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Novel Insights on Gastrointestinal Drug Delivery of Phytoactive Drugs and Their Delivery System

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ABSTRACT:

A significant amount of progress has been made in the delivery of drugs to the gastrointestinal system in recent years, particularly gastrointestinal dispensing. A growing body of research has focused on the therapeutic potential of phytoactive drugs, which are derived from natural sources. This paper aims to provide a comprehensive review of novel insights into the gastrointestinal drug delivery of phytoactive drugs and to describe innovative delivery systems designed to enhance the effectiveness and bioavailability of these drugs. The review highlights the inherent challenges regarding stabilization, solubility, and permeability within the gastrointestinal tract that are inherent to phytoactive drugs. The article then discusses the latest developments in drug delivery technologies tailored specifically to phytoactive compounds. Several special delivery systems are discussed, including nanoparticles, liposomes, and microspheres. These systems are capable of overcoming limitations associated with conventional dosage forms. Moreover, the review also highlights the complex interactions between phytoactive drugs and the gastrointestinal environment with respect to their absorption, distribution, metabolism, and excretion. Several formulation strategies are discussed in detail in relation to modulating drug release kinetics and optimizing therapeutic outcomes. In order to design effective delivery systems, phytoactive drugs must be understood in terms of their physicochemical properties. The book discusses the relationship between biopharmaceutical factors and drug release and absorption, such as pH of gastrointestinal fluids and enzymatic environment.

INTRODUCTION

Gastrointestinal drug delivery has emerged as a pivotal area in pharmaceutical research, continually evolving to overcome the challenges associated with the effective administration of therapeutic compounds [1]. Within this landscape, the utilization of phytoactive drugs bioactive compounds derived from natural sources has garnered significant attention due to their diverse pharmacological properties and potential health benefits [2]. As the demand for alternative and complementary medicines grows, understanding and optimizing the delivery of phytoactive drugs become imperative for realizing their full therapeutic potential [3]. This paper aims to provide novel insights into the realm of gastrointestinal drug delivery, focusing specifically on the challenges and innovations associated with the delivery of phytoactive drugs 4. Phytoactive compounds, ranging from flavonoids and alkaloids to terpenoids, exhibit a wide array of biological activities, including anti-inflammatory, antioxidant, and anticancer effects [5]. However, their translation into effective therapies is often hindered by inherent limitations such as poor solubility, instability, and limited bioavailability [6].

The integration of innovative drug delivery systems has become a key strategy in addressing these challenges [7]. This review explores the recent advancements in delivery technologies tailored to enhance the bioavailability and therapeutic efficacy of phytoactive drugs within the gastrointestinal tract [8]. From nanoparticles and liposomes to microspheres, the paper delves into the diverse range of formulations designed to optimize drug release kinetics and improve overall pharmacokinetics [9]. Moreover, this exploration extends beyond formulation strategies, delving into the dynamic interactions between phytoactive drugs and the gastrointestinal environment [10]. Factors influencing drug absorption, distribution, metabolism, and excretion are scrutinized, offering a holistic understanding of the intricate interplay between phytoactive compounds and

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the physiological conditions of the gastrointestinal tract [11].

PHYTOACTIVE DRUGS: CHARACTERISTICS AND CHALLENGES

Phytoactive drugs refer to bioactive compounds derived from plants that exhibit pharmacological or therapeutic effects on the human body [12]. These compounds are naturally occurring and are often extracted from various parts of plants, such as leaves, stems, roots, fruits, or seeds [13]. Phytoactive drugs encompass a wide range of chemical classes, including alkaloids, flavonoids, terpenoids, glycosides, and others [14]. These plant-derived compounds have been traditionally used in herbal medicine and are increasingly gaining attention in contemporary pharmaceutical research due to their potential health benefits [15]. Phytoactive drugs can exert various physiological actions, such as anti-inflammatory, antioxidant, antimicrobial, anticancer, and other therapeutic effects [16]. Their diverse pharmacological properties make them valuable candidates for drug development and complementary or alternative medicine [17].

Table No. 1 Classification of Phytoactive Drugs with drug delivery system

Phytoactive Drug	Biological Name	Family	Chemical Constituents	Gastrointestinal Drug Delivery System	Pharmacological Properties	Ref
Curcumin	Curcuma longa	Zingiberaceae	Curcuminoids [Curcumin, Demethoxycurcumin]	Nanoemulsions, nanoparticles, liposomes	Anti-Inflammatory, Antioxidant, Gastroprotective	[18]
Gingerol	Zingiber officinale	Zingiberaceae	Gingerols, Shogaols	Microspheres, gastroretentive systems	Antiemetic, Anti-Inflammatory, Prokinetic	
Peppermint Oil	Mentha piperita	Lamiaceae	Menthol, Menthone	Enteric-coated capsules, emulsions	Antispasmodic, Gastroprotective, Carminative	[19]
Aloe Vera Extracts	Aloe barbadensis miller	Asphodelaceae	Aloin, Aloe Emodin, Acemannan	Gel-based formulations, oral solid dosage forms	Laxative, Gastroprotective, Anti-Inflammatory	[20]
Berberine	Berberis vulgaris	Berberidaceae	Berberine	Microencapsulation, nanocrystals	Antimicrobial, Anti-Inflammatory, Laxative	[21]
Licorice Root Extract	Glycyrrhiza glabra	Fabaceae	Glycyrrhizin, Liquiritin, Isoliquiritin	Solid lipid nanoparticles, tablets	Gastroprotective, Anti-Ulcer, Anti-Inflammatory	
Chamomile	Matricaria chamomilla	Asteraceae	Apigenin, Chamazulene, Matricin	Lipid-based formulations, herbal teas	Anti-Inflammatory, Antispasmodic, Carminative	
Senna Glycosides	Cassia angustifolia,	Fabaceae	Sennosides [Sennoside A, B]	Immediate-release tablets, controlled-release	Laxative, Prokinetic,	

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	Senna alexandrina				Anthraquinone action	
Green Tea Catechins	Camellia sinensis	Theaceae	Epicatechin, Epigallocatechin, Catechins	Polymeric nanoparticles, tea extracts	Antioxidant, Gastroprotective, Anti-Inflammatory	[22]
Ashwagandha	Withania somnifera	Solanaceae	Withanolides [Withaferin A, Withanone]	Liposomes, solid dispersions	Adaptogenic, Anti-Inflammatory, Gastroprotective	
Peppermint Tea	Mentha x piperita	Lamiaceae	Menthol, Mentone	Herbal tea infusions, enteric-coated capsules	Antispasmodic, Gastrointestinal Soothing	
Meadowsweet	Filipendula ulmaria	Rosaceae	Salicylates, Flavonoids, Tannins	Decoctions, extracts	Gastrointestinal Soothing, Anti-Inflammatory	[23]
Psyllium	Plantago ovata	Plantaginaceae	Psyllium Husk	Oral powders, capsules	Laxative, Bulking Agent, Gastroprotective	[24]
Fennel	Foeniculum vulgare	Apiaceae	Anethole, Fenchone	Oil-based formulations, gastroretentive systems	Prokinetic, Antispasmodic, Carminative	
Holy Basil	Ocimum sanctum	Lamiaceae	Eugenol, Ursolic Acid, Rosmarinic Acid	Microemulsions, lipid-based formulations	Adaptogenic, Gastroprotective, Anti-Inflammatory	
Marshmallow Root	Althaea officinalis	Malvaceae	Mucilage, Flavonoids, Polysaccharides	Aqueous extracts, mucilage-based formulations	Gastrointestinal Soothing, Demulcent	[25]

INNOVATIVE DRUG DELIVERY SYSTEMS FOR PHYTOACTIVE COMPOUNDS

Innovative drug delivery systems for phytoactive compounds play a pivotal role in addressing challenges such as poor solubility and bioavailability [26]. These systems aim to enhance the therapeutic efficacy and targeted delivery of phytoactive drugs [27]. Nanotechnology has emerged as a promising avenue, with the development of nanoparticles and nanocarriers allowing for improved solubility, controlled release, and increased bioavailability of phytoactive compounds [28]. Lipid-based formulations, such as liposomes and micelles, facilitate the delivery of lipophilic phytoactive drugs, overcoming limitations in solubility [29]. Furthermore, the use of cyclodextrin complexes, solid dispersions, and prodrug approaches contributes to optimized drug delivery by improving solubility and stability [30]. These innovative systems offer a diversified and tailored approach to enhance the overall performance of phytoactive drugs, fostering advancements in the field of gastrointestinal drug delivery and promoting their therapeutic potential [31].

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Table No. 2. Novel drug delivery system with drugs for Gastrointestinal Drug Delivery of Phytoactive Drugs

Drug Delivery system	Materials Used	Phytoactive Drug	Properties	Application	Ref.
Liposomes	Lipids [e.g., liposomes]	Curcumin	Improved solubility; enhanced bioavailability	anti-inflammatory effects.	[32]
Polymeric Nanoparticles	Polymers [e.g., PLGA, chitosan]	Quercetin [encapsulated]	Sustained release; protection of quercetin from degradation	antioxidant properties	[33]
Micelles	Amphiphilic block copolymers	Resveratrol [encapsulated]	Improved solubility; controlled release	antioxidant and anti-inflammatory effects	[33]
Nanocrystals	Drug crystals at nanoscale	Paclitaxel	Enhanced dissolution; improved bioavailability	anticancer properties	[34,35]
Dendrimers	Branched, highly functionalized polymers	Catechin [encapsulated]	Targeted delivery; sustained release	antioxidant and anticancer effects	[36]
Nanoemulsions	Oil-in-water or water-in-oil emulsions	Gingerol [encapsulated]	Improved solubility; enhanced bioavailability	anti-inflammatory effects	[37]
Carbon-Based Nanoparticles	Carbon nanotubes, graphene	Quercetin [conjugated]	Multifunctional carriers; potential for controlled release	antioxidant propertie	[38]
Silica Nanoparticles	Mesoporous silica structures	EGCG [Epigallocatechin gallate]	High surface area; controlled release	anticancer and antioxidant effects	[39]
Conventional Liposomes	Phospholipids [e.g., DPPC, DSPC]	Curcumin	Improved solubility; enhanced bioavailability	anti-inflammatory effects	[40]
PEGylated Liposomes	Phospholipids with PEG coating	Quercetin	Sustained release; protection of quercetin from degradation	antioxidant properties	[41]
Stealth Liposomes	Modified lipids for stealthiness	Resveratrol	Improved solubility; controlled release	antioxidant and anti-inflammatory effects	[42]
pH-Sensitive Liposomes	pH-responsive lipids	Berberine	pH-triggered release; enhanced bioavailability	antimicrobial properties	[43]

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Targeted Liposomes	Ligand-conjugated liposomes	EGCG	Targeted delivery; sustained release	antioxidant and anticancer effects	[44]
Multifunctional Liposomes	Incorporation of additional functionalities	Gingerol	Improved solubility; enhanced bioavailability	anti-inflammatory effects	[45]
Chitosan Microspheres	Chitosan	Quercetin	Sustained release; protection of quercetin	antioxidant properties	[46]
Alginate Microspheres	Alginate	Curcumin	Improved stability; controlled release	anti-inflammatory effects	[47]
PLGA Microspheres	PLGA [Poly[lactic-co-glycolic acid]	Resveratrol	Controlled release; enhanced stability	antioxidant effects	[48]
Starch Microspheres	Starch	Berberine	pH-responsive release; enhanced bioavailability	enhanced bioavailability	[49]
Gelatin Microspheres	Gelatin	EGCG	Controlled release; improved stability	antioxidant/anticancer effects	[50]
Polymeric Microspheres	Various biodegradable polymers	Gingerol	Tailored release; enhanced bioavailability	anti-inflammatory effects	[51]

PHYSICOCHEMICAL CONSIDERATIONS IN GASTROINTESTINAL DRUG DELIVERY

Physicochemical considerations play a pivotal role in the success of gastrointestinal drug delivery systems for phytoactive drugs [52]. The unique characteristics of the gastrointestinal environment, including varying pH levels, enzymatic activities, and complex physiological processes, necessitate careful attention to the following aspects:

Solubility

The solubility of phytoactive drugs significantly impacts their absorption [53]. Formulating drugs in systems that enhance solubility, such as lipid-based carriers or inclusion complexes, is crucial to overcome limitations associated with poor water solubility and improve bioavailability [54].

Stability

The stability of phytoactive drugs, susceptible to degradation due to factors like pH changes and enzymatic activity, is a critical consideration [55]. Protective formulations, including microspheres, liposomes, and polymeric nanoparticles, can shield drugs from degradation and ensure their stability throughout the gastrointestinal tract[56].

Partition Coefficient

Understanding the partition coefficient of a drug between the gastrointestinal fluid and the epithelial cells is essential [57]. Formulations that modify this coefficient, such as lipid-based carriers, can influence drug absorption and bioavailability by enhancing permeation through cell membranes[58].

Particle Size and Surface Area

Nanotechnological approaches, like nanoparticles and nanosuspensions, take advantage of increased surface area and reduced particle size to improve dissolution rates and absorption [59]. These strategies aim to enhance the interactions between phytoactive drugs and gastrointestinal tissues [60].

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pH-Dependent Properties

The pH variation along the gastrointestinal tract necessitates formulations with pH-dependent properties [61]. pH-responsive systems, including enteric-coated formulations or pH-responsive nanoparticles, enable targeted drug release at specific sites, optimizing absorption [62].

Biological Membrane Permeability

The ability of drugs to permeate biological membranes is a key determinant of absorption [63]. Strategies such as prodrug design or co-administration with absorption enhancers can enhance membrane permeability, facilitating efficient drug transport [64].

Interactions with Food and Other Drugs

The presence of food and potential interactions with other drugs in the gastrointestinal tract can affect drug absorption [65]. Formulations that consider these interactions and design delivery systems to minimize interference with food components or other medications contribute to optimal drug delivery [66].

Mucoadhesion

Mucoadhesive formulations, like chitosan-based microspheres, can improve drug residence time in the gastrointestinal tract, enhancing absorption by promoting interactions with mucosal surfaces [67].

Interactions Between Phytoactive Drugs and Gastrointestinal Environment

The interactions between phytoactive drugs and the gastrointestinal environment are complex and dynamic, influenced by various physiological factors within the digestive system [68]. Understanding these interactions is crucial for designing effective drug delivery systems. Key considerations include**:**

Gastrointestinal pH

The pH gradient along the gastrointestinal tract significantly influences the ionization state and solubility of phytoactive drugs. Formulations must account for these variations to optimize drug stability and absorption [69]. Enteric-coated formulations, for example, can protect drugs from acidic environments in the stomach, releasing them in the more neutral pH of the small intestine [70].

Enzymatic Activity

The presence of digestive enzymes, such as gastric lipase and pancreatic enzymes, can impact the stability and bioavailability of phytoactive drugs [71]. Designing drug delivery systems that resist enzymatic degradation or promote controlled release in specific gastrointestinal segments is crucial for ensuring optimal drug efficacy [72].

Interactions with Food

Co-administration of phytoactive drugs with food can influence drug absorption. Formulations should consider the potential interactions with food components, as well as the effects of food on gastrointestinal motility and absorption rates, to enhance overall drug delivery.

Mucus Layer

The mucus layer covering the gastrointestinal mucosa serves as a protective barrier. Drug delivery systems, including mucoadhesive formulations, must consider the interactions with this layer to achieve prolonged drug residence time and improved absorption [73].

Transport Mechanisms

Understanding the various transport mechanisms, such as passive diffusion and active transport, involved in drug absorption is essential. Drug delivery systems can be designed to exploit these mechanisms, enhancing drug permeation across the intestinal epithelium [74].

Microbiota Influence

The gut microbiota can metabolize phytoactive compounds, affecting their bioavailability and pharmacological activity [75]. Probiotics or prebiotics may be incorporated into formulations to modulate the gut microbiome and optimize drug-microbiota interactions.

Bile Salt Interactions

Interaction with bile salts is crucial for the solubilization of lipophilic phytoactive drugs. Formulations should consider bile salt interactions to facilitate the absorption of lipophilic compounds in the small intestine [76].

Gastrointestinal Motility

The rate of gastrointestinal transit influences the time available for drug absorption [77]. Formulations should account for variations in motility patterns, ensuring

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sustained drug release and absorption in specific segments of the gastrointestinal tract.

FORMULATION STRATEGIES TO ENHANCE BIOAVAILABILITY

To enhance the bioavailability of phytoactive drugs in gastrointestinal drug delivery, innovative formulation strategies have been explored [78]. Lipid-based formulations, including liposomes, micelles, and nanoemulsions, address poor solubility by mimicking natural digestive processes and improving the absorption of lipophilic compounds [79]. Polymeric nanoparticles, such as PLGA, offer controlled release and protection against enzymatic degradation, ensuring prolonged drug presence in the gastrointestinal tract [80]. Microspheres and microparticles, composed of materials like chitosan or alginate, provide stability and controlled release, withstanding harsh gastrointestinal conditions. Nanostructured Lipid Carriers [NLCs] combine solid and liquid lipids, offering improved drug loading capacity and controlled release. Inclusion complexation with cyclodextrins enhances solubility, while prodrug design chemically modifies compounds to improve their bioavailability. Nanosuspensions reduce drug particles to nanoscale sizes, enhancing dissolution rates [81]. Co-administration with absorption enhancers and pH-responsive delivery systems target specific gastrointestinal segments, and combination therapies with enhancers like Piperine further inhibit drug metabolism, collectively contributing to optimized bioavailability of phytoactive drugs in gastrointestinal drug delivery. These formulations address challenges related to solubility, stability, and absorption, promising enhanced therapeutic efficacy.

FUTURE PERAPECTIVES AND CHALLENEGES

Looking ahead, the future of gastrointestinal drug delivery for phytoactive drugs and their delivery systems presents exciting prospects and formidable challenges. Future research is expected to witness the refinement of nanotechnological approaches, enabling the creation of more sophisticated and targeted drug delivery systems. The integration of personalized medicine, considering individual variations in drug response, holds promise for optimizing therapeutic outcomes. Combination therapies, leveraging the synergistic effects of phytoactive drugs and conventional pharmaceuticals, may become a focus for comprehensive treatment strategies. However, the field faces challenges such as ensuring biocompatibility and safety, addressing the cost-effectiveness of advanced technologies, and navigating the complexities of clinical translation. Overcoming these hurdles requires interdisciplinary collaboration, standardized protocols for herbal extracts, and innovative strategies to enhance patient compliance. As researchers explore these avenues, the future holds potential for transformative advancements in gastrointestinal drug delivery, ushering in a new era of targeted, efficient, and patient-centric therapeutic interventions.

CONCLUSION

In conclusion, this exploration into the novel insights on gastrointestinal drug delivery of phytoactive drugs and their delivery systems underscores the growing significance of innovative approaches in enhancing the therapeutic potential of natural compounds. Phytoactive drugs, derived from plant sources, possess immense therapeutic value, but their effective delivery to the gastrointestinal tract poses challenges such as poor solubility and bioavailability. The multifaceted strategies discussed in this review, ranging from liposomes and microspheres to advanced nanotechnologies, offer promising solutions to overcome these challenges. The diverse classification of phytoactive drugs, their modes of action, and the exploration of various delivery systems highlight the intricate nature of this field. As researchers continue to unravel the complexities, the potential for tailored and targeted delivery of phytoactive drugs to specific regions of the gastrointestinal tract holds great promise for optimizing therapeutic outcomes and advancing the integration of traditional medicinal knowledge with modern drug delivery technologies. This review not only consolidates current knowledge but also serves as a springboard for future research endeavors aimed at unlocking the full therapeutic potential of phytoactive drugs in gastrointestinal health.

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CONFLICT OF INTEREST: None

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