synthetic porous materials [24-27]. It can be used as a legitimate substitute for manufactured porous silica in the administration of drugs using nanotechnology as it is a sedimentary-derived natural porous silica substance. The perspective of Diatomite Nanoparticles (DNPs) for drug delivery aims to increase the intracellular uptake in cancer cells, improve the physicochemical and biological properties of the particles, and the improvement of biocompatibility of the APT (3-aminopropyltriethoxysilane) modified-DNPs [28]. Moreover, diatomites are still underutilized in nanomedicine, and lately, they have been investigated for microcapsules as an oral drug delivery system. As a result, a non-cytotoxic biomaterial has been created that has the potential to significantly boost the absorption and uptake of preloaded oral drugs by delaying the release of the drug and boosting the drug permeability [29].

Due to their high stability, low toxicity, aptitude, and biocompatibility for cellular absorption, NPs are particularly well-suited to serve as drug delivery devices. It was studied if DNPs' surfaces might be biofunctionalized to enhance their physical, chemical, and biological characteristics, such as cellular internalization and biocompatibility [30]. DNPs can be highly favorable for the heaping of a huge variety of compounds, from small molecules to antibodies, oligonucleotides, proteins, and peptides, for the creation of tailored NPs for the applications of drug delivery because of their unusual porosity nature [31]. To obtain a successful DNP PEGylation, the hydroxylated NPs were revealed to increase the reactivity of their silica surface [32, 30]. It was discovered that the creation of the covalent bond between PEG and DNP required the introduction of highly reactive amino groups (-NH2) that may be chemically coupled with the carboxyl group of polyethylene glycol monomers onto the NP surface *via* the process of DNP salinization. Hence, stable covalently bound PEG compounds could not be produced without this two-step biochemical surface treatment [33]. This improves the stability of NPs in an aqueous medium as well as their cellular absorption and biocompatibility, which reduces the toxicity of the NPs to RBCs and breast cancer cells as well as their hemotoxicity. The free –NH2 (amino groups) of this complex were then chemically coupled with carboxyl groups (COOH) of cell-penetrating peptide (CPP-peptide) to enhance the DNPs' cellular absorption. Genes, peptides, proteins, and NP have all been reported to be delivered through cell membranes with great ease, as shown in Fig. (**3**) [34].

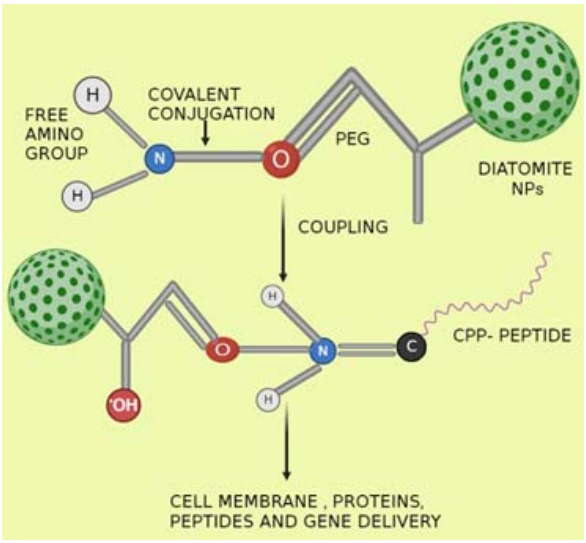

Fig. (3). A visual depiction of proteins, cell membrane, peptides, and gene delivery *via* diatomite nanoparticle. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The surface functionalization of the NPs increased the pre-loading efficiency of diatomite NPs and enabled the prolonged release of the insufficiently water-soluble antineoplastic medication, according to investigations on drug loading and release. Moreover, DNPs were discovered to be a favorable nano-vector for tumor therapy due to their low toxicity, superior cellular absorption, and drug loading and release features. With forthcoming scenarios to develop bioengineered diatomite NPs for localized Drug Delivery Systems (DDS). This shows that the potential of natural, low--cost, and biocompatible DNP was discovered to be a workable substitute for synthetic NPs and efficient biofunctionalized nano vectors for enhanced intracellular localization and drug administration in cancer cells [35].

4. BIOENGINEERED *THERMOTOG MARITIMA* ENCAPSULIN AS TARGETED DRUG DELIVERY SYSTEM

The recently found bacterial organelles (*Thermotog maritima* encapsulin) are native, naturally self-assembling proteins that can overcome the drawbacks of other NPs, such as their high cost of manufacture, immunogenicity, toxicity, etc. Genetically encoded protein nanocages (encapsulin) are very intriguing DDS prospects due to their modular structure, ease of recombinant manufacture, in a range of control over cargo molecule assembly, loading, hosts, and biodegradability [36-40]. Encapsulins are a very attractive element for usage in multifunctional drug delivery systems because of their biodegradability and clearly defined topologies [41]. Encapsulins work to reduce oxidative stress in prokaryotes by packing enzymes, mineralizing iron-containing proteins, or peroxidase. Encapsulins have been used in a broad range of biotechnological applications because they may be functionalized from a single protomer and use the well-known cargo loading technique [42]. The crystal structures of several encapsulins have been clarified at the atomic level by bioengineering these particles, giving researchers additional control [43]. Encapsulins are used as imaging agents in chimeric vaccines, as immunotherapeutic agents, in functional nanoarchitecture, and the establishment of functionalization by chemical crosslinking and interactions between proteins [44, 45]. The creation of the fusion protein by joining the *Thermotog maritima* encapsulant gene with the genetically modified antibody imitation peptide called designed ankyrin repeat proteins (DARP) is the first step towards the concept of a genetically expressed tailored drug delivery method. A small Singlet Oxygen Generator (miniSOG) or Reactive Oxygen Species Generator is a cytotoxic prototype cargo that was created by fusing the minimal targeting peptide domain from the *Thermotog maritima* ferritin-like cargo protein onto the C terminus of miniSOG [46]. MiniSOG is a perfect therapeutic protein candidate for encapsulation because the release of protein cargo from an encapsulant shell either necessitates disassembling under challenging circumstances or sophisticated capsule engineering and *in-vivo* endosomal evacuation and release of cargo remain a significant obstacle for DDs [47, 48]. When this drug delivery system binds to the HER2 receptor on breast cancer cells, it causes the targeted cell to undergo apoptosis. Reactive Oxygen Species (ROS) are produced as a result of the drug's acquisition and lighting, as shown in Fig. (**4**) [36].

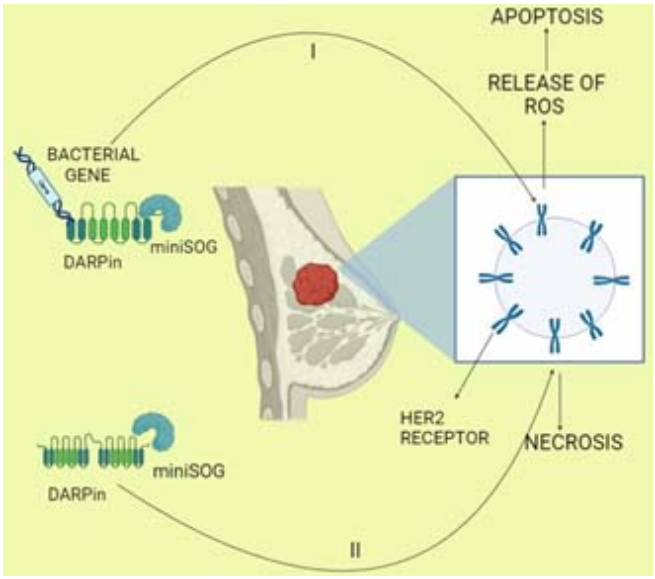

Fig. (4). A graphical representation of (I): DARPin conjugated with miniSOG binds to HER2 receptor with a further fusion of T. maritima and leads to apoptosis of the targeted cell. (II): DARPin and miniSOG directly bind to HER2 receptor and lead to necrosis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another targeted delivery method revealed that DARPin and miniSOG are directly fused genetically to target HER2 as well as produce phototoxicity. The DARPin-miniSOG fused proteins were readily absorbed, however, necrosis rather than apoptosis is observed (Fig. **4**). This suggests that the same cell line has a separate cell death mechanism. The packaging of miniSOG probably alters the pace at which proteins are taken in, and reactive oxygen species are released, which might impact cell death pathways [49]. When some control cells, such as SK-BR-3 and MSCs, were put against one another in a cell-killing experiment, it was discovered that more apoptotic cells were seen in SK-BR-3, and when cells were illuminated, apoptosis occurred at its highest rate. Since direct comparison of cell viability has been challenging, a more reliable control cell line (other than the MSCs) might need to be used in the future before analyzing the system's functionality and effectiveness *in-vivo* studies [36].

Additionally, encapsulin, a unique protein enclosure, can also be used as a platform at the nanoscale for the selective insertion of medicinal compounds and/or diagnostic probes by chemical and genetic modifications. The addition of six successive histidines with additional residues between Wild Type (WT) encapsulin provided infrequent heat steadiness and made the possibility of quickly purifying it on a huge scale. As a result, the modified encapsulin may be used as a multifunctional theranostic nano platform to concurrently get particular diagnostic probes, cell target ligands, and therapeutical medicines [50]. Therefore, with a few minor

tweaks, such as tag-less purification, the direct fusion of the *Thermotog maritima* encapsulant monomer with a DARPin offers an opportunity for large-scale production in a trustworthy and affordable approach. Also, DARPins are a group of contacts that mimic antibody-like particular reactions and may be linked with encapsulants of different sizes, each carrying a different sort of cargo. The approach laid the groundwork for a modular as well as multimodal tailored drug delivery platform that has a strong affinity for tumor cells, reduces undesirable side effects, increases safety, and has the potential to lead to the development of specialized and personalized therapies [51].

5. MISCELLANEOUS APPLICATIONS IN DRUG DELIVERY

5.1. Drug Delivery *via* 3D-printed Microfluidic Technology

Standard drug therapy encounters difficulties with medication absorption and distribution throughout the body, quick elimination and degradation, and numerous undesirable reactions. Microfluidics, in contrast with standard large-scale synthetic systems, enables liquefied modification at the micro-scale and has enormous capability for medication delivery and personalized medicine [52].

Physics, microfabrication, chemistry, engineering, and other academic fields all play significant roles in the progress of microfluidic technology [53]. The fluids in microfluidic chips have distinctive properties that distinguish them from fluids at a larger scale because of the size dependency of the heat and mass transport processes at the microscale [54]. In other words, the device is mostly affected by surface tension and capillary forces, with little gravitational or inertial force of action. The primary elements influencing fluid behavior are interface elements like diffusion, surface tension, and viscosity [55]. Moreover, the substantial surface area-to-volume ratios promote thermal uniformity and quick heat transmission. These essential characteristics result in a wide range of benefits, such as the need for minimal chemicals, low energy consumption, quick reaction times, and high simultaneous procedures [56]. Microfluidical technology is, therefore, frequently employed in both commercial and academic research. Proteases, temperature, and pH can threaten the *in-vivo* stability of protein therapeutics after injection. For nucleic acid medications to work, they must be transported to the cytoplasm. It is vital to create suitable medication delivery methods to overcome these issues. Effective drug delivery enables both accurate pharmacokinetics management and on-demand distribution of the active medication to on-site cells or tissues [57]. Several release mechanisms exist for drugs inside a delivery system, including drug diffusion, delivery material degradation, and external stimulation. Drug-eluting stents, for example, need to be surgically implanted and might cause a fibrocystic response. The macroscopic delivery system also features a unique pattern for medication release [58]. Nanoparticle delivery methods have various benefits over macroscopic ones, including the ability to adjust drug release patterns, preserve protein and nucleic acid medications from deterioration, make hydrophobic pharmaceuticals more soluble in tiny molecules, and target specific tissues [59]. With the use of microfluidic technology, monodisperse droplet emulsions may be produced by carefully controlling and adjusting fluids in a bottom-up fashion [60].

Microfluidic device fabrication is now being done using alternative manufacturing techniques, such as 3D printing [61]. Stereolithography, fused deposition modeling, inkjet 3D printing, and two-photon polymerization processes are only a few examples of traditional 3D printing methods [62]. Microfluid chips with intricate 3-D geometries may be made *via* three-dimensional printing, which also makes it possible to quickly change a device's functionality by improving the design. Moreover, it enables the manufacture of microfluidic devices at high throughput [63]. Also, there has been a rise in demand for 3D cell culture models. Microfluidic channels have a diameter that is well-matched to the size of many cell types. Microfluidic chips can be used to create in-vitro micro-physiological systems that can replicate organ-level and organism-level activities in addition to producing multifunctional functional delivery carriers [64]. Different microfluidic cell cultured chips, often known as organ-on-a-chips, are considered for personalized medicine [65]. Nevertheless, most organ-on-a-chips generally disregard the lymphatic drainage's role [66]. For accurate modeling of cancer pathophysiology, it is crucial to create both the vascular and lymphatic systems at the same time, as lymphatic vessels play an important part in regulating the concentration of fluids inside the tissue. Lymphatic endothelial cells (LECs) and human umbilical vein endothelial cells are co--cultured in a collagen gel-embedded microfluid device using a perfusion culture approach [67]. Improved modeling of organ function and disease states is made possible by *in-vitro* rebuilding of lymphatic channel architecture. The tumor-lymphatic vessels model was implemented on a more complicated microfluidic device, which also included blood vessels. By using bioprinting technology, it is feasible to make lymphatic tubes with blind holes at one end and hollow blood arteries with open ends. As a result of the enhanced transport of drugs in lymphatic channels, the two-vessel chip is more effective in moving the medication than a single vessel [68]. Hence, the delivery vehicles may be made of pH, acid, light, osmotic pressure, temperature, and other sensitive stimuli by carefully designing and selecting the material of microfluidic chips.

5.2. Bioengineered Elastin-like Protein as Drug Delivery System

A component of the extracellular matrix (ECM), elastin, is a protein that is present in almost all higher mammals. It has domains that can adopt several different conformations and is held together by cross-linking [69]. Protein-based drug delivery systems may now be developed with precisely tailored physicochemical characteristics because of advancements in genetic engineering, allowing for a greater degree of customization, which is not possible with synthetic polymers. Elastin-like proteins (ELP) are suitable applicants for

usage as pharmaceutical delivery systems due to their distinct chemical and physical characteristics and the simplicity of engineering provided by recombinant DNA technology [70]. Tumor tissues have an increased vascular density and poor lymphatic outflow, allowing macromolecular medicines to aggregate and be retained selectively [71-73]. ELPs can remain water-soluble below their critical Tt (transition temperature) due to their inverse temperature transition behavior, but above Tt, the polymeric chains coil hydrophobically and gather themselves into an additional organized assembly that is more suited for drug administration. ELP NPs are also immune-response-free and biocompatible alternatives to natural elastin and are established by thermo-responsive self-assembly [74, 75]. There are risks associated with using ELP NPs for drug administration, including the fact that they tend to aggregate, resulting in bigger assemblies and that they could have an improperly low critical transition temperature, which might cause cell and organ damage. By attaching poly-aspartic acid chains to ELPs, amphiphilic di-block peptides have been produced by experts with a higher critical transition temperature and reduced propensity for aggregation [76]. Thermo-responsive cross-linked capsules were created utilizing microemulsion to better regulate the loading and release of payload [77].

Although bioengineered proteins are excellent raw materials for the development of modular, solid delivery systems, their usage has been restricted thus far. Implanted devices can have their surface qualities altered and their integration with live tissues facilitated by the application of thin films. Thin films containing peptide sequences of solid arginine-glycine-aspartic acid in ELPs, for instance, were pH and temperature-sensitive, allowing for the tuning of surface attributes like wettability and topography. It is an optical application for sustained drug delivery and bioavailability [78]. Also, hydrogels, which are three-dimensional cross-linked polymeric networks, can be used as medical applicants, for instance drug delivery, tissue engineering, and implant materials. Hydrogels may be produced with ease, injected for non-invasive distribution, and put to good use in interactions with biological materials. Hydrogels are promising biomaterials because their high porosity, swelling ratios, and soft consistency are reminiscent of biological tissue [79-83].

The ELP was also given a cell-penetrating peptide (CPPs) to aid in the effective absorption of the DDS into the cell. Doxorubicin (Dox) was finally conjugated to the carrier using an acid-sensitive linker. This enables a specific delivery of Dox whenever the drug delivery system reaches cancerous cells and is then subjected to a low pH. Genetic fusion allowed the CPP to be incorporated into the ELP carrier without additional functionalization or chemical conjugation [84]. In recent research, it was observed that an exceptionally aggressive kind of cancer called glioblastoma was treated using ELPs. The prognosis for patients is still grave despite various attempts to create DDS specifically aimed at this malignancy. ELP systems that selectively and effectively destroyed glioblastoma cells were created using temperature-responsive properties for the agglomeration or deposition of the drug delivery system in tumor cells at a certain temperature exceeding physiological values. Additionally, the coupling of thiol maleimide to three cysteine residues on the elastic-like protein enabled the insertion of the drug molecule and the acid-sensitive linker in a very predictable and selective way. A trustworthy and measurable measurement of drug conjugation is made possible by this exact stoichiometric control [84, 85]. Hence, to anticipate future demands with specialized or selective DDS, such a bioengineered protein-polymer approach provides exquisite customization and control. Compatibility with tunable targeting, complex peptides and assemblies, degradation, proteins, biocompatibility, stability features, and safe degradation products are just a few of these system's significant benefits that may be attained even though still preserving the mechanical benefits of natural elastin's elasticity. When choices to directly encode target sequences, treatments, as well as associated control points are coupled, new opportunities for bioengineering protein-polymers in the arena of drug delivery systems are achieved [86, 87].

5.3. Drug Delivery *via* Bioengineered Thermo-responsive Scaffold

Scaffolds are the structures of support that replicate an ECM environment and are biocompatible and biodegradable [88, 89]. Thermo-responsive polymers are incredibly useful for scaffold building due to their outstanding performance under a particular temperature change (such as localized inflamed tumors in inflammatory processes). As a result of this transformation, a loaded antibacterial, wound-care, and anti-inflammatory medication may be released, which may result in a phase transition in the polymer [90, 91]. These refined thermos-responsive biomaterials have three-dimensional structures like those of humans and offer physical support for tissue regeneration and cell development. These structures are also employed as cutting-edge drug delivery approaches. Also, because of their unique qualities over other graphene-based materials like carbon nanotubes, graphene nanoribbons (GNRs) were selected for study in the field of medical science. The results show that GNRs have a great deal of potential for application as an efficient agent in photothermal therapy, DNA assembly, drug delivery, and anti-cancer treatments. Using oxidative unzipping of the multi--wall carbon nanotubes and subsequent deoxygenation by hydrazine and bovine serum albumin, single-layer reduced graphene oxide nanoribbons were used to report the efficient concentration-dependent genotoxicity effects on human mesenchymal stem cells [92, 93]. Additionally, the design of the scaffold must take into account several aspects, including vascularization, cell-tissue interaction, loading with medications, cells, antimicrobial substances, scaffold degradation, and growth factors. To provide a biocompatible, non-immunogenic, and quality product that quickens the healing process of localized tissue, pre-formulation and logical scaffold designs for biomedical devices or drug delivery systems are essential [94, 95]. Numerous innovative manufacturing processes are used, including electrospinning and 3D bioprinting [96, 97]. However, not all thermo-responsive polymers can be used in 3D printing. The processing of poly-

mers into drug delivery systems needed by specific populations to cure uncommon illnesses is being investigated using fused deposition modeling (FDM). For thermo-responsive polymers, this extrusion technique is frequently used since it enables bigger structures than other options. Another method is stereolithography, a laser-based 3D printing process that creates 3D things using UV-sensitive liquid resins [98, 99]. Additionally, due to their safety profile, a novel approach to the administration of medications for wound healing is offered by electro-spun nanofibers constructed of thermo-responsive polymers [100-103]. Furthermore, the discipline of nanomedicine is addressing the rising need for customized treatments. The challenges of effective medication delivery can be solved with the use of thermo-responsive polymers. These biomaterials can improve the drug's poor bioavailability, solubility, quick clearance rates, protection from enzymatic degradation, and inability to traverse biological obstacles by being incorporated into scaffolds [104, 105].

The scaffolds and the biomaterials carried out certain biological reactions that design novel methods for drug delivery systems. These systems may be utilized to speed up tissue recovery, prevent scarring, and control inflammatory reactions throughout the healing process of wounds. Small pharmaceuticals or biomacromolecules (like proteins and poly-nucleic acids) are loaded into scaffolds constructed of synthetic, natural, and modified biopolymers [106-108]. However, polyvinyl povidone (PVP), a hydrophilic polymer, may encapsulate pharmaceuticals that are either hydrophilic or have low water solubility. The created chitosan/polyurethane scaffold for skin tissue engineering was improved by using its swelling and pore-forming abilities. Additionally, due to its adaptability, it is a suitable polymer for making scaffolds and other products used in biomedicine using 3D printing and electrospinning [109-112]. Additionally, thermo-responsive scaffolds offer one or multiple APIs temporally and spatially regulated drug release mechanisms. These structures can delay medication delivery while minimizing the burst impact. This is a crucial factor to consider to keep the body's therapeutic levels stable and lower the needed dose. More importantly, these methods enable the controlled drug release that is desired by only releasing the API in response to temperature stimulation. The presence of a localized inflamed tumor while inflammaging, whether brought on by histological damage or as a reaction of a biomaterial, permits boosting the delivery because of the shrinking of polymer chains [113, 114]. Thermo-responsive scaffolds also aim to increase patient adherence to treatments. For the prolonged release of the herbal remedy of the composition of five bark medications from Ayurveda called Panchavalkala, a scaffold was created using electro-spinning. Since polylactic acid (PLA) is biodegradable, the researchers utilized it as the carrier and it was observed that the scaffold steadily delivered 80% of the medication for five days. Comparing the constructed scaffold to the conventional unstable drug dispersion, a scaffold was shown to be more effective in healing wounds. Because of the improved bioavailability of this biomaterial, the inflammatory process can be successfully controlled [115, 116]. Hence, for the construction of scaffolds, thermo-responsive polymers are now one of the utmost crucial resources in the domains of nanotechnology, tissue engineering, nanomedicine, and biomedicine. Due to their amphiphilic nature, the simplicity with which their physicochemical properties may be modified by innovative techniques, and the impact of physiological reactions, various drug moieties and biomolecules for wound healing can be supplied. Since these systems can orthogonally react to many stimuli, multi-responsive amphiphilic polymer assemblies are also relatively more important. An often-seen system incorporates reactions to heat, light, acidity, and base. The ability to use one stimulus for guest loading and another for guest release is another benefit of such multi-stimuli-responsive systems [117].

Moreover, there are various techniques that researchers have innovated for targeted drug delivery *via* microrobots, vector drug delivery, bioengineered bacterial (*Thermotog maritima*) drug delivery, 3D printed microfluidic technology, and many more, as shown in Table **1**.

Table 1. Recent Applications of Bioengineering Products in Drug Delivery.

S. No.	Bioengineering Products	Applications	Reference
1	Micro-robots	Targeted drug delivery	[9]
2	Organ-on-a-chip	Improve Biocompatibility	[5, 63]
3	*Thermotog martima*	Improve Patient Compliance	[40]
4	3D-printed technology	Peptide and gene therapy	[59]
5	Diatomite-based vector	Anti-cancer activity	[27]
6	Elastin-like Protein	Tissue Engineering	[68]
7	Thermo-responsive Scaffold	Improve the drug's poor bioavailability, solubility, and quick clearance rates	[86]
8	Biorobots	Personalized medicines	[16, 17]
9	Microfluidic technology	Improve the efficiency and sustainability	[52]
10	Encapsulin protein	Improves biodegradability	[49, 118]

CONCLUSION

The rapid advancement of synthetic biology, system biology, and biotechnological molecular biology tools and methods, together with biotechnological devices and approaches for the creation of novel strategies for medicines outline, are all heavily reliant on the bioengineered tools in the current study. It concluded that efforts to increase the exploration, rational variation, manufacture, and purification of significant biopharmaceuticals are ongoing. Bioengineering technologies are increasingly being used in pharmaceutical delivery to enhance metabolites, enhancing their endurance and bioactivities. These technologies include biochips, diatomite nanoparticles, encapsulin, 3D-printed microfluids, and more. The pharmaceutical industry is increasingly employing bioengineering tools to improve the efficiency and sustainability of their products. Biopharmaceuticals, such as antigens, immunosera, vaccines, blood, cell therapies, monoclonal antibodies, hormones, enzymes, cytokines, allergens, gene remedies, and other bioproducts made from recombinant DNA

(rDNA), are effective in treating diseases safely and effectively. The acceptance of bioengineered tools is now widely acknowledged for the creation of pharmaceuticals owing to the current approval from the drug development authority on the most recent investigation and expansion of animal, plant, and bacterial-based manufacturing techniques, synthetic biology, as well as molecular bioengineered approaches. This is because bioengineered tools are effective in the past. The main issues with nanoengineered tools still need to be resolved, including measuring the health risks of nanomaterials, their impacts, how people are exposed to them, how to use them safely in the environment, how much they cost to make, and how user-friendly they are in remote areas.

AUTHORS' CONTRIBUTION

The authors confirm their contribution to the paper as follows: study conception and design: SV, KT; Validation: NV; analysis and interpretation of results: AM; draft manuscript: MS. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

NPs	=	Nanoparticles
rDNA	=	Recombinant DNA
TDDS	=	Targeted Drug Delivery System
DNPs	=	Diatomite Nanoparticles
ROS	=	Reactive Oxygen Species
WT	=	Wild Type

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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