

## Biochemical and Microbial Interactions in Advanced Drug Delivery Systems: Implications for Therapeutic Efficacy

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### Abstract

Advanced drug delivery systems have undergone rapid evolution to address limitations associated with conventional dosage forms, including poor bioavailability, non-specific distribution, and inadequate control over drug release. Increasing evidence indicates that biochemical and microbial environments play a decisive role in modulating delivery system performance and therapeutic outcomes. This review aims to critically analyze advanced drug delivery technologies through the lens of biochemical and microbial interactions, with emphasis on their influence on stability, targeting efficiency, controlled release, and clinical performance. A comprehensive evaluation of recent literature was conducted focusing on nanoparticle-based, polymeric, hydrogel, liposomal, biomimetic, and stimuli-responsive delivery platforms. Particular attention was given to protein corona formation, enzyme-mediated degradation, immune interactions, microbial biofilms, and microbiota-driven modulation of drug delivery behavior. Findings indicate that biochemical determinants such as protein adsorption, enzymatic activity, redox potential, and immune recognition significantly influence carrier biodistribution and release kinetics. Microbial factors, including gut microbiota and biofilm-forming pathogens, further affect drug stability, penetration, and efficacy. Advanced delivery platforms incorporating bio-responsive materials and biomimetic strategies demonstrate improved site-specific delivery, enhanced therapeutic outcomes in cancer and infectious diseases, and broader clinical applicability. Integration of biochemical and microbial insights into drug delivery design enhances therapeutic precision and translational potential. Future advancements are expected to rely on microbiome-aware, precision-driven, and smart bio-responsive systems to achieve improved clinical performance in modern pharmaceuticals.

**Keywords:** Drug delivery systems; Biochemical interactions; Microbial interfaces; Stimuli-responsive delivery; Nanotechnology

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### 1. Introduction

Modern pharmaceuticals has been based on the advanced drug delivery technology, necessitating the use of such technology to increase the treatment efficacy, reduce the adverse effects, and patient compliance. Traditional dosage forms are often associated with shortcomings of low bioavailability, lack of specificity of distribution, fast degradation, and insufficient drug release control. The challenges have led to the rapid rise in the realization of advanced drug delivery systems that combine material science, nanotechnology and biological knowledge. Over the last several years, there was a growing tendency towards the study of the interaction of biochemical and microbial environments

with delivery systems and their effect on their work and clinical results.

The development of drug delivery technologies is an expression of a change in the simple formulations towards highly engineered systems that are aimed at overcoming physiological barriers. Initial developments aimed at altering oral dosage forms in order to enhance absorption and stability, resulting in sustained-release tablets, enteric coatings and mucoadhesive systems.<sup>1</sup> Although these methods enhanced the convenience of dosing, they provided weak control of local delivery. The advent of nanotechnology was a significant advancement in the field of pharmaceuticals, and it is now possible to design nanoscale carriers that can entrap a multiplicity of therapeutic agents. The use of metal and

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polymeric nanoparticles also became popular because they could be used due to their ability to be tuned in terms of physicochemical features, drug-loading capacity, and their surface functionalization potential.<sup>2</sup> With these systems, better solubility of drugs that dissolve poorly in water could be achieved and options of targeted and controlled release systems were available. Later inventions consisted of multistage and stimulus-responsive delivery systems that react dynamically to the biological microenvironment. In other examples, tumour microenvironment-responsive platforms, including those based on differences in pH, enzyme activity and redox potential, have been used to release drugs locally.<sup>3</sup> Additional developments in the field of nanomaterials engineering enhanced the level of precision with regard to targeting using ligand-mediated interactions and smart carrier structures<sup>4</sup>. All these developments have collectively brought about a paradigm shift of passive drug delivery towards adaptive biologically informed technologies.

With the advancement in technology, an improved technological development of drug delivery systems is heavily dependent on biochemical interactions at the nano- bio interface. When delivered, proteins, enzymes, immune elements and cell membranes interact with the delivery carriers, all of which regulate the circulation time, biodistribution, and therapeutic activity. Therapeutic activity of nanoparticles, e.g. depend greatly on the route of administration and the biochemical environment around it, which implies the significance of the compatibility of nanoparticles with system-biological systems.<sup>5</sup> Other than the biochemicals, the microbial environments are a very important but old, underestimated determinant of the drug delivery performance. Biomimetic and immune cell-based delivery methods, including neutrophil-based systems, have already proved to be able to navigate through an inflammatory and infectious microenvironment successfully.<sup>6</sup> Likewise, nano-drug delivery strategies have been considered in the case of cardiovascular and systemic diseases, in which biochemical signalling pathways and inflammatory mediators have a strong impact on carrier behaviour.<sup>7</sup> Interactions between microbes are of particular importance when using oral and infection-targeted drug delivery. Delivery systems necessary to protect drugs against enzymatic degradation and interaction with resident microbiota effectively during oral administration of antimicrobial peptides and other labile therapeutics.<sup>8</sup> Nanocarriers used as tumour targeting systems in the field of oncology should also consider the effects of microbial regulation of drug metabolism and immune activity.<sup>9</sup> Moreover, biofilms of microbes present serious resistance to the diffusion of drugs, and to overcome biofilm shells, nanotechnology-based methods are required to be designed to specifically interfere with or avert biofilm shells.<sup>10</sup> Cases involving biochemical and microbial approaches into the design of delivery systems are therefore crucial to enhance reliability, safety and therapeutic outcomes.

The growing sophistication of technologies used to deliver drugs highlights the necessity to conduct

thorough analyses that can connect the science of formulations to the biological reality. Although many studies have been done on the individual delivery systems, there is a lack of consolidated knowledge concerning the performance of a delivery system influenced by biochemical and microbial interactions. The problems that are currently being faced, such as stability, scalability, and the barrier of translating research findings, are highlighted by recent reviews and support the role of biologically informed design strategies.<sup>11</sup> This review will critically analyze the advanced drug delivery systems in the light of biochemical and microbial interactions, which are concerned with their implications for therapeutic efficacy. These include nanoparticle-based, polymeric and biomimetic delivery platforms, where protein interactions, enzyme activity, immune response, and microbial environment have an impact on drug release, targeting and safety. Particular focus is made on the surface engineering techniques, e.g., stealth, which improves systemic circulation and undesirable biological recognition.<sup>12</sup>

Through integration of information in these fields, the review aims at giving practical information on how the next-generation drug delivery technologies can be rationally designed to suit the current pharmaceutical and clinical needs.

## **2. Biochemical Determinants Influencing Drug Delivery System Performance**

### **2.1 Protein Interactions and Biomolecular Corona Formation**

At the contact of the drug delivery carriers with biological fluids, it is immediately subjected to adsorption of plasma proteins leading to the appearance of a biomolecular corona, which changes the identity of the carriers. Fenton et al.<sup>13</sup> pointed out that this corona controls both cellular uptakes, biodistribution and clearance pathways, and typically overrides material properties inherent to a material. The protein composition varies depending on the surface chemistry and particle size with respect to targeting accuracy and therapeutic reliability. Rational biomaterial design methods are an attempt to control the formation of corona to attain predictable in vivo performance.

### **2.2 Enzyme-Mediated Drug Release and Carrier Degradation**

Behavioural control in drug release and carrier degradation of active materials in physiological conditions is critically regulated by enzyme activity. Garg et al.<sup>14</sup> stated that the nanoparticles made of chitosan could be structurally modified by the action of enzymes and could be localized and released in a sustained manner. This enzymatic responsiveness can be used to deliver a particular enzyme with minimal systemic exposure. But the variation in release kinetics as a result of the differences between tissue-to-tissue enzyme expression clarifies why optimization of polymers and crosslinking control of polymers will be essential to ensuring uniform therapeutic results, in more advanced delivery systems.

### 2.3 Redox-, pH-, and Stimuli-Responsive Biochemical Triggers

Exploitable triggers to smart drug delivery systems include biochemical gradients (such as pH differences and redox potential differences). Gimenez-Bastida et al.<sup>15</sup>, showed that these stimuli-responsive platforms are able to increase selective drug release in pathological conditions, but are able to remain stable in normal physiological conditions. Simultaneously, microbial metabolite biochemical modulation has an impact on drug efficacy and drug toxicity, as evidenced by Hajialyani et al.<sup>16</sup>, which underscores the necessity to consider biochemical responsiveness in the design of drug deliveries.

### 2.4 Immune System Interactions Affecting Carrier Stability and Circulation

Circulation time and stability of drug delivery systems depend on the immune system, as it is either decisive. Homayun et al.<sup>17</sup> explained that immune recognition has the capacity to restrain therapeutic functionality by promptly eliminating or triggering inflammatory responses, especially in wound and tissue repair therapy. State-of-the-art micro- and nanoscale delivery vehicles used in systemic and cardiovascular use, e.g. the examples of Iravani and Varma [18], use immune-modulating techniques to extend circulation and site-specific drug targeting (Figure 1).

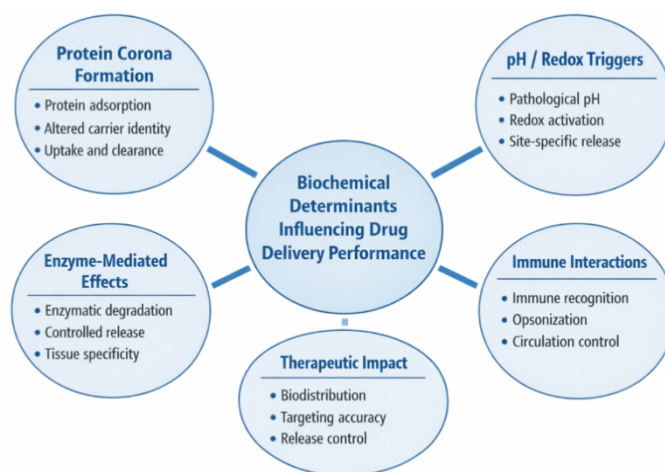


Figure 1. Key biochemical factors governing advanced drug delivery performance

## 3. Microbial Interfaces in Drug Delivery Systems

### 3.1 Microbial Biofilms and Barriers to Drug Penetration

Microbial biofilm develops thick extracellular polymeric scaffolds, which greatly restrict drug diffusivity and therapeutic efficacy. Jahangirian et al.<sup>19</sup> have stated that nanotechnology-based delivery systems, especially those prepared with the concept of green chemistry, increase permeability into biofilm structures by increasing the reactivation of the surface and a long-term release characteristic. The growing macromolecular complexity of delivery platforms further facilitates contact with heterogeneous microbial environments and facilitates transport across biofilm barriers, and enhances more effective antimicrobial drug delivery strategies.<sup>20</sup>

### 3.2 Gut Microbiota and Its Influence on Drug Delivery and Bioavailability

The gut microbiota is known to play a central role in regulating drug absorption and metabolism and bioavailability after oral delivery. The ability to respond to biochemical indicators of microbiota has resulted in stimuli-responsive delivery systems which have been utilized to enhance delivery specificity. Li et al.<sup>21</sup> revealed that supramolecular nanovalve-based systems could have localized biochemical release due to

controlled release, and such systems could be used to enhance stability and bioavailability in complex gastrointestinal settings affected by the presence of microglia.

### 3.3 Microbe-Responsive and Infection-Targeted Drug Delivery Platforms

Infection-based delivery systems use microbial presence and infection related biochemical as a method to localized therapeutic action. Bacteria-based delivery systems that have been engineered through both chemical and biological means have proven to be capable of accomplishing this with great specificity, being able to accumulate at disease foci and deliver therapeutic payloads with a high degree of specificity, as discussed by Li et al.<sup>22</sup> Liposomal delivery technologies are additional complementary methods to such strategies because they allow the encapsulation of antimicrobial agents and allow the localization of drugs in the infected tissues by optimally designed carriers.<sup>23</sup>

### 3.4 Bacteria-Based and Microbial Vector-Assisted Delivery Systems

A new approach to precision therapeutics is bacteria-based and microbial vectors-assisted delivery systems, especially in wound and infection therapy (Table 1). Liu et al.<sup>24</sup> reported the use of functional chitosan-based

hydrogels that can provide sustained antimicrobial effect as well as drug release, and were demonstrated to have potential in the wound healing process. Also, liposomal drug delivery systems that have been clinically approved

still have translational benefits because of the well-defined regulatory routes and high efficacy in therapeutic uses related to infection.<sup>25</sup>

**Table 1.** Microbial interfaces influencing drug delivery system performance

Microbial interface	Key barrier or mechanism	Drug delivery strategy	Representative reference
Microbial biofilms	Dense extracellular polymeric matrix limiting drug penetration	Nanotechnology-driven systems with enhanced surface reactivity and sustained release	Jahangirian et al. <sup>19</sup> ; Kakkar et al. <sup>20</sup>
Gut microbiota	Microbial metabolism affecting drug stability and bioavailability	Stimuli-responsive systems enabling microbiota-triggered controlled release	Li et al. <sup>21</sup>
Infection microenvironment	Infection-associated biochemical signals enabling site-specific targeting	Engineered bacteria-based and infection-responsive delivery platforms	Li et al. <sup>22</sup>
Wound- and infection-associated microbes	Localized microbial burden and inflammation	Chitosan-based hydrogels and clinically approved liposomal systems for localized delivery	Liu et al. <sup>24</sup> ; Liu et al. <sup>25</sup>

#### 4. Advanced Drug Delivery Platforms Modulated by Biochemical and Microbial Factors

##### 4.1 Nanoparticle-Based Drug Delivery Systems

Drug delivery systems through nanoparticles offer adaptable platforms of controlled and targeted delivery of therapies. The biochemical and microbial environments can be interacted with using smart nanoparticles engineered with tunable size, surface chemistry and responsiveness. As Lombardo et al.<sup>26</sup> stressed, these nanocarriers have a higher flexibility to biological conditions, enhancing stability of drugs and targeting efficacy. The systems interfere with the regulation of release-behavioural changes in response to physiological cues, to enhance better therapeutic performance in various disease conditions.

##### 4.2 Polymeric and Hydrogel-Based Controlled Release Systems

Hydrogel and polymeric delivery systems can provide sustained and localized drug delivery via biodegradable and biocompatible delivery systems. Platforms made of polysaccharide allow the release kinetics to be controlled with high accuracy, and in addition, polysaccharides have the ability to be used together with biological tissues. Miao et al.<sup>27</sup> has shown that these systems successfully combine biochemical responsiveness and structural stability, which are useful in tissue engineering and drug delivery. Such materials are useful in solving the biological barriers and are also available over a long therapeutic period.

##### 4.3 Liposomal and Vesicular Drug Delivery Technologies

Liposomal and vesicular carriers are considered to be one of the most clinical established drug delivery technology. Nano-based vesicular systems have the advantage of improving the delivery of drugs to tumor

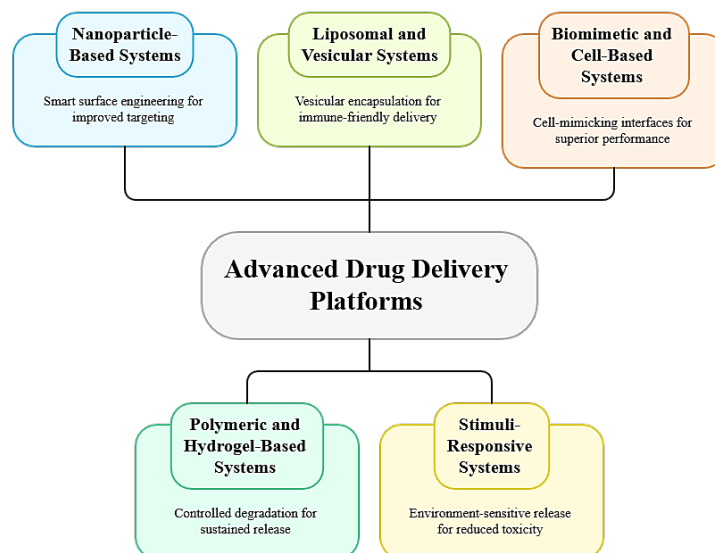
microenvironment and immune regulation in cancer therapy. Mu et al.<sup>28</sup> stated that these delivery platforms enhance the work of chemioimmunotherapy with its controlled release of drugs and targeted delivery. They can carry both hydrophilic and hydrophobic agents within them and this adds to their importance in the biochemical complex therapeutic settings.

##### 4.4 Smart and Stimuli-Responsive Drug Delivery Systems

Smart drug delivery systems can provide responses to biochemical and microbial stimuli including pH, enzymes or ionic variations in a dynamic manner. Such natural polymers as carrageenan have been studied due to their responsiveness and biomedical compatibility. As stressed by Pacheco-Quito et al.<sup>29</sup>, these materials allow the release of drugs in a specific site and also preserve structure integrity despite the physiological conditions. The platforms that are responsive to stimuli thus improve the precision of the therapy and minimize the off-target effects in complex biological environments.

##### 4.5 Cell- and Biomimetic-Based Drug Delivery Approaches

Biological components make cell-based and biomimetic drug delivery methods advantageous in targeting and immune compatibility (Figure 2). Taking the example of nanoparticles that deliver antimicrobials, Patel et al. describe the art of surface mimicry in order to improve the contact with a microbial environment<sup>30</sup>. More comprehensive nano-based systems of delivery, described by Patra et al.<sup>31</sup>, also facilitate the principles of biomimetic strategies based on the rational design, and the ideas of the delivery system frameworks, which Poon et al.<sup>32</sup> presented, enhance biological performance and translational toughness.



**Figure 2.** Overview of Advanced Drug Delivery Platforms

**5. Implications for Therapeutic Efficacy and Clinical Performance**

**5.1 Impact on Drug Stability, Targeting Accuracy, and Controlled Release**

The use of advanced drug delivery systems have a great impact on the stability of drugs, their delivery targeting, and the control of their release with physiological conditions. As illustrated by Saravanakumar et al.<sup>33</sup>, by employing reactive oxygen species-responsive platforms, the delivery of drugs can selectively be released in diseased tissues without the system becoming labile. This kind of biochemical responsiveness enhances spatial and temporal regulation of drug delivery at the expense of off-target effects. The increased accuracy of targeting via stimulus sensitive carriers is a direct result of the increased pharmacological performance and reliable therapeutic functionality.

**5.2 Drug Delivery Strategies for Infectious and Biofilm-Associated Diseases**

The strategies of drug delivery to infectious and biofilm-associated diseases need to have systems that can overcome microbial barriers. Microbe-based delivery systems build on the biological recognition pathways to increase the localization of the drug and penetration to the site of infection. According to Shende and Basarkar<sup>34</sup>, the systems enhance the effect of antimicrobials by allowing them to be delivered and released in a localized fashion inside the microbial environment. These methods overcome the shortcomings of the traditional antibiotics and provide

the future solutions to the problems of resistant and chronic infections.

**5.3 Enhancement of Therapeutic Outcomes in Cancer Therapy**

Advanced delivery systems are used in cancer treatment to enhance tumor targeting and immune responses, thus enhancing better therapeutic results. The polymeric drug delivery systems offer the benefit of controlled release and long circulation in favor of anticancer persistence. As pointed out by Sung and Kim<sup>35</sup>, the new polymeric carriers enhance the concentration of drugs in tumor tissues and decrease the toxicity of the systems. These innovations enable combination therapies and enhance treatment responsiveness which support the clinical usefulness of delivery technologies in cancer treatments.

**5.4 Role in Wound Healing, Cardiovascular, and Systemic Therapies**

The use of advanced drug delivery technologies in wound healing, cardiovascular care, and systemic therapies is increasingly important to provide a chance of localized and sustained drug delivery. Controlled release systems enhance tissue regeneration, minimise inflammation and increase therapeutic retention at the target sites (Table 2). Delivery systems that enhance the results of treatment are based on prolonged circulatory and biological compatibility in cardiovascular and systemic conditions. These uses demonstrate the general clinical applicability of delivery technologies to non-disease-specific intervention.

**Table 2.** Therapeutic and clinical implications of advanced drug delivery systems

Clinical aspect	Key technological impact	Therapeutic implication	Representative reference
Drug stability and controlled release	Stimuli-responsive and ROS-sensitive delivery platforms	Improved release precision, reduced off-target effects, enhanced efficacy	Saravanakumar et al. <sup>33</sup>
Infectious and biofilm-associated diseases	Microbe-based and targeted delivery strategies	Enhanced antimicrobial penetration and sustained local drug action	Shende & Basarkar <sup>34</sup>

Cancer therapy	Polymeric and targeted delivery systems	Increased tumor accumulation, reduced systemic toxicity, improved outcomes	Sung & Kim <sup>35</sup>
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## 6. Formulation Challenges and Technological Limitations

### 6.1 Stability, Scalability, and Manufacturing Constraints

Advanced drug delivery systems can be associated with stability of the formulation and large-scale drug production. Such complex systems as enzyme-based and cell-based delivery systems demand a precise control over material properties and biological operation during manufacturing. As pointed out by Tang et al.<sup>36</sup>, the strength of biohybrid delivery systems to withstand storage and scale-up is one of the major limitations. The barrier to the clinical translation of highly sophisticated delivery technologies remain reproducibility, batch consistency and affordable manufacturing.

### 6.2 Safety, Toxicity, and Immunogenicity Considerations

In the development of the advanced drug delivery systems, safety and immunogenicity are still of concern. Specific nanomedicine platforms can cause unintended immune response or chronic toxicity as a result of the accumulation of materials. As noted by Tewabe et al.<sup>37</sup>,

despite the improved accuracy of therapy in terms of precision, biocompatibility, degradable products, and immune response should be thoroughly considered. In depth toxicity profiling and long term safety testing are thus essential elements of development of the delivery system.

### 6.3 Regulatory and Translational Challenges in Drug Delivery Technologies

The complexity of characterization requirements and inadequate standard assessment systems have a tendency to obstruct regulatory approval and clinical translation of advanced drug delivery systems. The differences in design of the formulation, composition of the materials and the interaction it has with the body make it hard to assess regulations (Figure 3). To address the gap between laboratory innovation and clinical use, it is necessary to balance every guideline, quality control plan, and integrate regulatory issues into the process of developing a formulation. These issues are critical in speeding up the process of successful delivery technology translation.

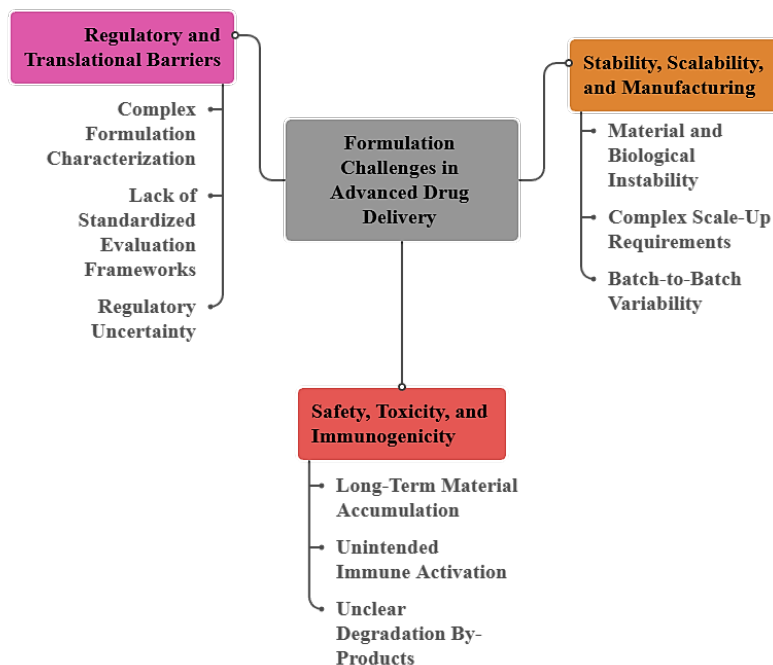


Figure 3. Formulation Challenges in Advanced Drug Delivery Systems

## 7. Emerging Trends and Future Directions in Drug Delivery Technology

### 7.1 Microbiome-Aware Drug Delivery Design

Microbiome based drug delivery design is a recent concept in the pharmaceuticals field, where the microbiota is identified as a decisive factor in therapeutic efficacy. Vargason et al.<sup>38</sup> emphasised that there is a growing trend of commercial drug delivery technologies becoming biologically informed to consider host-microbe

interactions. The introduction of microbiome-sensitive materials and release mechanisms allows enhancement of predictability of drug stability, metabolism, and bioavailability. This way of doing things helps in delivering oral and infection-focused delivery behaviors, and in this way, next-generation systems may be developed so that drug release behavior is coupled to dynamic microbial conditions.

### 7.2 Personalized and Precision Drug Delivery Systems

Individualized and accurate drug delivery system is meant to be able to customize the therapeutic interventions based on the patient-specific biological and pathological states. The progress in micro and nanoscale engineering has provided the delivery platforms which can adjust to heterogeneous disease conditions. Wang and Liao<sup>39</sup> showed that the microrobotic delivery systems provide the accurate navigation and focused drug delivery in tumor tissue, thereby increasing the accuracy of treatment. These technologies aid in personalized dosing, enhanced targeting resolution, and minimized systemic toxicity, and the precision delivery technologies represent a major trend in cancer therapy and complicated illness management in the future.

### 7.3 Integration of Smart Materials and Bio-Responsive Technologies

Design of drug delivery systems are changing due to the integration of smart materials and bio-responsive technologies. Nano-based agents that can react to biochemical and microbial cues can be used to provide regulated and targeted therapeutic delivery. The importance of responsive nanocarriers in wound care and in tissue regeneration was highlighted by Wang et al.<sup>40</sup>, whereas Yeh et al.<sup>41</sup> discussed the progress of nano-targeting techniques to eliminate bacteria to prevent infections. Yusuf et al.<sup>42</sup> also revealed that the biological responses and the delivery efficiency of nanoparticles are highly tuned by their physicochemical properties to enhance the logic of designing adaptive platforms (Table 3).

**Table 3.** Emerging trends and future directions in drug delivery technology

Emerging trend	Technological focus	Expected impact on drug delivery	Representative reference
Microbiome-aware delivery design	Biologically informed materials and microbiota-sensitive release mechanisms	Improved predictability of drug stability, metabolism, and bioavailability	Vargason et al. <sup>38</sup>
Personalized and precision delivery systems	Microrobotic and adaptive micro/nanoscale platforms	Enhanced targeting accuracy, individualized dosing, reduced systemic toxicity	Wang & Liao <sup>39</sup>
Smart and bio-responsive materials	Stimuli-responsive nanocarriers reacting to biochemical and microbial cues	Site-specific release, improved infection control, enhanced tissue regeneration	Wang et al. <sup>40</sup>
Advanced antimicrobial targeting	Nano-based systems designed to eradicate pathogenic bacteria	Improved infection mitigation and reduced antimicrobial resistance risk	Yeh et al. <sup>41</sup>
Physicochemical optimization of nanoparticles	Fine-tuning size, charge, and surface properties	Enhanced biological compatibility and delivery efficiency	Yusuf et al. <sup>42</sup>

### 8. Conclusion

The review presents the importance of biochemical and microbial interactions in the functionality, dependability, and clinical achievement of advanced drug delivery systems. Important discoveries show that the various forms of drug delivery have moved away with the traditional dosage delivery to highly engineered platforms that can respond to multifaceted biological conditions. The carrier stability, targeting specificity, and controlled release characteristics are all dependent on protein adsorption, enzymatic retention, immune recognition and the biochemical stimuli like pH and redox gradients. Of equal importance, microbial conditions, such as biofilms, gut microbiota, and microenvironments related to infections, prove to be the crucial determinants of drug bioavailability and therapeutic efficacy. More sophisticated delivery vehicles like nanoparticles, polymeric and hydrogel-based delivery systems, liposomes, and biomimetic carriers have a high degree of flexibility in their development in consideration of biological contexts. The combination of biologically inspired and stimuli-responsive materials enhance site-specific delivery, reduce off-target effects, and provides extended

therapeutic effect in the same way that it is used in cancer, infectious diseases, wound healing, cardiovascular, and systemic therapies. Nevertheless, scalability, regulatory complexity, immunogenicity, and formulation stability are issues that pose a major challenge to translation. In general, the results highlight the fact that further development of drug delivery technology is based on the alignment of material design with biochemical and microbial reality. Smart bio-responsive products, microbiome conscious, precision-based are the ways to go in future therapeutic applications. Integrating biological intelligence into delivery design, high-tech drug delivery technologies may attain a better clinical performance, patient outcome, and increased translatability in contemporary pharmaceuticals.

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