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EMERGING TRENDS IN BIOMARKER-GUIDED DRUG DELIVERY FOR IMPROVED ORAL BIOAVAILABILITY

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ABSTRACT

Biomarker-based medication delivery is a novel method to precision medicine that targets therapy using biological indicators to optimize dose and timing. This technology provides tailored therapies by leveraging physiological or molecular signatures, which improves efficacy and safety. Although oral drug delivery is recommended for compliance, variables such as poor solubility and enzymatic degradation reduce bioavailability, resulting in varying effects. Biomarker guidance helps to address these challenges by targeted release and real-time dose changes. Recent breakthroughs include pH-sensitive formulations and responsive nanocarriers, which show promise in oncology and metabolic illnesses. However, greater clinical applications necessitate biomarker validation, scalable manufacturing, and regulatory alignment. Future integration with technology such as artificial intelligence and wearable sensors could further customize and improve oral medicines.

KEYWORDS: Bio-marker, Drug delivery, Oral Solubility, Targeted drug delivery, Exosomes.

INTRODUCTION

Drug delivery systems have changed over the past 20 years from generic formulations to precision medicine that is customized to meet the needs of specific patients. Stability and convenience are given priority in current formulations, however patient response variability is not taken into account. Because of this progress, delivery systems that target particular tissues and adjust to changing disease states have been developed. These systems make extensive use of biomarkers for patient stratification and real-time monitoring of therapeutic effects. These advancements seek to minimize side effects while maximizing therapeutic efficacy. Oral administration is the most popular approach since it is simple and easy to follow, but its efficacy is hampered by issues such poor permeability, low solubility, and gastrointestinal instability. These elements lead to uneven bioavailability and call for creative formulation techniques to improve therapeutic stability and medication delivery.[1,2] A major development in personalized medicine that improves therapeutic efficacy is the incorporation of biomarkers into oral medication delivery. By connecting biomarkers with pharmacokinetic events, formulation scientists can fine-tune medication exposure by gaining insights into individual heterogeneity in drug kinetics. Pharmacodynamics biomarkers also help with treatment monitoring and dose modifications to preserve the best possible drug efficacy and safety. By maximizing bioavailability, minimizing side effects, and enhancing treatment outcomes, this novel technique makes it possible to build responsive drug delivery systems that adjust according to a patient's biological profile.[3,4] By combining biomarker-directed methods with oral bioavailability augmentation, a new paradigm is developing at the nexus of personalized medicine, formulation science, and therapeutic optimization. Conventional approaches frequently ignore individual differences in drug disposition caused by physiological and genetic factors. A foundation for customized oral delivery that can adjust to a person's biological profile is provided by biomarker-guided technologies, which address issues including high first-pass metabolism and poor solubility. This review highlights existing release methods, explores regulatory constraints in the shift to tailored drug delivery systems, and expounds on biomarker detection and its application in overcoming oral drug delivery obstacles. It highlights the importance of different biomarkers, such as transporters and inflammatory indicators, in creating responsive and tailored drug delivery vehicles, combining formulation design and biomarker science to promote oral therapies in precision medicine.[5-7]

BASICS OF BIOMARKERS IN DRUG DELIVERY

Classification of Biomarkers

In medication research, therapeutic monitoring, and individualized treatment regimens, biomarkers function as objective indicators. Pharmacokinetic, pharmacodynamic, predictive, and safety biomarkers are the four primary groups that are pertinent to drug delivery. Pharmacokinetic biomarkers, such as transporter levels and metabolite profiles, predict systemic exposure by providing information on drug absorption, distribution, metabolism, and excretion. Pharmacodynamic biomarkers enable real-time therapy optimization by evaluating the biological effects of medications. While safety biomarkers forecast possible toxicity or negative consequences, predictive biomarkers identify people who are likely to benefit from particular treatments. Biomarkers can be used in dynamic system engineering to enable regulated and targeted drug delivery in response to physiological changes. Precision treatments are made easier by this integration, especially in oral medication delivery, where efficacy is impacted by individual variability. Developing next-generation drug delivery platforms requires an understanding of biomarker classifications and detection techniques. The main biomarker classes relevant to biomarker-guided oral drug delivery systems are depicted in a schematic, emphasizing their functions in pharmacological response, patient stratification, safety assessments, and absorption monitoring.[8,9]

Analytical and Detection Methods

For drug delivery systems to be effective, biomarkers must be accurately detected and quantified. For low-abundance biomarkers, advanced analytical technologies offer great sensitivity and specificity, especially mass spectrometry-based devices like LC-MS/MS. While genomic technologies like NGS and PCR aid in the profiling of drug transporters and the identification of genetic polymorphisms, immunoassays like ELISAs are preferred for protein detection. Real-time biomarker monitoring is made possible by innovative biosensors, and imaging technologies like PET and MRI monitor drug distribution and molecular fingerprints. In preclinical and clinical stages, incorporating these platforms into drug release systems improves patient stratification, therapy optimization, and formulation evaluation.[10,11]

Biomarkers in Oral Drug Disposition

Physiological and molecular biomarkers associated with absorption, metabolism, and excretion have an impact on oral medication disposition. Predictive biomarkers for oral

exposure and sensitivity can be derived from variations in transporter expression caused by genetic factors or medication interactions. Sahoo et al.'s study examined transporter gene polymorphisms in 120 chemotherapy-treated oral cancer patients and found certain variants linked to side effects such nausea and anemia but not to progression-free survival.[12] According to the results, these genetic variations could be helpful in predicting toxicity when managing oral chemotherapy. First-pass metabolism and systemic drug concentration depend heavily on enzyme activity biomarkers, especially cytochrome P450 isoforms (CYP3A4, CYP2C9) and phase II enzymes such UDP-glucuronosyltransferases (UGTs). In 3D-cultured human renal proximal tubule epithelial cells, Hashiba et al. examined these enzymes and discovered higher expression of several CYP and UGT isoforms in comparison to 2D cultures, indicating the kidney's important metabolic role.[13] Drug release mechanisms can be influenced by physiological indicators, such as gut microbiota and gastrointestinal pH, as well as disease-specific biomarkers associated with inflammation. Jiang et al.'s recent research emphasizes the potential of NEDD4-binding protein 3 as a biomarker for drug delivery systems by highlighting its regulatory function in inflammatory reactions.[14] The significance of transcriptional networks in drug disposal is further highlighted by Li et al.'s review. The goal of incorporating these biomarkers into delivery system design is to improve therapeutic efficacy and decrease interpatient variability.[15]

ORAL BIOAVAILABILITY CHALLENGES

The percentage of an oral dose that enters the systemic circulation in an active form is known as oral bioavailability. It can be hampered by a number of physicochemical, physiological, and biochemical aspects, especially for BCS Class II and IV compounds, which frequently have problems such low aqueous solubility that limits absorption and dissolution. Low membrane permeability can prevent drugs from passing through the intestinal epithelium even when they are sufficiently soluble. Additionally, the amount of intact medication accessible for absorption may be decreased by the stomach's acidic environment and enzymatic activity. Additionally, medications go through significant first-pass metabolism, which further reduces the active ingredient through efflux transporters and metabolic enzymes that return pharmaceuticals to the intestinal lumen. Furthermore, variability among patients due to genetic variables, nutrition, gut flora, age, and health condition add to the uncertainty in oral drug exposure.[16]

Multifactorial barriers demand improved formulation strategies, including biomarker-guided design, to improve absorption and therapeutic results. Akhilesh et al. created a cationic liposome nanoformulation with siRNA targeting the TRPA1 receptor to treat chemotherapy-induced peripheral neuropathy (CINP), which causes TRPA1 overexpression and neuroinflammation.[17] This liposomal delivery approach allows siRNA to circumvent barriers that limit its efficiency. The results showed that the intravenous (IV) route had the best silencing effect and anti-inflammatory effects, enabling for the regulation of TRPA1 and inflammatory markers such as IL-6 and ICAM-1 to address the disease's complexities.

Table 1: Few biomarkers and there area of use.

Biomarker	Associated Barrier	Type	Key Findings	Reference
OCTN1 (Ergothioneine)	Tissue distribution barrier	Transporter Biomarker	Altered AUC, clearance, and tissue partitioning	[18]
OCT2 (Creatinine)	Renal elimination variability	Transporter Biomarker	Reduced renal clearance following modulation	[19]
OATP1B1 (Coproporphyrin I)	Hepatic uptake limitation; DDI risk	Transporter Biomarker	CP-I correlates with OATP1B1 inhibition and DDI magnitude	[20]
Glucose	Hyperglycemic microenvironment	Metabolite Biomarker	Controlled insulin release; prolonged glucose control	[21]
Colonic pH (≈7.5)	Gastric degradation	pH Biomarker	Gastric protection; colonic-specific release	[22]
UGT isoforms	Phase II metabolism variability	Metabolic Enzyme Biomarker	Enhanced expression in physiologically relevant model	[13]
Gut dysbiosis profile (e.g., Bacteroides spp.)	Microbiota-mediated metabolism	Microbiome Biomarker	Restored microbial balance; targeted colonic delivery	[22]

BIOMARKER-GUIDED DRUG DELIVERY SYSTEMS

Individual biological indicators are used by biomarker-guided drug delivery systems to precisely regulate drug release, improving therapeutic outcomes and reducing off-target effects. Predictive biomarkers that strike a compromise between safety and efficacy are essential because of safety concerns about unintentional biological activations, especially in immune checkpoint inhibitor therapy.[23] To ensure successful translation, adaptive drug

delivery systems must include safety feedback mechanisms and known biomarker responses. These systems provide targeted medication release depending on the circumstances at the disease or drug action site by reacting to endogenous indicators, such as pH variations or enzyme activity. To enable targeted medication release, enzyme-responsive systems make use of overexpressed proteases or glycosidases in sick tissues.[24] Drugs can be released by metabolite-responsive carriers, such those created by Fruehauf et al., in reaction to particular metabolites like lactate or glucose. When linked to lactate dehydrogenase (LDH), their study with N-isopropylacrylamide (NIPAM) nanoparticles conjugated to an oxamate derivative shown up to 65% ballooning in response to lactic acid in hypoxic tumor settings. This method shows how protein conjugation can improve bioavailability and therapeutic targeting by increasing nanoparticle sensitivity to disease-specific metabolites.[25]

Aptamers, antibodies, and molecular switches are examples of biomarker recognition elements that improve specificity and responsiveness in therapeutic applications. Using fluorocarbon-modified chitosan (FCS) as a carrier, Zhu et al. devised an oral delivery approach for therapeutic antibodies that produced nanoparticles that were lyophilized with excipients for improved distribution.[26] By reordering tight junction proteins, FCS facilitates protein transport and efficient absorption. Oral administration of αPD1, either with or without αCTLA4, reduced unfavorable immunological responses while producing therapeutic outcomes comparable to intravenous techniques. The results establish FCS as a revolutionary instrument for oral protein treatments. By controlling release kinetics through mechanisms including solubility changes and degradation, these systems show significant promise for enhancing oral bioavailability through controlled release and individualized treatment.[27]

Types of Biomarker-Responsive Drug Delivery Systems

Innovative platforms known as biomarker-guided drug delivery systems release medications in response to particular biological cues. Notable examples include core-shell nanoparticles that may efficiently distribute insulin in a glucose-dependent way while maintaining biocompatibility, and pH-gated systems that use pH changes to release pharmaceuticals. Furthermore, metabolite-sensitive platforms react to metabolites to control insulin release, improving bioavailability for diabetes patients, while enzyme-responsive systems administer medications in reaction to increased enzyme levels in medical situations. Furthermore, hybrid systems incorporate several triggers for better selectivity and adaptable drug delivery, particularly in oral therapies, whereas protein/antibody-responsive systems use molecular

recognition to release drug cargo. All things considered, these developments demonstrate how responsive systems might improve therapeutic efficacy.[28,29]

Table 2: Types of Biomarker-Responsive Drug Delivery Systems.

Type	Biomarker	Mechanism	Delivery System
Enzyme-responsive	Disease-associated enzymes (proteases, phospholipases, glycosidases)	Enzyme-cleavable linkers or substrates degrade matrix	Enzyme-sensitive polymeric carriers
Protein/antibody-responsive	Disease-related proteins or biomarkers	Molecular recognition	Aptamer- or antibody-functionalized carriers
pH-responsive	pH changes	Swelling or hydrolysis	Core–shell nanoparticles with mesoporous silica and polymer shells
Metabolite-responsive	Metabolites (e.g., glucose, lactate)	Metabolite-induced swelling or structural changes	Glucose-sensitive CPL hydrogel
Hybrid multi-responsive	Combination of pH, enzymes, metabolites, or proteins	Swelling, Degradation, Molecular Switching	Multi-stimuli responsive nanocarriers

Formulation Approaches

Biomarker-directed oral drug delivery systems use materials science, nanotechnology, and molecular engineering to provide tailored and responsive drug release. Polymeric nanoparticles, liposomes, micelles, and solid lipid nanoparticles are important nanocarriers because of their adaptive qualities. Aptamers and antibodies, for example, allow for selective targeting and release in response to biomarker signals. Stimulus-responsive polymers, which react to enzymes or pH changes, improve medication release in the gastrointestinal tract. Innovative techniques, such as molecular switches, enable gradual release in response to biomarker identification. Additionally, mucoadhesive characteristics enhance medication retention at target areas. Real-time monitoring advances, such as wearable devices, enable dynamic dosage adjustment based on continuous biomarker measurements. Early investigations demonstrate that this strategy has potential in personalized medicine, with increases in safety and precision for therapeutic modifications, resolving oral bioavailability problems via adaptive delivery systems.[30,31]

CURRENT APPLICATIONS AND CASE STUDIES

Glucose-responsive insulin release systems for diabetes are an example of how biomarker-regulated oral medication delivery systems have great potential in customized treatment.

These systems target insulin delivery based on blood glucose levels, including a new one created by Yu et al. Fc receptor-targeted liposomes with a glucose-responsive hyaluronic acid shell make up the system. When intestinal glucose levels rise, the liposomes release insulin by exposing Fc groups for improved uptake via FcRn-mediated transport.[32] This breakthrough offers a viable method for managing diabetes since it successfully controls postprandial blood glucose in type 1 diabetic mice and is the first oral insulin delivery triggered by postprandial glucose indicators.

Chemotherapy can be delivered locally with less systemic damage when using pH- and enzyme-sensitive oral formulations that target the acidic tumor microenvironment. Palmer et al. recently used patient-derived xenografts (PDX) to assess tailored therapy based on biomarkers for advanced ovarian cancer. Three monotherapies and one combination were found to be successful for particular PDX subsets out of the 21 monotherapies and combination therapies they examined. Nearly 90% of PDXs, including those resistant to conventional treatments, responded to at least one biomarker-guided therapy, even when individual drugs were less successful than chemotherapy. The Cancer Genome Atlas data supported this finding, supporting precision therapy in ovarian cancer.[33]

Reactive oxygen species (ROS) and cytokine-responsive systems are examples of biomarker-responsive delivery systems that allow for localized drug delivery to improve efficacy while lowering side effects in inflammatory bowel disease. For the purpose of treating ulcerative colitis, Kumari et al. created a ROS-activatable nanogel that releases polymeric chloroquine (PCQ). The nanogels (180–680 nm; +13 to +24 mV) target inflammatory colonic tissue specifically, breakdown in ROS-rich conditions, and remain stable in gastrointestinal fluids. They performed better than hydroxychloroquine in mice models for immune suppression, epithelial repair, and histological cure.[34] Significant local immunomodulation was revealed by profiling, and T1 showed the best local activity, making biomarker-responsive nanogels a viable and secure treatment option for ulcerative colitis.

Enzymatic inhibitors have improved bioavailability when co-delivered employing metabolic biomarker signatures, especially in situations with high first-pass clearance. Aβ40, Aβ42, and sAPPβ were assessed by Kennedy et al. as pharmacodynamic biomarkers for BACE1 inhibition in Alzheimer's disease. Following both acute and chronic dosing across species, the BACE1 inhibitor Verubecestat dramatically decreased these indicators in a variety of bodily fluids, exhibiting a positive safety profile.[35] With encouraging preclinical and early clinical

data showing enhanced pharmacokinetics and therapeutic efficacy for orally delivered medicines, our findings underscore the significance of biomarker-guided techniques in improving dosing and advancing clinical advancements.

Table 3: Challenges, Knowledge Gaps, and Future Perspectives in Biomarker-Guided Oral Drug Delivery Systems.[36-40]

Category	Key Issues / Description	Implications	Future Perspectives / Solutions
Biomarker Identification & Qualification	Difficulty in identifying and validating clinically relevant biomarkers with reproducible predictive capacity	Limits reliability in predicting drug absorption, metabolism, and therapeutic outcomes	Advanced validation strategies; integration of multi-omics data; development of standardized biomarker qualification frameworks
Interpatient Variability & Biomarker Dynamics	High variability in biomarker expression among individuals and over time	Challenges in designing universal or adaptive drug delivery systems	Personalized medicine approaches; real-time biomarker monitoring; adaptive dosing systems
Patient Heterogeneity	Differences in genetic, physiological, and pathological conditions	Reduced effectiveness of one-size-fits-all therapeutic systems	Use of stratified medicine and predictive modeling to tailor therapies
Quantitative Systems Pharmacology (QSP) Limitations	Limited integration of multi-scale biological data and clinical validation	Incomplete prediction of drug response and immune interactions	Expansion of QSP models for dose optimization, responder identification, and minimizing adverse effects
Manufacturing Complexity	Difficulty in translating biomarker-responsive materials into scalable, cost-effective oral dosage forms	Hinders commercialization and widespread adoption	Development of scalable fabrication technologies; process standardization
Scalability & Reproducibility	Challenges in maintaining batch-to-batch consistency for complex systems	Regulatory and quality control issues	Implementation of robust quality-by-design (QbD) approaches; automation in manufacturing
Multifunctional Platform Integration	Complexity in integrating sensors, actuators, and drug components	Increased design and validation challenges	Modular design strategies; simplified integrated systems
Regulatory Challenges (cGMP & Combination Products)	Lack of clear guidelines for hybrid systems (drug + device + software)	Delays in approval and commercialization	Regulatory harmonization; development of specific guidelines for adaptive systems
Biocompatibility & Long-term Safety	Insufficient data on long-term safety of biomaterials and	Potential toxicity risks and translational barriers	Long-term clinical studies; development of safer, biodegradable materials

	nanocarriers		
Limited Clinical Translation	Majority of systems remain at preclinical stage	Gap between research and real-world application	Rigorous clinical validation; biomarker qualification studies
Biosensing Limitations	Limited real-time, multiplexed biomarker monitoring systems	Restricts feedback-controlled drug delivery	Development of wearable and implantable biosensors; multiplex biomarker panels
AI & Data Integration Challenges	Handling and interpretation of large biomarker datasets	Difficulty in accurate prediction and decision-making	Application of AI/ML for dose optimization, predictive modeling, and formulation design
Smart Delivery System Design	Limited sensitivity and specificity of current systems	Reduced precision in drug targeting and response	Advancements in synthetic biology and molecular engineering
Regulatory Harmonization	Lack of global approval pathways and post-marketing frameworks	Slows global adoption	Establishment of unified global regulatory standards and surveillance systems
Adaptive & Autonomous Systems Validation	Lack of validation protocols across diverse populations	Uncertainty in performance consistency	Development of standardized validation and performance assessment protocols
Digital Health Integration	Challenges in integrating wearable devices with therapeutic systems	Limits real-time adaptive therapy	Integration of digital health technologies with drug delivery platforms

CONCLUSIONS

One significant development in the field of precision oral medicine is biomarker-driven medication administration. This strategy addresses major oral bioavailability issues like low solubility, permeability barriers, enzymatic degradation, and first-pass clearance by combining novel formulation techniques with physiological and molecular markers. Reducing inter-subject variability, improving therapeutic efficacy, and avoiding negative side effects are all potential benefits of dynamically adjusting medication delivery in line with individualized biomarkers. In preclinical and clinical trials, recent advancements in biomarker-sensitive materials, nanocarriers, and biosensing technologies have shown promising efficacy for a number of disorders, including inflammatory diseases, diabetes, and cancer. However, resolving problems with biomarker validation, manufacturing process scalability, regulatory permissions, and guarantees of long-term safety are necessary for successful clinical adoption. The development of next-generation, context-responsive, and customized oral therapies is anticipated to be accelerated by the potential integration of artificial intelligence, multiplex biosensors, and sophisticated delivery systems. Biomarker-

driven oral medication administration has the potential to transform therapeutic approaches, making them more effective and customized to each patient's needs, as long as biomarker science and drug delivery technology continue to advance.

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