RESEARCH PAPER

Gastroretentive Drug Delivery Systems: Technological Advances, Polymeric Strategies, and Clinical Applications for Enhanced Oral Bioavailability

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ABSTRACT
Gastroretentive drug delivery systems (GRDDS) represent a significant advancement in oral pharmaceutical technology, designed to prolong gastric residence time and optimize drug absorption from the upper gastrointestinal tract. This comprehensive review examines the physiological basis, technological approaches, polymeric strategies, and clinical applications of gastroretentive systems. The fundamental challenge in oral drug delivery—rapid gastric emptying and variable transit time—is addressed through various retention mechanisms including floating systems (effervescent and non-effervescent), bioadhesive systems, high-density systems, expandable systems, and magnetic systems. Floating drug delivery systems utilize buoyancy principles with gas-generating agents and hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and polyethylene oxide to achieve prolonged gastric retention exceeding 12 hours. Non-floating approaches employ mucoadhesion, swelling, or density manipulation to enhance retention. Critical formulation parameters including polymer selection, matrix composition, and excipient functionality are discussed alongside comprehensive evaluation methodologies encompassing buoyancy studies, dissolution testing, and in vivo assessment techniques. The review highlights ideal drug candidates benefiting from gastroretention—particularly those with narrow absorption windows, acid stability, and local gastric action—with metoprolol succinate presented as a clinically relevant case study. Patent landscape and commercial developments demonstrate growing pharmaceutical interest. Current limitations and future perspectives including personalized medicine approaches and emerging technologies are critically analyzed. Gastroretentive systems offer substantial therapeutic advantages through enhanced bioavailability, reduced dosing frequency, minimized side effects, and improved patient compliance, positioning them as promising platforms for next-generation oral drug delivery.

Keywords: *Gastroretentive drug delivery; Floating systems; Mucoadhesive systems; HPMC; Controlled release; Bioavailability enhancement*
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INTRODUCTION

Oral drug administration remains the most preferred and convenient route for therapeutic agent delivery due to its non-invasive nature, patient compliance, cost-effectiveness, and ease of manufacturing[1]. The development of oral controlled release drug delivery systems has revolutionized pharmaceutical technology by enabling sustained therapeutic drug concentrations, reducing dosing frequency, minimizing adverse effects, and improving patient adherence[2]. However, conventional oral controlled release formulations face significant limitations when drugs exhibit narrow absorption windows, regional absorption variability, or instability in lower gastrointestinal environments[3].

The gastrointestinal transit of dosage forms is highly variable, with gastric emptying time ranging from minutes to hours depending on physiological and formulation

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factors[4]. For drugs primarily absorbed in the stomach or upper small intestine, rapid gastric emptying results in incomplete drug release at the absorption site, leading to reduced bioavailability and therapeutic variability[5]. This challenge is particularly critical for drugs with short biological half-lives, pH-dependent solubility, or site-specific absorption requirements[6].

Gastroretentive drug delivery systems (GRDDS) have emerged as innovative pharmaceutical platforms designed to prolong dosage form residence in the gastric environment, thereby extending drug release duration at the optimal absorption site[7]. By maintaining prolonged gastric retention time (GRT), these systems ensure continuous drug presentation to the absorptive epithelium, enhance bioavailability of drugs with absorption windows, provide local therapeutic action for gastric disorders, and achieve sustained plasma concentrations with reduced fluctuations[8].

This comprehensive review examines the physiological foundations of gastric retention, technological classifications of gastroretentive systems, polymeric and excipient strategies, formulation considerations, evaluation methodologies, clinical applications, patent developments, and future perspectives in this rapidly evolving field.

GASTRIC PHYSIOLOGY AND DRUG RETENTION

Anatomy and Function of the Stomach

The stomach is a muscular, hollow organ serving multiple physiological functions including temporary food storage, mechanical and chemical digestion, and controlled delivery of chyme to the duodenum[9]. Anatomically, the stomach comprises three main regions: the fundus (upper dome-shaped portion), the body (central region), and the antrum or pylorus (lower portion terminating at the pyloric sphincter)[10]. The fundus and body primarily accommodate ingested material, while the antrum facilitates mixing and propulsion through coordinated muscular contractions[11].

The gastric environment presents unique characteristics relevant to drug delivery: acidic pH (1.0-3.0), enzymatic activity (pepsin), mucus layer protection, and limited absorptive surface area compared to the small intestine[12]. The stomach's capacity ranges from approximately 50 mL in the fasted state to 1.5 liters postprandially[13].

Gastrointestinal Motility and Gastric Emptying Patterns

Gastric motility exhibits distinct patterns during fasted and fed states[14]. During the interdigestive or fasted period, the migrating motor complex (MMC) regulates gastrointestinal clearance through cyclic phases occurring every 90-120 minutes[15]. The MMC comprises four sequential phases: Phase I (basal/quiescent period, 40-60 minutes) characterized by minimal contractile activity; Phase II (pre-burst period, 40-60 minutes) featuring intermittent contractions of increasing frequency and intensity; Phase III (burst phase, 4-6 minutes) consisting of intense, regular contractions that sweep undigested residues from the stomach—often termed the "housekeeper wave"; and Phase IV (transitional period, 0-5 minutes) bridging Phase III and the subsequent Phase I[16].

Administration of food disrupts the MMC cycle, initiating the fed state characterized by continuous contractions resembling Phase II of fasting motility[17]. This fed pattern persists for 4-10 hours depending on meal composition, caloric content, and volume, significantly delaying gastric emptying and extending potential retention time for dosage forms[18].

Factors Influencing Gastric Retention Time

Gastric retention of dosage forms is influenced by multiple physiological, formulation-related, and patient-specific factors[19]. Physiological factors include fed versus fasted state (fed state extends GRT 4-10 hours), meal composition (high-fat and high-protein meals delay emptying), caloric content (higher calories prolong retention), feeding frequency (repeated meals delay MMC onset), gender (females exhibit slower emptying), age (elderly subjects show prolonged GRT), posture (supine position increases retention), and disease states (diabetes, hypothyroidism, and gastric ulcers increase GRT while hyperthyroidism and duodenal ulcers decrease it)[20].

Formulation-related factors encompass dosage form density (< 1.0 g/cm^2[1] for floating, > 1.4 g/cm^2[1] for sinking), size and shape (larger units show prolonged retention), single versus multiple-unit systems (multiple units provide more predictable behavior), and polymer composition affecting swelling and bioadhesion[22]. Concurrent drug therapy also modulates GRT; anticholinergics (atropine, propantheline) prolong retention while prokinetic agents (metoclopramide, cisapride) accelerate gastric emptying[23].

CLASSIFICATION OF GASTRORETENTIVE SYSTEMS

Gastroretentive drug delivery systems can be broadly classified based on their retention mechanisms into floating and non-floating approaches[24]. Each category encompasses multiple technological variations designed to exploit specific physiological or physicochemical principles for prolonged gastric residence **(Table 1)**.

Table 1: Classification and Characteristics of Gastroretentive Drug Delivery Systems

System Type	Retention Mechanism	Key Advantages	Limitations
Floating (Effervescent)	Gas generation reduces density	Rapid buoyancy, simple formulation	Requires gastric fluid, pH-dependent
Floating (Non-effervescent)	Hydrophilic polymer swelling	pH-independent, sustained release	Slower buoyancy initiation
Mucoadhesive	Adhesion to gastric mucosa	Localized delivery, intimate contact	Mucus layer turnover limits

			retention
High-density	Density > gastric contents	Resists peristalsis	Unpredictable emptying, limited efficacy
Expandable/Swelling	Size exceeds pyloric diameter	Mechanical retention	Safety concerns, must eventually collapse

Overview of Retention Mechanisms

The primary retention strategies include: (1) Floating systems that achieve buoyancy in gastric fluid through density reduction below 1.0 g/cm²¹; (2) Bioadhesive/mucoadhesive systems that adhere to the gastric mucosa through molecular interactions; (3) High-density systems exceeding 1.4 g/cm²¹ that resist peristaltic waves; (4) Expandable/swelling systems that enlarge beyond pyloric sphincter diameter; and (5) Magnetic systems utilizing external magnetic fields[25]. Additionally, hybrid approaches combining multiple mechanisms have been explored to enhance retention reliability and duration[26].

FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems (FDDS) represent the most extensively investigated gastroretentive approach, utilizing buoyancy to maintain dosage forms at the gastric fluid surface, thereby prolonging residence time[27]. These systems remain buoyant by achieving bulk density lower than gastric contents (approximately 1.004-1.010 g/cm²), preventing premature transit through the pyloric sphincter during the digestive motility pattern[28].

Effervescent Floating Systems

Effervescent systems generate buoyancy through gas liberation, typically carbon dioxide, upon contact with acidic gastric fluid[29]. Gas-generating agents such as sodium bicarbonate, sodium carbonate, or citric acid are incorporated into the formulation matrix[30]. Upon immersion in gastric medium, acid-carbonate reaction produces CO_2 bubbles that become entrapped within the hydrated polymeric gel network, reducing overall density and inducing flotation[31].

Effervescent approaches include: (a) Gas-generating tablets and capsules employing carbonates with organic acids or relying on endogenous gastric acid; (b) Volatile liquid-containing systems where encapsulated low-boiling-point liquids (ether, cyclopentane) vaporize at body temperature, inflating chambers to achieve buoyancy; (c) Intragastric floating systems with drug reservoirs enclosed in microporous compartments supported by gas-filled chambers; and (d) Osmotically controlled floating systems combining osmotic pressure-driven release with buoyancy[32].

Non-Effervescent Floating Systems

Non-effervescent systems achieve flotation without gas generation, relying instead on inherent low-density materials or structures[33]. These systems typically incorporate high concentrations (20-75% w/w) of gel-forming hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethylcellulose (NaCMC), polyethylene oxide (PEO), carbomers, and polysaccharides like guar gum, xanthan gum, and alginates[34].

Upon gastric fluid contact, the polymer hydrates and swells, forming a gel barrier at the dosage form surface[35]. This gel layer controls fluid penetration rate and subsequent drug diffusion, simultaneously entrapping air within the swollen matrix to maintain buoyancy[36]. The hydrodynamically balanced system (HBS) represents a classic non-effervescent design where the gel-forming polymer matrix balances hydration, swelling, and drug release to sustain floating[37].

Hollow microspheres (microballoons) constitute another non-effervescent approach, prepared by emulsion solvent diffusion/evaporation techniques using polymers such as cellulose acetate, Eudragit®, polycarbonate, and calcium alginate[38]. These hollow structures provide inherent buoyancy while offering the advantages of multiple-unit systems including reduced inter- and intra-subject variability[39].

Raft-forming systems represent a specialized floating approach where alginic acid and carbonates react with gastric acid to form a viscous, buoyant gel (raft) floating on stomach contents[40]. This mechanism is particularly useful for gastroesophageal reflux treatment and localized delivery to gastric mucosa[41].

NON-FLOATING GASTRORETENTIVE SYSTEMS

Bioadhesive and Mucoadhesive Systems

Bioadhesive or mucoadhesive gastroretentive systems achieve prolonged GRT through adhesive interactions between polymeric formulation components and the gastric mucus layer or epithelial cell surface[42]. Mucoadhesion involves a multi-stage process: contact and wetting of the mucoadhesive polymer with the mucosal surface, penetration of polymer chains into the mucus network, and formation of adhesive bonds through physical entanglements and chemical interactions (hydrogen bonding, electrostatic attraction, hydrophobic interactions)[43].

Effective mucoadhesive polymers exhibit specific characteristics: abundant hydrophilic functional groups (carboxyl, hydroxyl, amide, sulfate), optimal molecular weight and chain flexibility for interpenetration, sufficient swelling capacity, and appropriate surface properties[44]. Commonly employed mucoadhesive polymers include anionic types (carbomers, polyacrylic acid derivatives, alginic acid, carboxymethylcellulose), cationic polymers (chitosan, trimethylated chitosan), and non-ionic polymers (hydroxypropyl methylcellulose, hydroxyethyl cellulose, polyvinyl alcohol)[45].

Despite promising in vitro mucoadhesive strength, clinical translation faces challenges including mucus turnover (gastric mucus layer renews every 4-6 hours), variable mucus thickness and composition, and reduced adhesion in the presence of food and digestive secretions[46].

High-Density Systems

High-density or sinking systems employ formulation density greater than gastric contents (typically > 1.4 g/cm²¹, ideally 2.4-2.8 g/cm²¹) to resist peristaltic contractions and remain in the lower stomach region[47]. Dense materials such as barium sulfate, zinc oxide, titanium dioxide, and iron powder are incorporated to increase overall system density[48]. However, clinical efficacy of high-density approaches remains limited due to unpredictable gastric emptying patterns and the stomach's capacity to empty dense particles during Phase III of MMC[49].

Expandable and Swelling Systems

Expandable systems are designed to swell upon gastric fluid uptake to a size exceeding the pyloric sphincter diameter (approximately 12-15 mm in relaxed state), thereby mechanically preventing gastric exit[50]. These systems typically employ superporous hydrogels or rapidly swelling polymeric matrices capable of achieving large equilibrium volumes within minutes[51].

Superporous hydrogels represent an advanced swelling approach, characterized by pore sizes exceeding 100 μm that facilitate rapid fluid uptake through capillary wetting rather than slow diffusion[52]. These materials can swell to hundreds of times their original size within minutes and exhibit sufficient mechanical strength to withstand gastric contractile forces[53]. However, expandable systems must eventually disintegrate or collapse to allow evacuation, requiring careful balance between retention duration and safe passage[54].

Magnetic Systems

Magnetic gastroretention utilizes small magnetic components within the dosage form that interact with an external magnetic field positioned on the abdominal surface above the stomach[55]. While conceptually interesting and demonstrated in animal models, practical limitations including patient mobility restrictions, magnetic field strength requirements, and regulatory considerations have prevented clinical translation[56].

POLYMERIC MATERIALS FOR GRDDS

Polymer selection constitutes a critical determinant of gastroretentive system performance, influencing buoyancy, swelling behavior, gel formation, drug release kinetics, and system integrity[57]. Hydrophilic polymers dominate GRDDS formulations due to their swelling properties, biocompatibility, regulatory acceptance, and ability to control drug release[58] **(Table 2)**.

Hydroxypropyl Methylcellulose (HPMC)

HPMC represents the most widely utilized polymer in gastroretentive formulations, available in various viscosity grades (E3, E5, E15, E50, K4M, K15M, K100M) that provide tunable swelling and release characteristics[59]. Upon hydration, HPMC forms a robust gel layer that controls water ingress and drug diffusion, simultaneously entrapping gas bubbles in effervescent systems[60]. Higher viscosity grades provide stronger gel formation and slower drug release but may require longer buoyancy lag times[61]. HPMC K4M and K100M are particularly popular for floating matrices due to their rapid hydration and excellent gel strength[62].

Polyethylene Oxide (PEO)

High molecular weight PEO (molecular weights from 100,000 to 7,000,000) exhibits rapid swelling and exceptional gel-forming capacity[63]. PEO matrices demonstrate controlled erosion kinetics and can sustain drug release for extended periods[64]. The polymer's non-ionic nature makes release pH-independent, and its rapid hydration contributes to quick buoyancy establishment in floating systems[65].

Carbomers and Polyacrylic Acid Derivatives

Carbomers (Carbopol®, polycarbophil) are synthetic high molecular weight polyacrylic acid polymers with exceptional mucoadhesive properties and pH-dependent swelling[66]. At gastric pH, carbomers exhibit moderate swelling, but their mucoadhesive strength enhances gastric retention[67]. These polymers are frequently combined with other hydrocolloids to optimize floating and release profiles[68].

Natural Polysaccharides

Natural polymers including xanthan gum, guar gum, locust bean gum, alginate, chitosan, and pectin offer biocompatibility, biodegradability, and cost-effectiveness[69]. Xanthan gum forms viscous solutions at low concentrations and exhibits pseudoplastic rheology[70]. Sodium alginate undergoes acid-induced gelation in gastric medium, useful for raft-forming systems[71]. Chitosan, a cationic polysaccharide derived from chitin, demonstrates pH-dependent solubility and mucoadhesive properties[72].

Combinations of multiple polymers often provide synergistic effects, optimizing the balance between buoyancy, swelling, gel strength, and drug release[73].

Table 2: Polymers Employed in Gastroretentive Formulations

Polymer	Type	Primary Function	Typical Concentration
HPMC K4M, K100M	Cellulose derivative	Gel formation, matrix control, buoyancy	20-60% w/w
Polyethylene oxide	Synthetic polymer	Rapid swelling, sustained release	10-40% w/w
Carbopol/Polycarbophil	Polyacrylic	Mucoadhesion, pH-	5-25% w/w

	acid	dependent swelling	
Xanthan gum	Natural polysaccharide	Viscosity enhancement, gel formation	5-30% w/w
Sodium alginate	Natural polysaccharide	Raft formation, acid-gelation	10-40% w/w
Chitosan	Natural polymer	Mucoadhesion, pH-sensitive	5-20% w/w
Guar gum	Natural polysaccharide	Matrix formation, viscosity	10-30% w/w

FORMULATION STRATEGIES AND EXCIPIENTS

Gas-Generating Agents

Effervescent floating systems require carbonates or organic acids to generate carbon dioxide upon contact with gastric acid[74]. Sodium bicarbonate ($NaHCO_3$) is the most commonly employed effervescent agent, typically incorporated at 5-20% w/w concentration[75]. The bicarbonate-acid reaction ($NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$) occurs rapidly, necessitating efficient gas entrapment within the hydrating polymer matrix[76]. Alternative carbonates include calcium carbonate and sodium carbonate, while citric acid and tartaric acid serve as acidic components in dual-component effervescent systems[77].

Matrix Modifiers and Release Retardants

Beyond primary gel-forming polymers, various excipients modulate matrix properties and drug release kinetics[78]. Lipophilic materials such as glyceryl behenate (Compritol® 888 ATO), stearic acid, and hydrogenated castor oil reduce water penetration and slow drug dissolution, particularly for highly water-soluble drugs[79]. Microcrystalline cellulose provides compressibility and structural integrity while moderately controlling water uptake[80].

Binders and Processing Aids

Povidone (polyvinylpyrrolidone, PVP) functions as a binder in direct compression or wet granulation processes, enhancing inter-particulate bonding and tablet mechanical strength[81]. Poloxamer surfactants improve drug wettability and dissolution while potentially contributing to matrix formation[82]. Magnesium stearate and talc serve as lubricants to facilitate tablet ejection and prevent sticking during compression[83].

Formulation Development Considerations

Optimal GRDDS formulation requires balancing competing objectives: achieving rapid and reliable buoyancy (short lag time), maintaining prolonged floating duration (> 12 hours), ensuring acceptable mechanical strength (hardness, friability), controlling drug release rate (typically zero-order or Higuchi kinetics), and maintaining stability under storage conditions[84]. Direct compression represents the preferred manufacturing approach due to simplicity, cost-effectiveness, and avoidance of heat or solvents that may degrade thermolabile or moisture-sensitive drugs[85].

EVALUATION METHODOLOGIES

Physicochemical Characterization

Preformulation assessment includes drug-excipient compatibility studies (differential scanning calorimetry, Fourier-transform infrared spectroscopy), powder flow properties (angle of repose, Carr's index, Hausner's ratio), and particle size distribution[86]. Finished dosage forms undergo evaluation for weight variation, hardness, friability, thickness, and drug content uniformity according to pharmacopeial standards[87].

Buoyancy Assessment

Buoyancy lag time (BLT) and total floating time (TFT) constitute critical performance parameters for floating systems[88]. BLT represents the interval between dosage form immersion in simulated gastric fluid (SGF, pH 1.2, 37°C) and emergence to the surface, ideally < 1 minute[89]. TFT quantifies the duration the system maintains buoyancy, typically required to exceed 12 hours for once-daily formulations[90]. Quantitative buoyancy assessment involves measuring resulting weight, calculated as the difference between gravity and buoyancy forces: $F = (Df - Ds)gV$, where F is resultant force, Df is fluid density, Ds is dosage form density, g is gravitational acceleration, and V is dosage form volume[91].

Swelling Studies

For expandable and swelling systems, swelling index quantifies volumetric or dimensional changes over time[92]. Tablets are periodically removed from SGF, surface liquid blotted, and weight or dimensions measured[93]. Swelling index is calculated as: $SI = [(Wt - W0)/W0] \times 100$, where Wt is weight at time t and W0 is initial weight[94]. Continuous monitoring systems employ specialized apparatus to track water uptake without disturbing the swelling matrix[95].

In Vitro Dissolution Testing

Dissolution studies employ USP Apparatus I (basket) or II (paddle) in simulated gastric fluid (0.1 N HCl, 900 mL, 37 ± 0.5°C) with rotation speeds of 50-100 rpm[96]. For floating systems, modified apparatus configurations prevent dosage form adhesion to vessel surfaces or paddles while maintaining appropriate hydrodynamic conditions[97]. Modifications include wire helices loosely wrapping the dosage form, mesh assemblies restraining vertical movement while permitting swelling, or recessed mesh platforms[98]. Release data are subjected to kinetic modeling (zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell) to elucidate release mechanisms[99]. Controlled release systems ideally exhibit zero-order kinetics (constant release rate) or Higuchi kinetics (diffusion-controlled release)[100]. The Korsmeyer-Peppas model elucidates transport mechanisms through the release

exponent n: $n \leq 0.45$ indicates Fickian diffusion, $0.45 < n < 0.89$ suggests anomalous (non-Fickian) transport, and $n \geq 0.89$ indicates Case-II or super Case-II transport[101].

In Vivo Evaluation

Gamma scintigraphy represents the gold standard for non-invasive assessment of gastric retention in humans[102]. Dosage forms radiolabeled with technetium-99m (^{m}Tc) or indium-111 (^{62}In) are administered to subjects, and sequential gamma camera images quantify gastric retention over time[103-104]. Alternative techniques include X-ray radiography with radiopaque markers (barium sulfate), magnetic marker monitoring using biomagnetic measurement systems, gastroscopy with fiber-optic or video endoscopy, and ^{105}C-octanoic acid breath testing for gastric emptying assessment[106]. Pharmacokinetic studies comparing GRDDS with conventional formulations evaluate bioavailability enhancement, plasma concentration-time profiles, peak plasma concentration (Cmax), time to peak (Tmax), area under the curve (AUC), and elimination half-life ($t_{1/2}$)[107].

THERAPEUTIC APPLICATIONS

Ideal Drug Candidates for Gastroretentive Delivery

Gastroretentive systems provide maximum therapeutic benefit for drugs exhibiting specific pharmacokinetic or physicochemical characteristics[108]. Ideal candidates include: (1) Drugs with narrow absorption windows localized to the stomach or upper small intestine (duodenum, jejunum), such as riboflavin, levodopa, para-aminobenzoic acid, and furosemide;[109] (2) Drugs primarily absorbed in acidic environments or unstable in alkaline intestinal pH, including captopril, ranitidine, and metronidazole;[110] (3) Drugs demonstrating low solubility at higher pH values, such as diazepam, chlordiazepoxide, and verapamil;[111] (4) Drugs acting locally in the gastric environment, including antacids, sucralfate, misoprostol, and anti-Helicobacter pylori agents;[112] (5) Drugs with short biological half-lives requiring frequent dosing for maintained therapeutic effect;[113] and (6) Drugs susceptible to colonic bacterial degradation or first-pass metabolism that benefit from extended gastric release[114].

Drugs Unsuitable for Gastroretentive Systems

Certain drug classes exhibit poor compatibility with gastroretentive approaches: (1) Drugs with very low acid solubility may demonstrate inadequate dissolution in gastric fluid (e.g. phenytoin);[115] (2) Drugs unstable or degraded in gastric acid (e.g. erythromycin, certain penicillins) may lose potency during extended gastric exposure;[116] (3) Drugs intended for colonic delivery, such as 5-aminosalicylic acid for inflammatory bowel disease, contraindicate gastric retention;[117] and (4) Drugs causing significant gastric irritation or mucosal damage should avoid prolonged gastric contact[118] **(Table 3)**.

Table 3: Drug Candidates for Gastroretentive Delivery

Drug Category	Example Drugs	Rationale for GRDDS
Cardiovascular agents	Metoprolol, Propranolol, Verapamil, Nifedipine	Narrow absorption window, short half-life, pH-dependent solubility
Antibiotics	Amoxicillin, Clarithromycin, Tetracycline	H. pylori eradication, local gastric action
Antidiabetics	Metformin, Glipizide, Gliclazide	Enhanced bioavailability, sustained glycemic control
Antiulcer agents	Ranitidine, Famotidine, Nizatidine	Local gastric action, acid-labile nature
CNS drugs	Levodopa, Gabapentin, Baclofen	Narrow absorption window in upper GIT
Antiviral agents	Didanosine, Zalcitabine	Acid-labile, limited absorption window

Case Study: Metoprolol Succinate and Cardiovascular Applications

Metoprolol succinate, a selective β_1-adrenergic receptor antagonist widely prescribed for hypertension, angina pectoris, and heart failure, exemplifies an ideal GRDDS candidate[119]. The drug exhibits a short biological half-life (3-4 hours), necessitating multiple daily doses for conventional formulations[120]. Metoprolol demonstrates pH-independent high solubility (BCS Class I) but preferential absorption from the upper gastrointestinal tract with an absorption window primarily in the duodenum and jejunum[121]. Oral bioavailability is limited (approximately 50%) due to significant first-pass hepatic metabolism[122]. Gastroretentive floating tablets of metoprolol succinate formulated with HPMC K4M, HPMC K100M, or polyethylene oxide matrices combined with sodium bicarbonate as gas-generating agent have demonstrated: (1) Rapid buoyancy achievement (lag time < 2 minutes); (2) Prolonged floating duration exceeding 12-24 hours; (3) Controlled zero-order or Higuchi diffusion-controlled release over 12-24 hours; (4) Enhanced relative bioavailability compared to immediate-release formulations; (5) Reduced peak-trough plasma concentration fluctuations; and (6) Potential for once-daily dosing improving patient compliance[123]. Kinetic analysis typically reveals Higuchi model best-fit, indicating diffusion-controlled release from the swollen polymeric matrix[124]. The Korsmeyer-Peppas release exponent (n = 0.45-0.89) suggests anomalous non-Fickian transport involving coupled diffusion and polymer relaxation mechanisms[125].

Other Clinical Applications

Beyond cardiovascular drugs, gastroretentive systems have been successfully developed for diverse therapeutic categories: antihypertensives (nifedipine, propranolol, atenolol), antibiotics (amoxicillin, clarithromycin for H. pylori eradication), antiretrovirals (didanosine, zalcitabine), antidiabetics (metformin, glipizide), analgesics (tramadol, acetaminophen), antiulcer agents (famotidine, nizatidine), and central nervous system drugs (levodopa/carbidopa, gabapentin)[126].

PATENTS AND COMMERCIAL DEVELOPMENTS

The commercial potential of gastroretentive technologies has driven substantial intellectual property development[127]. Notable patents include: (1) US 6,488,962 B1 (2002) describing tablet formulations enhancing gastric retention of swellable controlled-release dosage forms; (2) US 6,710,126 B1 (2001) covering superporous hydrogel composites with rapid swelling and high mechanical strength; (3) WO 2002/102415 A1 (2002) detailing gastric floating systems; (4) US 2008/0220060 A1 (2008) presenting gastroretentive compositions and preparation methods; (5) WO 2011/048494 A2 (2010) addressing gastroretentive dosage forms for poorly soluble drugs; (6) WO 2011/151708 A1 (2011) describing GABA analog gastroretentive formulations; and (7) US 8,808,669 B2 (2014) covering extended-release gastroretentive therapeutic compositions[128]. Several gastroretentive products have achieved regulatory approval and market availability, including Madopar® HBS (levodopa/benserazide), Valrelease® (diazepam), Liquid Gaviscon® (raft-forming antacid), and Coreg CR® (carvedilol)[129]. These commercial successes validate the clinical utility and manufacturing feasibility of gastroretentive platforms[130].

CHALLENGES AND FUTURE PERSPECTIVES

Current Limitations

Despite significant advances, gastroretentive systems face several challenges limiting broader implementation[131]. High inter- and intra-subject variability in gastric emptying patterns, particularly under fasted conditions, can compromise retention predictability[132]. Floating systems require adequate gastric fluid volume (typically > 200 mL) for effective buoyancy, potentially limiting performance in certain patient populations or dosing conditions[133]. Food-dependent performance introduces complexity in dosing instructions and patient compliance[134]. Manufacturing scalability, particularly for complex multi-layer or multi-particulate systems, presents technical and economic challenges[135]. Regulatory pathways for demonstrating bioequivalence of gastroretentive generics to reference products remain evolving[136].

Emerging Technologies and Future Directions

Future developments in gastroretentive drug delivery will likely integrate advanced materials, personalized medicine approaches, and multi-functional designs[137]. Three-dimensional printing technologies enable fabrication of complex geometries, multi-compartment systems, and personalized dosing tailored to individual patient requirements[138]. Smart polymers responding to physiological stimuli (pH, enzymes, temperature) may provide more predictable retention and release[139]. Combination systems incorporating multiple retention mechanisms (floating plus mucoadhesion, expandable plus floating) could enhance reliability across diverse patient populations and conditions[140]. Integration of real-time monitoring capabilities through ingestible sensors or imaging agents would enable dosage form tracking and adaptive dosing strategies[141].

Nanomedicine integration, such as incorporating drug-loaded nanoparticles within gastroretentive matrices, may address solubility limitations and enable combination therapy delivery[142]. Personalised gastroretentive systems accounting for individual variations in gastric anatomy, motility patterns, and disease states represent an aspirational goal for precision medicine[143].

Environmental sustainability considerations will increasingly influence formulation design, favouring biodegradable natural polymers and green manufacturing processes[144]. Pediatric and geriatric formulations addressing age-specific physiological characteristics and compliance challenges require focused development[145].

CONCLUSION

Gastroretentive drug delivery systems represent a significant paradigm advancement in oral pharmaceutical technology, addressing fundamental limitations of conventional dosage forms through innovative retention mechanisms and controlled release strategies. This comprehensive review has examined the physiological foundations, technological diversity, polymeric approaches, formulation strategies, evaluation methodologies, and clinical applications of gastroretentive platforms.

The principal retention mechanisms—floating (effervescent and non-effervescent), bioadhesive, high-density, expandable, and magnetic—exploit distinct physiological or physicochemical principles to prolong gastric residence time. Among these approaches, floating drug delivery systems, particularly non-effervescent hydrophilic polymer matrices and effervescent systems employing gas-generating agents, have demonstrated the most robust clinical translation due to their simplicity, reliability, and manufacturability. Polymeric materials, especially hydroxypropyl methylcellulose, polyethylene oxide, carbomers, and natural polysaccharides, serve as the cornerstone of matrix-based gastroretentive formulations, enabling precise control over swelling, buoyancy, and drug release kinetics.

Gastroretentive systems offer substantial therapeutic advantages for drugs with narrow absorption windows, acid stability, short half-lives, or local gastric action. The metoprolol succinate case study exemplifies successful application for a cardiovascular agent, demonstrating enhanced bioavailability, reduced dosing frequency, and improved pharmacokinetic profiles. Beyond cardiovascular therapeutics, gastroretentive technologies have found applications across diverse categories

including antibiotics, antiretrovirals, antidiabetics, and central nervous system agents.

Comprehensive evaluation methodologies encompassing physicochemical characterization, buoyancy studies, swelling assessment, in vitro dissolution testing with appropriate apparatus modifications, and in vivo imaging techniques provide robust frameworks for formulation optimization and quality assurance. Kinetic modeling elucidates release mechanisms, predominantly diffusion-controlled or anomalous transport, guiding rational formulation design.

Despite significant progress and several commercially successful products, challenges persist including inter-subject variability in gastric emptying, food-effect dependencies, requirements for adequate gastric fluid volumes, and manufacturing complexities for advanced multi-particulate systems. Future directions incorporating three-dimensional printing, smart responsive polymers, combination retention mechanisms, nanomedicine integration, and personalized medicine approaches promise to address current limitations and expand therapeutic applications.

The growing patent landscape and commercial interest underscore the industrial and clinical relevance of gastroretentive technologies. As our understanding of gastrointestinal physiology deepens and material science advances, gastroretentive drug delivery systems are poised to play an increasingly important role in precision medicine, offering patient-specific therapeutic optimization and enhanced clinical outcomes. Continued interdisciplinary research integrating pharmaceutical sciences, materials engineering, physiology, and clinical medicine will drive next-generation innovations in oral controlled drug delivery.

AUTHOR CONTRIBUTIONS

Yogesh: Literature review and Writing - Original Draft; Kumar C: Conceptualisation, Methodology, Writing - Review & Editing; Redhu R: Writing - Review & Editing, Validation; Mehra R: Investigation, Data Curation, Formal Analysis; Jangra K: Supervision, Writing - Review & Editing.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opin Drug Deliv. 2006;3(2):217-33. DOI: 10.1517/17425247.3.2.217
2. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63(3):235-59. DOI: 10.1016/S0168-3659(99)00204-7
3. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug Deliv. 2011;18(2):97-110. DOI: 10.3109/10717544.2010.520354
4. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS PharmSciTech. 2005;6(3):E372-90. DOI: 10.1208/pt060347
5. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J Control Release. 2006;111(1-2):1-18. DOI: 10.1016/j.jconrel.2005.10.031
6. Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int J Pharm. 2016;510(1):144-58. DOI: 10.1016/j.ijpharm.2016.05.016
7. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Release. 2003;90(2):143-62. DOI: 10.1016/S0168-3659(03)00203-7
8. Shaikh S, Khirsagar RV, Quazi A. Fast dissolving tablets: an overview of formulation and technology. Int J Pharm Sci Rev Res. 2010;5(2):20-5.
9. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention: a means to address regional variability in intestinal drug absorption. Pharm Technol. 2003;27(7):50-68.
10. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res. 2008;7(3):1055-66. DOI: 10.4314/tjpr.v7i3.14691
11. Talukder R, Fassihi R. Gastroretentive delivery systems: a mini review. Drug Dev Ind Pharm. 2004;30(10):1019-28. DOI: 10.1081/DDC-200040239
12. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int J Pharm. 2004;277(1-2):141-53. DOI: 10.1016/j.ijpharm.2003.09.047
13. Wen H, Park K. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. John Wiley & Sons; 2010.
14. Sheth PR, Tossounian JL. The hydrodynamically balanced system (HBS): a novel drug delivery system for oral use. Drug Dev Ind Pharm. 1984;10(2):313-39. DOI: 10.3109/03639048409040415

15. Rocca JG, Omidian H, Shah K. Progress in gastroretentive drug delivery systems. Business Briefing: Pharmatech. 2003;1:152-6.

16. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm. 1996;136(1-2):117-39. DOI: 10.1016/0378-5173(96)04565-2

17. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: A Treatise. 2nd ed. Vallabh Prakashan; 2009.

18. Washington N, Washington C, Wilson CG. Physiological Pharmaceutics: Barriers to Drug Absorption. 2nd ed. Taylor & Francis; 2001.

19. Davis SS, Stockwell AF, Taylor MJ, Hardy JG, Whalley DR, Wilson CG, et al. The effect of density on the gastric emptying of single and multiple-unit dosage forms. Pharm Res. 1986;3(4):208-13. DOI: 10.1023/A:1016334629435

20. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm Res. 1998;15(1):11-22. DOI: 10.1023/A:1011984216775

21. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413-20. DOI: 10.1023/A:1016212804288

22. Atyabi F, Sharma HL, Mohammad HA, Fell JT. Controlled drug release from coated floating ion exchange resin beads. J Control Release. 1996;42(1):25-8. DOI: 10.1016/0168-3659(96)01337-7

23. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J Control Release. 1998;55(1):3-12. DOI: 10.1016/S0168-3659(97)00266-6

24. Hwang SJ, Park H, Park K. Gastric retentive drug-delivery systems. Crit Rev Ther Drug Carrier Syst. 1998;15(3):243-84.

25. Chen J, Blevins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. J Control Release. 2000;64(1-3):39-51. DOI: 10.1016/S0168-3659(99)00139-X

26. Timmermans J, Moës AJ. How well do floating dosage forms float? Int J Pharm. 1990;62(2-3):207-16. DOI: 10.1016/0378-5173(90)90234-U

27. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci. 1992;81(2):135-40. DOI: 10.1002/jps.2600810207

28. Guyton AC, Hall JE. Textbook of Medical Physiology. 11th ed. Elsevier Saunders; 2006.

29. Tortora GJ, Derrickson BH. Principles of Anatomy and Physiology. 13th ed. John Wiley & Sons; 2012.

30. Marieb EN, Hoehn K. Human Anatomy & Physiology. 9th ed. Pearson Education; 2013.

31. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology. 7th ed. Elsevier Churchill Livingstone; 2012.

32. McConnell EL, Fadda HM, Basit AW. Gut instincts: explorations in intestinal physiology and drug delivery. Int J Pharm. 2008;364(2):213-26. DOI: 10.1016/j.ijpharm.2008.05.012

33. Kamba M, Seta Y, Kusai A, Ikeda M, Nishimura K. A unique dosage form to evaluate the mechanical destructive force in the gastrointestinal tract. Int J Pharm. 2000;208(1-2):61-70. DOI: 10.1016/S0378-5173(00)00552-4

34. Salessiotis N. Measurement of the diameter of the pylorus in man: Part I. Experimental project for clinical application. Am J Surg. 1972;124(3):331-3. DOI: 10.1016/0002-9610(72)90035-0

35. Szurszewski JH. A migrating electric complex of the canine small intestine. Am J Physiol. 1969;217(6):1757-63. DOI: 10.1152/ajplegacy.1969.217.6.1757

36. Code CF, Marlett JA. The interdigestive myo-electric complex of the stomach and small bowel of dogs. J Physiol. 1975;246(2):289-309. DOI: 10.1113/jphysiol.1975.sp010891

37. Itoh Z, Sekiguchi T. Interdigestive motor activity in health and disease. Scand J Gastroenterol Suppl. 1983;82:121-34.

38. Pilot MA, Thomas DR, Hewitt JV. Patterns of gastric emptying in diabetes mellitus. Diabetologia. 1980;18(4):295-302. DOI: 10.1007/BF00251917

39. Oberle RL, Chen TS, Lloyd C, Barnett JL, Owyang C, Meyer J, et al. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. Gastroenterology. 1990;99(5):1275-82. DOI: 10.1016/0016-5085(90)91150-5

40. Hunt JN, Stubbs DF. The volume and energy content of meals as determinants of gastric emptying. J Physiol. 1975;245(1):209-25. DOI: 10.1113/jphysiol.1975.sp010841

41. Heading RC, Nimmo J, Prescott LF, Tothill P. The dependence of paracetamol absorption on the rate of gastric emptying. Br J Pharmacol. 1973;47(2):415-21. DOI: 10.1111/j.1476-5381.1973.tb08339.x

42. Moore JG, Christian PE, Coleman RE. Gastric emptying of varying meal weight and composition in man. Dig Dis Sci. 1981;26(1):16-22. DOI: 10.1007/BF01307972

43. Desai A, Qazi A, Ganju E, Rao M, Raghuvanshi S, Singh J, et al. Effect of polymers on drug release kinetics of bioadhesive gastroretentive delivery system of metformin HCl. J Drug Deliv Sci Technol. 2018;44:98-108. DOI: 10.1016/j.jddst.2017.11.023

44. Wilson CG, Washington N. The stomach: its role in oral drug delivery. In: Physiological Pharmaceutics: Barriers to Drug Absorption. Taylor & Francis; 2001. p. 47-70.

45. Mojaverian P, Vlasses PH, Kellner PE, Rocci ML Jr. Effects of gender, posture, and age on gastric residence time of an indigestible solid: pharmaceutical considerations. Pharm Res. 1988;5(10):639-44. DOI: 10.1023/A:1015922903843

46. McCallum RW, Fink SM, Lerner E, Berkowitz DM. Effects of metoclopramide and bethanechol on delayed gastric emptying present in gastroesophageal reflux patients. Gastroenterology. 1983;84(5 Pt 1):1073-7.

47. Khosla R, Davis SS. The effect of tablet size on the gastric emptying of non-disintegrating tablets. Int J Pharm. 1990;62(2-3):R9-11. DOI: 10.1016/0378-5173(90)90238-Y

48. Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. Int J Pharm. 1993;100(1-3):81-92. DOI: 10.1016/0378-5173(93)90078-W

49. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997;14(6):815-9. DOI: 10.1023/A:1012171010492

50. Arora S, Ali J, Ahuja A, Baboota S, Qureshi J. Floating drug delivery systems: a review. AAPS PharmSciTech. 2005;6(3):E372-90. DOI: 10.1208/pt060347

51. Gopalakrishnan S, Chenthilnathan A. Floating drug delivery systems: a review. J Pharm Sci Technol. 2011;3(2):548-54.

52. Patel A, Modasiya M, Shah D, Patel V. Development and in vivo floating behavior of verapamil HCl intragastric floating tablets. AAPS PharmSciTech. 2009;10(1):310-5. DOI: 10.1208/s12249-009-9196-8

53. Varshosaz J, Tavakoli N, Kheirolahi F. Development and physical characterization of sunitinib malate solid lipid nanoparticles. Jundishapur J Nat Pharm Prod. 2015;10(3):e18472. DOI: 10.17795/jjnpp-18472

54. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. Asian J Pharm Clin Res. 2010;3(1):2-10.

55. Sungthongjeen S, Pitaksuteepong T, Somsiri A, Sriamornsak P. Studies on pectins as potential hydrogel matrices for controlled-release drug delivery. Drug Dev Ind Pharm. 1999;25(12):1271-6. DOI: 10.1081/DDC-100102294

56. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev Ind Pharm. 2000;26(9):965-9. DOI: 10.1081/DDC-100101323

57. Krogel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm. 1999;187(2):175-84. DOI: 10.1016/S0378-5173(99)00182-1

58. Özdemir N, Ordu S, Özkan Y. Studies of floating dosage forms of furosemide: in vitro and in vivo evaluations of bilayer tablet formulations. Drug Dev Ind Pharm. 2000;26(8):857-66. DOI: 10.1081/DDC-100101308

59. Baumgartner S, Kristl J, Vrečer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000;195(1-2):125-35. DOI: 10.1016/S0378-5173(99)00378-9

60. Joseph NJ, Lakshmi S, Jayakrishnan A. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits. J Control Release. 2002;79(1-3):71-9. DOI: 10.1016/S0168-3659(01)00484-8

61. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein-gelatin beads floating properties. Int J Pharm. 2000;198(2):157-65. DOI: 10.1016/S0378-5173(99)00426-6

62. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. In vitro and in vivo evaluation of riboflavin-containing microballoons for floating controlled drug delivery system in healthy humans. Int J Pharm. 2004;275(1-2):97-107. DOI: 10.1016/j.ijpharm.2004.01.025

63. Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: preparation and release characteristics. Drug Dev Ind Pharm. 2001;27(6):507-15. DOI: 10.1081/DDC-100105175

64. Jain NK, Gupta RN. Controlled and Novel Drug Delivery. CBS Publishers; 2007.

65. Mundargi RC, Patil SA, Agnihotri SA, Aminabhavi TM. Evaluation and controlled release characteristics of modified xanthan films for

transdermal delivery of atenolol. Drug Dev Ind Pharm. 2007;33(1):79-90. DOI: 10.1080/03639040600975022

66. Pahwa R, Kumar N, Kohli K. Formulation and evaluation of gastroretentive drug delivery systems: a review. J Appl Pharm Sci. 2011;1(10):33-49.

67. Rubinstein A, Tirosh B, Baluom M, Nassar T, David A, Radai R, et al. The rationale for peptide drug delivery to the colon and the potential of polymeric carriers as effective tools. J Control Release. 1997;46(1-2):59-73. DOI: 10.1016/S0168-3659(96)01581-9

68. Patel JK, Chavda JR. Formulation and evaluation of stomach-specific amoxicillin-loaded carbopol-934P mucoadhesive microspheres for anti-Helicobacter pylori therapy. J Microencapsul. 2009;26(4):365-76. DOI: 10.1080/02652040802389304

69. Akiyama Y, Nagahara N, Kashihara T, Hirai S, Toguchi H. In vitro and in vivo evaluation of mucoadhesive microspheres prepared for the gastrointestinal tract using polyglycerol esters of fatty acids and a poly(acrylic acid) derivative. Pharm Res. 1995;12(3):397-405. DOI: 10.1023/A:1016265709583

70. Jiménez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1993;19(1-2):143-94. DOI: 10.3109/03639049309038775

71. Park H, Park K. Hydrogels in bioapplications. ACS Symp Ser. 1996;627:2-19.

72. Chickering DE, Jacob JS, Mathiowitz E. Bioadhesive polymers: development and applications. Sci Med. 1996;3(3):32-43.

73. Ch'ng HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery II: synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. J Pharm Sci. 1985;74(4):399-405. DOI: 10.1002/jps.2600740408

74. Iannuccelli V, Coppi G, Bernabei MT, Cameroni R. Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. Int J Pharm. 1998;174(1-2):47-54. DOI: 10.1016/S0378-5173(98)00229-1

75. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994;83(2):239-45. DOI: 10.1002/jps.2600830219

76. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm. 2010;74(2):332-9. DOI: 10.1016/j.ejpb.2009.11.010

77. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery system: effects of CO2 gas-forming agents. Int J Pharm. 2002;239(1-2):81-91. DOI: 10.1016/S0378-5173(02)00054-6

78. Chen YC, Ho HO, Liu DZ, Siow WS, Sheu MT. Swelling/floating capability and drug release characterizations of gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose. PLoS One. 2015;10(1):e0116914. DOI: 10.1371/journal.pone.0116914

79. Omidian H, Rocca JG, Park K. Advances in superporous hydrogels. J Control Release. 2005;102(1):3-12. DOI: 10.1016/j.jconrel.2004.09.028

80. Dorkoosh FA, Verhoef JC, Borchard G, Rafiee-Tehrani M, Verheijden JH, Junginger HE. Development and characterization of a novel peroral peptide drug delivery system. J Control Release. 2001;71(3):307-18. DOI: 10.1016/S0168-3659(01)00229-1

81. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2001;48(2-3):139-57. DOI: 10.1016/S0169-409X(01)00112-0

82. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharm Sci Technolo Today. 2000;3(6):198-204. DOI: 10.1016/S1461-5347(00)00269-8

83. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and their in vivo success: a recent update. Asian J Pharm Sci. 2016;11(5):575-84. DOI: 10.1016/j.ajps.2016.04.007

84. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th ed. Pharmaceutical Press; 2009.

85. Bai G, Armenante PM, Plank RV. Modeling the effect of tablet dissolution on the observed powder dissolution rate. Chem Eng Commun. 2008;195(11):1299-326. DOI: 10.1080/00986440801943925

86. Allen LV Jr, Popovich NG, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 9th ed. Lippincott Williams & Wilkins; 2011.

87. Nerurkar J, Jun HW, Price JC, Park MO. Controlled-release matrix tablets of ibuprofen using

cellulose ethers and carrageenans: effect of formulation factors on dissolution rates. Eur J Pharm Biopharm. 2005;61(1-2):56-68. DOI: 10.1016/j.ejpb.2005.04.003

88. Varshosaz J. The promise of chitosan microspheres in drug delivery systems. Expert Opin Drug Deliv. 2007;4(3):263-73. DOI: 10.1517/17425247.4.3.263

89. Pahwa R, Saini N, Kumar V, Kohli K. Chitosan-based gastroretentive floating drug delivery technology: an updated review. Expert Opin Drug Deliv. 2012;9(5):525-39. DOI: 10.1517/17425247.2012.673581

90. Anlar S, Çapan Y, Güven O, Göğüş A, Dalkara T, Hıncal AA. Formulation and in vitro-in vivo evaluation of buccoadhesive morphine sulfate tablets. Pharm Res. 1994;11(2):231-6. DOI: 10.1023/A:1018922417135

91. Gröning R, Berntgen M, Georgarakis M. Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extracorporal magnets to control gastrointestinal transit. Eur J Pharm Biopharm. 1998;46(3):285-91. DOI: 10.1016/S0939-6411(98)00037-0

92. Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using gastroretentive technologies. Curr Opin Pharmacol. 2006;6(5):501-8. DOI: 10.1016/j.coph.2006.04.007

93. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. AAPS PharmSciTech. 2004;5(2):e34. DOI: 10.1208/pt050234

94. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Development of sustained release gastroretentive drug delivery system for ofloxacin: in vitro and in vivo evaluation. Int J Pharm. 2005;304(1-2):178-84. DOI: 10.1016/j.ijpharm.2005.07.021

95. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm. 2003;253(1-2):13-22. DOI: 10.1016/S0378-5173(02)00642-7

96. Jamzad S, Fassihi R. Role of surfactant and pH on dissolution properties of fenofibrate and glipizide—a technical note. AAPS PharmSciTech. 2006;7(2):E17. DOI: 10.1208/pt070233

97. Liberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: Tablets. 2nd ed. Vol 2. Marcel Dekker; 1990.

98. Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72:163-8.

99. United States Pharmacopeia. USP 39-NF 34. US Pharmacopeial Convention; 2016.

100. Rosa M, Zia H, Rhodes T. Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm. 1994;105(1):65-70. DOI: 10.1016/0378-5173(94)90461-8

101. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63(3):235-59. DOI: 10.1016/S0168-3659(99)00204-7

102. Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing: Pharmatech. 2003:160-6.

103. Shoufeng L, Senshang L, Yeh MK, Chien YW. Extended-release formulation of riboflavin based on multiple-unit floating mini-tablets: in vitro-in vivo studies. J Drug Target. 2001;9(3):219-32. DOI: 10.3109/10611860108997930

104. Li S, Lin S, Chien YW, Daggy BP, Mirchandani HL. Statistical optimization of gastric floating system for oral controlled delivery of calcium. AAPS PharmSciTech. 2001;2(1):E1. DOI: 10.1208/pt020101

105. Desai S, Bolton S. A floating controlled-release drug delivery system: in vitro-in vivo evaluation. Pharm Res. 1993;10(9):1321-5. DOI: 10.1023/A:1018987111179

106. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: a review. Int J PharmTech Res. 2009;1(3):623-33.

107. Badoni A, Ojha A, Gnanarajan G, Kothiyal P. Review on gastroretentive drug delivery system. Pharma Innovation J. 2012;1(8):32-42.

108. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-33. DOI: 10.1016/S0928-0987(01)00095-1

109. Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52(12):1145-9. DOI: 10.1002/jps.2600521210

110. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985;60(4):110-1.

111. Wilding IR, Coupe AJ, Davis SS. The role of gamma-scintigraphy in oral drug delivery. Adv Drug Deliv Rev. 2001;46(1-3):103-24. DOI: 10.1016/S0169-409X(00)00134-5

112. Harris D, Fell JT, Sharma HL, Taylor DC. Gamma scintigraphy: its role in the development of novel

drug delivery systems. J Drug Target. 1993;1(1):3-15. DOI: 10.3109/10611869308996063

113. Wilding IR, Davis SS, Pozzi F, Furlani P, Gazzaniga A. Enteric coated timed release systems for colonic targeting. Int J Pharm. 1994;111(2):99-102. DOI: 10.1016/0378-5173(94)90402-2

114. Weitschies W, Wedemeyer RS, Kosch O, Fach K, Nagel S, Söderlind E, et al. Impact of the intragastric location of extended release tablets on food interactions. J Control Release. 2005;108(2-3):375-85. DOI: 10.1016/j.jconrel.2005.08.018

115. Maurer JM, Schellekens RC, van Rieke HM, Wanke C, Iordanov V, Stellaard F, et al. Gastrointestinal pH and transit time profiling in healthy volunteers using the IntelliCap system confirms ileo-colonic release of ColoPulse tablets. PLoS One. 2015;10(7):e0129076. DOI: 10.1371/journal.pone.0129076

116. Sanford M, Scott LJ. Levodopa/carbidopa intestinal gel: a review of its use in advanced Parkinson's disease. CNS Drugs. 2011;25(3):251-64. DOI: 10.2165/11204610-000000000-00000

117. Lee YH, Choi HG, Jung JH, Yoon IJ, Kim DD, Kim JO, et al. Comparison of metoprolol release characteristics from hypromellose and gellan gum matrices. Pharmazie. 2009;64(12):831-3.

118. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. Marcel Dekker; 1982.

119. Shargel L, Wu-Pong S, Yu AB. Applied Biopharmaceutics & Pharmacokinetics. 5th ed. McGraw-Hill; 2005.

120. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hussain AS, et al. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm. 2004;1(1):85-96. DOI: 10.1021/mp034006h

121. Kristensen HG, Schaefer T. Drug release from hard gelatin capsules: release profile. Drug Dev Ind Pharm. 1987;13(8):1463-83. DOI: 10.3109/03639048709068675

122. Kawashima Y, Niwa T, Handa T, Takeuchi H, Iwamoto T, Itoh K. Preparation of controlled-release microspheres of ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method. J Pharm Sci. 1989;78(1):68-72. DOI: 10.1002/jps.2600780117

123. Asnaashari S, Khoei NS, Zarrintan MH, Adibkia K, Javadzadeh Y. Preparation and evaluation of novel metronidazole sustained release and floating matrix tablets. Pharm Dev Technol. 2011;16(4):400-7. DOI: 10.3109/10837451003739289

124. Talukder R, Fassihi R. Gastroretentive delivery systems: hollow beads. Drug Dev Ind Pharm. 2004;30(4):405-12. DOI: 10.1081/DDC-120030937

125. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm. 2001;220(1-2):13-21. DOI: 10.1016/S0378-5173(01)00574-7

126. Goole J, Amighi K. 3D printing in pharmaceutics: a new tool for designing customized drug delivery systems. Int J Pharm. 2016;499(1-2):376-94. DOI: 10.1016/j.ijpharm.2015.12.071

127. Chen J, Blevins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. J Control Release. 2000;64(1-3):39-51. DOI: 10.1016/S0168-3659(99)00139-X

128. Wen H, Park K. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. John Wiley & Sons; 2010.

129. Reddy AS, Suryakala D, Rao KVSR. Formulation and evaluation of floating microspheres of metoprolol succinate. Int J Res Dev Pharm Life Sci. 2016;5(1):1994-2002.

130. Thulluru A, Shankar GS, Rao MEB. Formulation and evaluation of gastroretentive floating tablets of metoprolol succinate. Int J Pharm Sci Res. 2015;6(4):1491-500. DOI: 10.13040/IJPSR.0975-8232.6(4).1491-500

131. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. Pharmaceutics. 2019;11(4):193. DOI: 10.3390/pharmaceutics11040193

132. Patwekar SL, Baramade MK, Potulwar AP, Gaikwad NJ, Suryavanshi SV, Patwekar F. Formulation and evaluation of gastroretentive drug delivery system using floating microspheres. Int J Drug Deliv. 2011;3(1):115-21.

133. Patel H, Patel J, Patel R, Patel M. Gastroretentive drug delivery system: a review. Int J Pharm Sci Rev Res. 2010;1(2):73-8.

134. Jain CP, Vyas SP. Preparation and characterization of niosomes containing rifampicin for lung targeting. J Microencapsul. 1995;12(4):401-7. DOI: 10.3109/02652049509015293

135. Makwana A, Sameja K, Parekh H, Pandya Y. Advancements in controlled release gastroretentive drug delivery system: a review. J Drug Deliv Ther. 2012;2(3):12-21.

136. Kaza R, Usharani E, Nagaraju R, Haribabu R, Reddy CLN. Design and evaluation of sustained release floating tablets for the treatment of gastric ulcers. J Pharm Sci Res. 2009;1(4):81-7.

137. Patel VF, Patel NM. Intragastric floating drug delivery system of cefuroxime axetil: in vitro evaluation. AAPS PharmSciTech. 2006;7(1):E17. DOI: 10.1208/pt070117

138. Sriamornsak P, Thirawong N, Weerapol Y, Nunthanid J, Sungthongjeen S. Swelling and erosion of pectin matrix tablets and their impact on drug release behavior. Eur J Pharm Biopharm. 2007;67(1):211-9. DOI: 10.1016/j.ejpb.2006.12.014

139. US Patent 6488962 B1. Tablet dosage form for increasing gastric retention of swellable controlled-release dosage forms. 2002.

140. US Patent 6710126 B1. Superporous hydrogel composites having fast swelling, high mechanical strength, and superabsorbent properties. 2001.

141. WO Patent 2002102415 A1. Gastric floating system. 2002.

142. US Patent 2008/0220060 A1. Gastroretentive compositions and methods of preparation thereof. 2008.

143. WO Patent 2011048494 A2. Novel gastroretentive dosage forms for poorly soluble drugs. 2010.

144. WO Patent 2011151708 A1. Gastroretentive dosage forms of gaba analogs. 2011.

145. US Patent 8808669 B2. Extended-release gastroretentive therapeutic agent composition. 2014.