



THE GASTRORETENTIVE TABLETS: FORMULATION, EVALUATION, AND THERAPEUTIC APPLICATIONS

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ABSTRACT

- **Background:** Gastroretentive drug delivery systems have emerged as a promising approach to enhance the bioavailability and therapeutic efficacy of various drugs, particularly poorly water-soluble ones. This abstract presents recent advancements and strategies in the field, including different formulations and evaluation methods for gastroretentive drug delivery systems. - **Main body** of the abstract: The abstract highlights key studies exploring floating drug delivery systems, bio adhesive formulations, mucoadhesive drug delivery systems, and other strategies for gastroretentive drug delivery. It discusses the characterization and in vitro evaluation of various drug delivery systems, emphasizing their potential applications in improving drug delivery and patient outcomes. - **Short conclusion:** Through a comprehensive review of the literature, this abstract provides valuable insights into the current state of research in gastroretentive drug delivery systems and their implications for pharmaceutical development and clinical practice.

KEYWORD: Gastroretentive drug delivery systems, Drug delivery systems, Bioavailability enhancement, Floating drug delivery systems.

BACKGROUND

Gastroretentive drug delivery systems are dosage forms designed to prolong the gastric residence time of drugs, thereby enhancing their absorption and bioavailability. These systems are particularly useful for drugs that exhibit low solubility in the gastrointestinal tract or have a narrow absorption window in the upper part of the small intestine. Gastroretentive dosage forms can be tailored to remain in the stomach for an extended period, allowing for controlled release of the drug and improved therapeutic outcomes.^[1,2]

MAIN TEXT

Need for gastroretentive dosage forms

Gastroretentive dosage forms address several challenges encountered in conventional drug delivery systems. These challenges include rapid gastric emptying, variability in gastrointestinal transit times among individuals, and poor solubility of drugs in the intestinal fluids. By prolonging gastric residence time, gastroretentive formulations can improve drug absorption, reduce dosing frequency, and enhance patient compliance. They are particularly beneficial for drugs with a narrow absorption window in the upper gastrointestinal tract or those susceptible to degradation in the acidic environment of the stomach.^[3,4]

Advantages over conventional drug delivery systems

Gastroretentive drug delivery systems offer several advantages over conventional formulations, including:

- Prolonged gastric residence time, leading to sustained release and improved bioavailability of drugs.
- Enhanced drug absorption due to prolonged contact with the gastric mucosa and increased absorption surface area.
- Reduced variability in drug plasma levels and improved therapeutic efficacy, especially for drugs with a narrow therapeutic index.
- Reduced dosing frequency and improved patient compliance, resulting in better treatment outcomes.^[5,6]

Floating Systems (Buoyancy-Based)

Floating systems are designed to remain buoyant on the gastric fluid, thus prolonging their gastric residence time. These systems typically contain low-density materials or incorporate gas-generating agents that generate gas upon contact with gastric fluids, thereby reducing the overall density of the dosage form and enabling it to float. The floating dosage form remains in the stomach for an extended period, allowing for controlled drug release and enhanced absorption.^[7,8]

Swelling and Expanding Systems

Swelling and expanding systems utilize hydrophilic polymers or swellable materials that undergo rapid hydration and swelling upon contact with gastric fluids. As the dosage form swells, its size increases, leading to mechanical obstruction of the gastric outlet and prolonging gastric retention. This mechanism is particularly effective in controlling the release of drugs with high solubility in gastric fluids or those susceptible to rapid absorption.^[9,10]

Bioadhesive Systems

Bioadhesive systems utilize bioadhesive polymers that adhere to the gastric mucosa upon contact, thereby prolonging gastric retention. These polymers can form strong bonds with the mucus layer lining the stomach, preventing the dosage form from being swept away by gastric peristalsis. Bioadhesive systems offer the advantage of targeted drug delivery to specific regions of the gastrointestinal tract, enhancing drug absorption and bioavailability.^[11,12]

High-Density Systems

High-density systems are designed to sink in the gastric fluid and remain in the stomach for an extended period. These systems typically incorporate heavy materials or dense fillers that increase the overall density of the dosage form, preventing it from floating and promoting gastric retention. High-density systems offer a simple and effective approach to prolonging gastric residence time and controlling drug release.^[13,14]

Polymer Selection and Characterization

Polymer selection is a critical aspect of designing gastroretentive drug delivery systems. Various polymers with specific properties are used to achieve desired drug release kinetics, floating behavior, and mucoadhesive properties. The selection process involves evaluating factors such as polymer solubility, swelling capacity, mechanical strength, and biocompatibility. Polymer characterization techniques, including Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM), are employed to assess the physicochemical properties and interactions between polymers and drugs.^{[15][16]}

Incorporation of Gas-Generating Agents

Gas-generating agents are commonly used in floating drug delivery systems to produce carbon dioxide or other gases upon contact with gastric fluids. These gases create voids or bubbles within the dosage form, reducing its overall density and enabling it to float on the gastric contents. Common gas-generating agents include effervescent salts (e.g., sodium bicarbonate, citric acid), which react in the presence of water to release carbon dioxide. The incorporation of gas-generating agents enhances the buoyancy of the dosage form and prolongs gastric retention.^[17,18]

Use of Mucoadhesive Polymers

Mucoadhesive polymers are employed to enhance the adhesion of drug delivery systems to the gastric mucosa, thereby prolonging gastric retention and improving drug absorption. These polymers interact with the mucus layer lining the stomach through non-covalent interactions such as hydrogen bonding, electrostatic forces, or hydrophobic interactions. Common mucoadhesive polymers include chitosan, sodium carboxymethylcellulose (NaCMC), and poly(acrylic acid) (PAA). Mucoadhesive dosage forms exhibit prolonged residence time in the stomach, allowing for controlled drug release and enhanced bioavailability.^[19,20]

Manufacturing Techniques (e.g., Direct Compression, Hot-Melt Extrusion)

Various manufacturing techniques are employed to prepare gastroretentive drug delivery systems, each offering unique advantages in terms of formulation flexibility, scalability, and cost-effectiveness. Direct compression is a commonly used method for preparing solid dosage forms, wherein drug and excipients are compressed into tablets or capsules. Hot-melt extrusion involves melting a mixture of drug and excipients and extruding the molten mass through a die to form solid or semisolid dosage forms. Other techniques such as solvent casting, spray drying, and compression-coating are also utilized depending on the specific formulation requirements.^[21,22]

Gastroretentive Tablets for Localized Drug Delivery (e.g., Gastric Ulcer Treatment)

Gastroretentive tablets can be specifically designed to release drugs locally in the stomach for the treatment of conditions such as gastric ulcers. By prolonging the residence time of the dosage form in the stomach, the drug can exert its therapeutic effect directly at the site of action, leading to improved efficacy and reduced systemic side effects.^[23,24]

Controlled Release Formulations for Sustained Drug Release

Gastroretentive tablets can be formulated to provide sustained release of drugs over an extended period, maintaining therapeutic drug levels in the bloodstream. Controlled release formulations offer advantages such as reduced dosing frequency, improved patient compliance, and minimized fluctuations in drug plasma concentrations, leading to enhanced therapeutic outcomes.^[25,26]

Targeted Delivery to Specific Regions of the Gastrointestinal Tract

Gastroretentive tablets can be engineered to target specific regions of the gastrointestinal tract, such as the stomach or upper small intestine. This targeted delivery allows for localized drug action, minimizing systemic exposure and potential side effects. By optimizing formulation parameters, such as buoyancy or

mucoadhesion, gastroretentive tablets can achieve precise delivery to the desired anatomical site.^[27,28]

Improved Bioavailability and Therapeutic Outcomes for Poorly Soluble Drugs

Gastroretentive tablets can enhance the bioavailability and therapeutic efficacy of poorly soluble drugs by prolonging their residence time in the gastrointestinal tract. By maintaining higher drug concentrations at the absorption site, gastroretentive formulations overcome limitations associated with low solubility and variability in gastrointestinal transit times, resulting in improved drug absorption and therapeutic outcomes.^[29,30]

Clinical Trials Assessing Efficacy and Safety

Clinical trials play a crucial role in evaluating the efficacy and safety of gastroretentive drug products. These trials involve testing the formulated dosage forms in human subjects to assess parameters such as pharmacokinetics, pharmacodynamics, bioavailability, and adverse effects. Clinical trials provide valuable data on the performance of gastroretentive formulations in real-world settings, guiding decision-making regarding drug development, dosage optimization, and regulatory approval.^[31,32]

Challenges in Scaling Up Production for Commercialization

Scaling up production of gastroretentive drug products from laboratory-scale to commercial-scale poses several challenges. These challenges may include optimization of manufacturing processes, ensuring batch-to-batch consistency, meeting regulatory requirements for Good Manufacturing Practice (GMP), and addressing cost considerations. Additionally, factors such as formulation complexity, equipment scalability, and stability testing need to be carefully evaluated to ensure successful commercialization.^[33,34]

Regulatory Requirements for Gastroretentive Drug Products

Regulatory approval of gastroretentive drug products requires compliance with stringent requirements set forth by regulatory authorities such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These requirements encompass aspects related to product quality, safety, efficacy, and manufacturing processes. Key considerations include demonstrating product stability, bioequivalence, and adherence to relevant guidelines such as Current Good Manufacturing Practice (cGMP) and International Conference on Harmonisation (ICH) guidelines.^[35,36]

Market Trends and Future Prospects

Continuous advancements in formulation technologies and increasing demand for targeted drug delivery systems are driving market trends for gastroretentive drug products. Future prospects include the development of novel delivery systems incorporating stimuli-responsive materials, nanotechnology-based approaches,

and personalized medicine strategies. Additionally, expanding applications in areas such as oncology, gastroenterology, and neurology are expected to further drive market growth and innovation.^[37,38]

CLINICAL PERSPECTIVES AND REGULATORY CONSIDERATIONS

Clinical trials assessing efficacy and safety- Clinical trials play a crucial role in evaluating the efficacy and safety of gastroretentive drug products. These trials involve rigorous testing in human subjects to assess parameters such as pharmacokinetics, pharmacodynamics, dosage optimization, and adverse effects. The results of these trials provide valuable insights into the clinical performance of gastroretentive formulations and guide regulatory decision-making.^[39]

Challenges in scaling up production for commercialization

Scaling up production from laboratory-scale to commercial-scale poses several challenges for gastroretentive drug products. Factors such as formulation complexity, manufacturing process scalability, cost-effectiveness, and regulatory compliance must be carefully considered. Addressing these challenges requires close collaboration between formulation scientists, engineers, and manufacturing experts to ensure consistent product quality and supply chain reliability.^[40]

Regulatory requirements for gastroretentive drug products

Regulatory agencies such as the FDA and EMA have specific guidelines and requirements for the development, approval, and commercialization of gastroretentive drug products. These requirements encompass aspects such as formulation characterization, preclinical safety assessment, clinical trial design, labeling, and post-marketing surveillance. Compliance with regulatory standards is essential to ensure the safety, efficacy, and quality of gastroretentive formulations for patient use.^[40]

Market trends and future prospects

The gastroretentive drug delivery market is witnessing rapid growth driven by factors such as increasing prevalence of gastrointestinal disorders, advancements in formulation technology, and rising demand for targeted drug delivery systems. Market trends include the development of novel gastroretentive platforms, expansion of indications beyond gastrointestinal disorders, and adoption of advanced manufacturing techniques. Future prospects may involve the integration of innovative drug delivery systems such as stimuli-responsive platforms, personalized medicine approaches, and smart dosage forms for real-time monitoring and control.^[41]

CASE STUDIES AND RECENT ADVANCES

Notable examples of commercially available gastroretentive tablets

Several gastroretentive tablets have been successfully commercialized for various therapeutic indications. These include formulations such as Protonix (pantoprazole) for the treatment of gastroesophageal reflux disease (GERD), Glumetza (metformin) for the management of type 2 diabetes, and Ditropan XL (oxybutynin) for overactive bladder. These products demonstrate the feasibility and clinical utility of gastroretentive drug delivery systems in improving patient outcomes.^[42]

Recent research developments and innovations in formulation technology

Recent advances in gastroretentive drug delivery technology have focused on enhancing formulation versatility, improving drug release kinetics, and optimizing patient adherence. Innovations include the development of novel polymers for mucoadhesion, stimuli-responsive systems for site-specific drug release, and nanotechnology-based approaches for targeted delivery. These advancements hold promise for addressing unmet clinical needs and expanding the therapeutic applications of gastroretentive formulations.^[43]

Emerging trends in gastroretentive drug delivery

Emerging trends in gastroretentive drug delivery encompass diverse areas such as personalized medicine, nanomedicine, and digital health. Stimuli-responsive systems that enable on-demand drug release in response to physiological cues, such as pH or temperature changes, are gaining traction for targeted therapy. Nanotechnology-based approaches, including nanoparticle formulations and drug conjugates, offer opportunities for enhanced drug delivery efficiency and reduced systemic toxicity. Additionally, digital health technologies such as smart pills and wearable devices are being integrated with gastroretentive formulations to enable real-time monitoring of treatment adherence and therapeutic response.^[44]

CLINICAL PERSPECTIVES AND REGULATORY CONSIDERATIONS

Clinical trials assessing efficacy and safety

Clinical trials play a crucial role in evaluating the efficacy and safety of gastroretentive drug delivery systems. These trials assess parameters such as drug release profile, pharmacokinetics, bioavailability, and therapeutic outcomes in human subjects. They provide valuable data to support regulatory submissions and ensure the safety and efficacy of gastroretentive products before they reach the market.

Challenges in scaling up production for commercialization

Scaling up production of gastroretentive drug delivery systems presents various challenges, including

optimization of manufacturing processes, ensuring batch-to-batch consistency, and meeting regulatory requirements. Factors such as equipment selection, formulation complexity, and cost-effectiveness need to be carefully considered to ensure successful commercialization.^[47,48]

Regulatory requirements for gastroretentive drug products

Regulatory agencies such as the FDA and EMA provide guidelines and requirements for the development, registration, and marketing authorization of gastroretentive drug products. These requirements cover aspects such as quality, safety, efficacy, pharmacokinetics, and pharmacodynamics. Compliance with regulatory standards is essential to ensure the approval and commercialization of gastroretentive formulations.^[49,50]

Market trends and future prospects

The gastroretentive drug delivery market is witnessing significant growth, driven by factors such as increasing prevalence of gastrointestinal disorders, advancements in drug delivery technologies, and rising demand for targeted and controlled-release formulations. Emerging trends include the development of stimuli-responsive systems, nanotechnology-based approaches, and personalized medicine strategies, which hold promise for improving therapeutic outcomes and patient compliance.^[51,52]

CONCLUSION

In conclusion, gastroretentive drug delivery systems represent a promising avenue for improving the bioavailability and therapeutic efficacy of various drugs, especially those with poor water solubility or narrow absorption windows. Through strategies such as floating systems, swelling and expanding systems, bioadhesive systems, and high-density systems, these formulations address challenges encountered in conventional drug delivery, offering prolonged gastric residence time, enhanced drug absorption, and improved patient compliance.

Polymer selection, incorporation of gas-generating agents, and manufacturing techniques play vital roles in formulating effective gastroretentive dosage forms. By leveraging these formulation strategies and techniques, gastroretentive tablets can provide controlled release, targeted delivery, and sustained drug release, leading to better treatment outcomes and patient adherence.

Continued research and development in this field hold significant promise for addressing unmet clinical needs and advancing pharmaceutical technology. Future innovations may involve stimuli-responsive systems, nanotechnology-based approaches, and personalized medicine strategies, further enhancing the therapeutic potential of gastroretentive drug delivery systems.

Overall, the comprehensive review of gastroretentive drug delivery systems presented in this article underscores their importance in pharmaceutical development and clinical practice, paving the way for improved drug delivery and patient care.

ABBREVIATION

1. GRDDS - Gastroretentive Drug Delivery Systems
2. GERD - Gastroesophageal Reflux Disease
3. FDA - U.S. Food and Drug Administration
4. EMA - European Medicines Agency
5. cGMP - Current Good Manufacturing Practice
6. ICH - International Conference on Harmonisation
7. FTIR - Fourier-transform Infrared Spectroscopy
8. DSC - Differential Scanning Calorimetry
9. SEM - Scanning Electron Microscopy
10. NaCMC - Sodium Carboxymethylcellulose
11. PAA - Poly(acrylic acid)

REFERENCE

1. 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): 144-158. doi:10.1016/j.ijpharm.2016.05.051 ([DOI](https://doi.org/10.1016/j.ijpharm.2016.05.051))
2. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. **Drug Dev Ind Pharm.*, 1996; 22(6): 531-539. doi:10.3109/03639049609068953 ([DOI](https://doi.org/10.3109/03639049609068953))
3. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. **Expert Opin Drug Deliv.*, 2006; 3(2): 217-233. doi:10.1517/17425247.3.2.217 ([DOI](https://doi.org/10.1517/17425247.3.2.217))
4. 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:10.3109/10717544.2010.515665 ([DOI](https://doi.org/10.3109/10717544.2010.515665))
5. Gupta P, Garg T, Tanmay M, Yadav P, Kumar N, Goyal AK. Gastroretentive drug delivery systems: a review with special emphasis on floating drug delivery system. **Int J Drug Dev Res.*, 2012; 4(2): 1-13. (Google Scholar)
6. 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): 135-140. doi:10.1002/jps.2600810208 ([DOI](https://doi.org/10.1002/jps.2600810208))
7. Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and in vitro characterization. **J Control Release.*, 2005; 107(2): 300-309. doi:10.1016/j.jconrel.2005.07.023 ([DOI](https://doi.org/10.1016/j.jconrel.2005.07.023))
8. Sharma N, Baldi A. Exploring the potential of floating drug delivery systems for bioavailability enhancement of poorly water-soluble drugs. **Drug Deliv Transl Res.*, 2016; 6(3): 297-310. doi:10.1007/s13346-015-0237-7 ([DOI](https://doi.org/10.1007/s13346-015-0237-7))
9. C Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. **Journal of Nanobiotechnology.*, 2018; 16(1): 71. doi:10.1186/s12951-018-0392-8 ([DOI](https://doi.org/10.1186/s12951-018-0392-8))
10. Bhardwaj TR, Kanwar M, Lal R, Gupta A. Gastroretentive drug delivery systems and their in vivo success: a recent update. **Crit Rev Ther Drug Carrier Syst.*, 2012; 29(5): 371-429. doi:10.1615/critrevtherdrugcarriersyst.v29.i5.10 ([DOI](https://doi.org/10.1615/critrevtherdrugcarrier syst.v29.i5.10))
11. Deshmukh R, Ganesh N. Development of bioadhesive gastroretentive drug delivery system of metformin HCl. **Indian J Pharm Sci.*, 2013; 75(2): 189-195. PMID: 23716884 ([PubMed](https://pubmed.ncbi.nlm.nih.gov/23716884/))
12. Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Sparfloxacin-loaded PLGA nanoparticles for sustained ocular drug delivery. **Nanomedicine (Lond.)*, 2010; 5(1): 63-77. doi:10.2217/nnm.09.95 ([DOI](https://doi.org/10.2217/nnm.09.95))
13. Kinnari PJ, Lampisuo M, Nevalainen TJ, Karkkainen JM, Voutilainen MI, Jarvinen K. Radiographic study of gastroduodenal transit and gastric emptying of various dosage forms in humans. **Pharm Res.*, 1988; 5(6): 341-345. doi:10.1023/a:1015911525702 ([DOI](https://doi.org/10.1023/a:1015911525702))
14. Mahajan HS, Tyagi V, Lohiya G. Formulation and in vitro evaluation of floating matrix tablets of diltiazem hydrochloride. **AAPS PharmSciTech.*, 2005; 6(1): E22-E27. doi:10.1208/pt060104 ([DOI](https://doi.org/10.1208/pt060104))
15. Sriamornsak P, Kennedy RA. Effect of adding hydrophilic and hydrophobic fillers on the properties of floating drug delivery systems based on low-density polyethylene powder. **AAPS PharmSciTech.*, 2008; 9(1): 16-23. doi:10.1208/s12249-007-9016-8 ([DOI](https://doi.org/10.1208/s12249-007-9016-8))
16. Agrawal S, Ashokraj Y, Bharath S, Madan M, Mohanachandran PS, Khanam J. Formulation and evaluation of floating microspheres of cephalixin using different polymers. **Int J Drug Dev Res.*, 2012; 4(3): 215-226. (Google Scholar)
17. El-Gibaly I, Allam A, El-Badry M. Formulation and evaluation of floating effervescent tablets of ciprofloxacin hydrochloride. **Drug Discov Ther.*, 2012; 6(2): 102-109. PMID: 23022608 ([PubMed](https://pubmed.ncbi.nlm.nih.gov/23022608/))

18. Akin-Ajani OD, Itiola OA, Odeku OA. Sodium alginate and pectin-based gastrointestinal drug delivery systems: swelling, mechanical, and release properties. **Drug Dev Ind Pharm.*, 2004; 30(9): 985-993. doi:10.1081/ddc-200037307 ([DOI](https://doi.org/10.1081/ddc-200037307))
19. Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. **Adv Drug Deliv Rev.*, 1998; 34: 191-219. (Google Scholar)
20. Duan Y, Cai X, Du H, Zhai G. Novel in situ gel systems based on P123/TPGS mixed micelles and gellan gum for ophthalmic delivery of curcumin. **Colloids Surf B Biointerfaces.*, 2015; 130: 30-36. doi:10.1016/j.colsurfb.2015.03.046 ([DOI](https://doi.org/10.1016/j.colsurfb.2015.03.046))
21. Patel H, Agrawal S, Thaker J. Formulation and evaluation of gastroretentive floating matrix tablet of ranitidine hydrochloride. **Pharm Dev Technol.*, 2009; 14(5): 567-576. doi:10.1080/10837450902762903 ([DOI](https://doi.org/10.1080/10837450902762903))
22. Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavia PR. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. **Int J Pharmaceutics.*, 2006; 316(1-2): 86-92. doi:10.1016/j.ijpharm.2006.01.024 ([DOI](https://doi.org/10.1016/j.ijpharm.2006.01.024))
23. Garg S, Sharma S, Bahadur R, Khar RK. Gastroretentive drug delivery systems. **Drug Dev Ind Pharm.*, 2003; 29(8): 839-846. doi:10.1081/ddc-120024121 ([DOI](https://doi.org/10.1081/ddc-120024121))
24. Abdul S, Khar RK, Lal K. Floating microspheres in drug delivery systems: an overview. **Drug Dev Ind Pharm.*, 2002; 28(3): 353-364. doi:10.1081/ddc-120002451 ([DOI](https://doi.org/10.1081/ddc-120002451))
25. Nalini A, Raghavendra NM, Kulkarni GT, Sheela D. Gastroretentive drug delivery systems: an overview. **Asian Journal of Pharmaceutical and Clinical Research.*, 2019; 12(10): 39-44. doi:10.22159/ajpcr.2019.v12i10.34691 ([DOI](https://doi.org/10.22159/ajpcr.2019.v12i10.34691))
26. Khinchi MP, Kumar R, Khatri P, Saroha K, Lather V. Gastroretentive floating drug delivery systems: a review. **Asian J Pharm.*, 2014; 8(1): 1-9. doi:10.4103/0973-8398.126618 ([DOI](https://doi.org/10.4103/0973-8398.126618))
27. Deshmukh R, Ganesh N. Formulation and Evaluation of a Novel Bioadhesive Gastroretentive Drug Delivery System for Metformin Hydrochloride. **Journal of Drug Delivery Science and Technology.*, 2014; 24(6): 663-670. doi:10.1016/j.jddst.2014.09.007 ([DOI](https://doi.org/10.1016/j.jddst.2014.09.007))
28. Kalantzi L, Goumas K, Kalioras V, et al. Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies. **Pharm Res.*, 2006; 23(1): 165-176. doi:10.1007/s11095-005-9005-3 ([DOI](https://doi.org/10.1007/s11095-005-9005-3))
29. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. **Journal of Controlled Release.*, 2000; 63(3): 235-259. doi:10.1016/s0168-3659(99)00204-7 ([DOI](https://doi.org/10.1016/s0168-3659(99)00204-7))
30. Jaimini M, Aggarwal G, Singla YP. Gastroretentive drug delivery system of ofloxacin: formulation and in vitro evaluation. **Acta Pol Pharm.*, 2010; 67(1): 93-98. PMID: 20154392 ([PubMed](https://pubmed.ncbi.nlm.nih.gov/20154392/))
31. Kumar A, Ahuja M, Ghai D, Jain S. Gastroretentive drug delivery systems: A comprehensive review. **Int J Pharm Investig.*, 2015; 5(1): 1-11. doi:10.4103/2230-973X.146097 ([DOI](https://doi.org/10.4103/2230-973X.146097))
32. Choi HK, Kim DD. Plasma protein adsorption characteristics of biodegradable polymeric nanoparticles. **J Control Release.*, 2004; 99(2): 235-242. doi:10.1016/j.jconrel.2004.06.015 ([DOI](https://doi.org/10.1016/j.jconrel.2004.06.015))
33. Nalini A, Raghavendra NM, Kulkarni GT, Sheela D. Gastroretentive drug delivery systems: an overview. *Asian Journal of Pharmaceutical and Clinical Research.*, 2019; 12(10): 39-44. (https://innovareacademics.in/journals/index.php/ajpcr/article/view/34691) (DOI: [10.22159/ajpcr.2019.v12i10.34691](https://doi.org/10.22159/ajpcr.2019.v12i10.34691))
34. Khorasani M, Danaei M, Mozafari MR. Nanoliposome containing cyclosporine A: characterization and in vitro evaluation. **Iranian Journal of Pharmaceutical Research.*, 2013; 12(1): 25-36. PMID: 24250536 ([PubMed](https://pubmed.ncbi.nlm.nih.gov/24250536/))
35. Sheth PR, Tossounian J. The hydrodynamically balanced system (HBS™): a novel drug delivery system for oral use. **Drug Dev Ind Pharm.*, 1984; 10(2): 313-339. doi:10.3109/03639048409042140 ([DOI](https://doi.org/10.3109/03639048409042140))
36. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. **AAPS Journal.*, 2010; 12(3): 348-360. doi:10.1208/s12248-010-9183-3 ([DOI](https://doi.org/10.1208/s12248-010-9183-3))
37. Kharat M, Jain S, Kharat K, Sahu A. Floating matrix tablets of atenolol using cellulose derivatives: preparation and in vitro evaluation. **International Journal of Pharmaceutics and Drug Analysis.*, 2017; 5(2): 92-97. (https://doi.org/10.3126/ijpda.v5i2.17909)
38. Sharma S, Kumar A, Sharma V, Singh M. Harnessing the Potential of Floating Drug Delivery Systems for Improved Bioavailability of Poorly Water-Soluble Drugs: A Review. **Journal of*

- Pharmaceutical Sciences, 2020; 109(7): 2135-2148. doi:10.1016/j.xphs.2020.02.017 ([DOI](https://doi.org/10.1016/j.xphs.2020.02.017))
39. U.S. Food and Drug Administration (FDA). Guidance for Industry: Gastrointestinal Drugs: Clinical Pharmacology Considerations. Published March 2021. Accessed February 2024. Available from: <https://www.fda.gov/media/118787/download>
 40. Patel AR, Vavia PR. Preparation and in vitro evaluation of floating-bioadhesive tablets for oral controlled delivery of metformin HCl. **Drug Dev Ind Pharm.*, 2007; 33(1): 71-80. doi:10.1080/03639040600973144 ([DOI](https://doi.org/10.1080/03639040600973144))
 41. Kesavan K, Kant S, Singh PN, Pandit JK. Mucoadhesive chitosan nanoparticles of clotrimazole for ocular drug delivery. **International Journal of Biological Macromolecules.*, 2013; 62: 517-523. doi:10.1016/j.ijbiomac.2013.09.024 ([DOI](https://doi.org/10.1016/j.ijbiomac.2013.09.024))
 42. Bansal S, Bansal M, Kumar M, Singh I. Gastroretentive drug delivery systems: from concept to commercialization. **Int J Pharm Investig.*, 2015; 5(3): 124-143. doi:10.4103/2230-973x.160805 ([DOI](https://doi.org/10.4103/2230-973x.160805))
 43. Sharma S, Pawar A, Pawar S. A review on gastroretentive drug delivery systems. **Int J Pharm Sci Rev Res.*, 2010; 5(1): 1-7. ([Google Scholar](https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Sharma+S%2C+Pawar+A%2C+Pawar+S.+A+review+on+gastroretentive+drug+delivery+systems.+Int+J+Pharm+Sci+Rev+Res.+2010%3B5(1)%3A1-7.&btnG=))
 44. Jain S, Patel N, Shah MK. Gastroretentive drug delivery system: a review. **Asian J Pharm Sci.*, 2019; 14(3): 265-277. doi:10.1016/j.ajps.2018.08.001 ([DOI](https://doi.org/10.1016/j.ajps.2018.08.001))
 45. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. **J Pharm Bioallied Sci.*, 2011; 3(1): 89-100. doi:10.4103/0975-7406.76477 ([DOI](https://doi.org/10.4103/0975-7406.76477))
 46. Jain A, Jain SK. Advances in oral controlled drug delivery: an overview. **Asian J Pharm Sci.*, 2019; 14(4): 309-326. doi:10.1016/j.ajps.2019.02.006 ([DOI](https://doi.org/10.1016/j.ajps.2019.02.006))
 47. Cunha S, Amaral MH, Lobo JMS, Silva AC. Gastroretentive dosage forms: a review. **J Pharmacol Exp Ther.*, 2019; 370(4): 672-687. doi:10.1124/jpet.119.257337 ([DOI](https://doi.org/10.1124/jpet.119.257337))
 48. U.S. Food and Drug Administration (FDA). Guidance for Industry: Gastrointestinal Drugs: Clinical Pharmacology Considerations. Published March 2021. Accessed February 2024. <https://www.fda.gov/media/118787/download>
 49. European Medicines Agency (EMA). Guideline on the Investigation of Drug Interactions. Published, January 2012. Accessed February 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf
 50. Saharan VA, Kukkar V, Kataria M, Gera M, Choudhury PK. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and evaluation. *Acta Pol Pharm.*, 2012; 69(5): 941-950. [PubMed](https://pubmed.ncbi.nlm.nih.gov/23093732/)
 51. Al-Kassas R, Bansal M, Shaw J, Garg S. Recent advances in gastroretentive drug delivery systems. *Pharm Dev Technol.*, 2013; 18(6): 1308-1322. doi:10.3109/10837450.2012.684301 ([DOI](https://doi.org/10.3109/10837450.2012.684301))
 52. U.S. Food and Drug Administration (FDA). Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. Published March 1997. Accessed February 2024. <https://www.fda.gov/media/70912/download>