

# Assessing the potential of gastroretentive technology for gastric cancer targeting

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## ABSTRACT

Gastric cancer is a multifactorial disease and a major cause of mortality across the globe. Initially, gastric cancer reveals no related symptoms; therefore, patients come to the notice of the clinicians only in advanced stages. Chemotherapy, radiation, surgery, immunotherapy, etc. are some of the common treatment interventions for stomach cancer. Traditional oral chemotherapy reveals several limitations, including inadequate oral bioavailability, repeated dosage, low solubility, short gastric residence period, etc. To address these issues, unique technological advancements recognized as gastroretentive drug delivery system (GRDDS) have been explored by scientists globally. The GRDDS has acquired tremendous significance in the avenue of oral drug delivery. This is a frequently utilized and encouraging methodology of retaining the dosage form in the stomach for a prolonged time and slowly releasing the drug, which can address many of the problems associated with traditional oral delivery. The current review addresses the causes of gastric cancer, significant insights, and classification along with treatment strategies for gastric cancer. Advancements in gastroretentive technology in the treatment of stomach cancer are also focused in the present paper.

## INTRODUCTION

Gastric carcinoma is an aggressive malignancy, the most common cancer worldwide and the leading cause of cancer mortality (Olmes and Martinson, 2021; Rawla and Barsouk, 2019). Gastric cancer is also known as stomach cancer. The mucous membrane lining the stomach is made up of columnar epithelial cells and glands. These cells are prone to gastritis, an inflammation that can progress to peptic ulcers and eventually stomach cancer (Rawla and Barsouk, 2019). Various risk factors which contribute to gastric cancer include *Helicobacter pylori* infection (Ahmed, 2005; Biagioni *et al.*, 2019), genetics (Boland and Yurgelun, 2017), intake of salty food (Biagioni *et al.*, 2019;

Tsugane and Sasazuki, 2007), alcohol consumption (Biagioni *et al.*, 2019; Ma *et al.*, 2017), tobacco smoking (Sadjadi *et al.*, 2014), gastroesophageal reflux disease (Wu *et al.*, 2003; Ye *et al.*, 2001), chemical exposure (Chang *et al.*, 2018), radiation (Ali *et al.*, 2018), pernicious anemia (Kuipers, 2015), gastric surgery (Ahn *et al.*, 2008; Komatsu *et al.*, 2012), obesity, and other environmental factors (Lin *et al.*, 2014). However, *H. pylori* infection is more closely associated with gastric cancer and related host gene polymorphism (He *et al.*, 2013; Herrera and Personnet, 2009).

### Classification of gastric cancer

Gastric cancer is a complicated, complex, and heterogeneous disease with various characteristics. The accessible diversity of histological classification systems is due to this variability. The Laurén, WHO, and Goseki classification systems are the most generally used. According to the Laurén classification, there are four forms of gastric adenocarcinomas as diffuse, intestinal, indeterminate, and mixed (Laurén, 1965). The WHO classification is based on the appearance of histomorphology. Gastric can-

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cer is classified as tubular, papillary, mucinous, weakly cohesive (including signet ring cell carcinoma), or mixed carcinomas by the World Health Organization (Berlth *et al.*, 2014; Nagtegaal *et al.*, 2020). The Goseki classification divides gastric cancer into four types based on intracellular mucin production and tubular differentiation. Tubules that are well differentiated but lacking in intracellular mucin are classified as Group I; tubules that are well differentiated but rich in intracellular mucin are classified as Group II; tubules that are poorly differentiated but lacking in intracellular mucin are classified as Group III; tubules that are poorly differentiated but rich in intracellular mucin are classified as Group IV (Fontana *et al.*, 2003; Goseki *et al.*, 1992; Martin *et al.*, 1994; Nagtegaal *et al.*, 2020).

Gastric cancer most likely begins with chronic active gastritis, which progresses through atrophic gastritis, intestinal metaplasia, and dysplasia, ultimately causing stomach cancer. Gastric cancer is attributed to *H. pylori* infection and host gene polymorphism in addition to environmental, dietary, and genetic variables (Fig. 1). Infection with *H. pylori* has been associated with the development of chronic active gastritis, leading to adenocarcinoma (Xiao *et al.*, 2017).

#### Therapeutic aspects of gastric cancer

Gastric cancer treatment requires a multidisciplinary approach for optimal therapy (Fabian and Michael, 2019). Common treatment approaches include surgery, radiation, targeted therapies, immunotherapy, chemotherapy, etc. (Jun *et al.*, 2021; Robert *et al.*, 2018). Surgical resection is one of the curative modalities for localized gastric cancer. However, survival is poor with surgery alone, perioperative chemotherapy or postoperative chemoradiotherapy is required to improve the outcomes of surgical treatment (Charalampakis *et al.*, 2018). Radiation therapy utilized

high-intensity rays for killing the cancerous cell in a specific part of the body (Baskar *et al.*, 2012). In cases of unresectable stomach cancer with anemia and/or pyloric blockage, radiotherapy is indicated. Although the effect is often brief (3–6 months), it is a simple therapeutic approach (Asakura *et al.*, 2011; Tey *et al.*, 2007). Multimodal therapy for gastric cancer also includes targeted therapy in the form of small molecule inhibitors and monoclonal antibodies (Fabian and Michael, 2019). It includes drugs that target human epidermal growth factor receptor, e.g., trastuzumab (Gravalos and Jimeno, 2008), drugs that target vascular endothelial growth factor receptor, e.g., ramucirumab (Fuchs *et al.*, 2014). Immunotherapy involves the utilization of drugs for helping a person's immune system to locate and inhibit cancerous cells significantly (Fabian and Michael, 2019; Jun *et al.*, 2021; Kang *et al.*, 2017; Mellman *et al.*, 2011). Currently, chemotherapy is the most common type of cancer treatment. Chemotherapy uses anticancer drugs that are injected into a vein or given by mouth as pills (Nygren *et al.*, 2001). High doses of chemotherapy drugs, on the other hand, have some side effects because of their rapid release into the gastrointestinal tract. Oral anticancer drugs are associated with a variety of side effects, including systemic side effects, diarrhea, and gastrointestinal disturbances, such as nausea and vomiting (GIT). Therefore, a gastroretentive dosage form with a proper release profile can be considered a fantastic and impressive technology to overcome various side effects associated with conventional formulations (Ehsan *et al.*, 2013).

#### Anticancer drugs for gastric cancer

For the treatment of gastric cancer, a variety of anticancer drugs are utilized, including docetaxel, doxorubicin hydrochloride, 5-fluorouracil, mitomycin, capecitabine, carboplatin, cisplatin, paclitaxel, irinotecan, oxaliplatin, etc. (Sastre *et al.*, 2006).

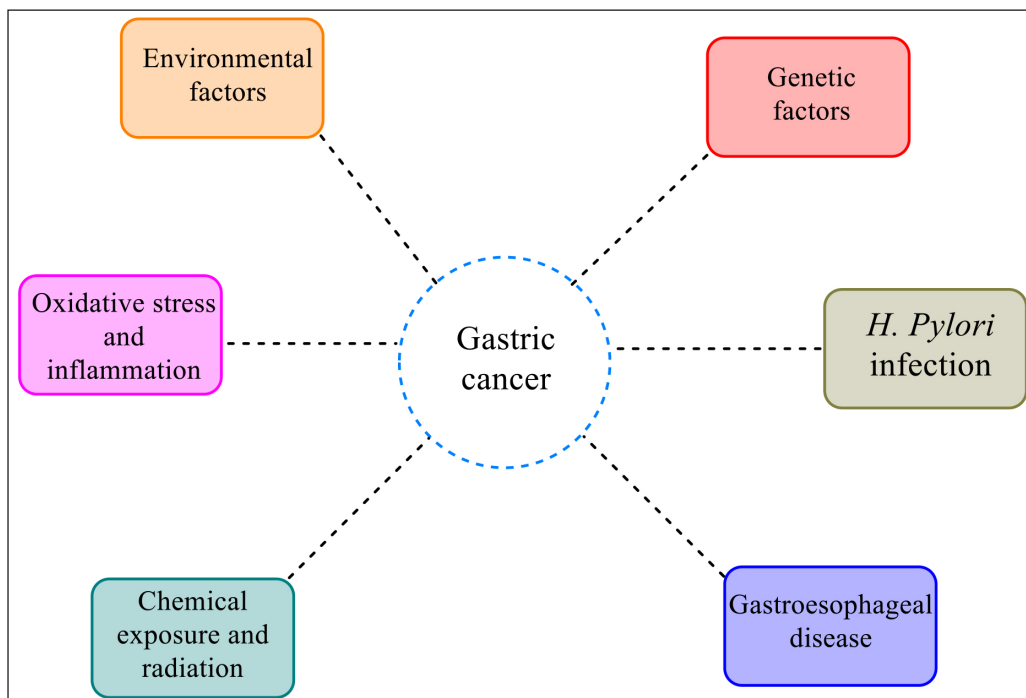


Figure 1. Factors influencing gastric cancer.

Chemotherapy is still the most effective treatment option for stomach cancer. However, traditional oral chemotherapy for gastric cancer suffers from significant limitations such as inadequate absorption, multiple doses, systemic toxicity, etc. (Fig. 2). All of which contribute to poor treatment outcomes. Also, oral chemotherapy may involve low or variable bioavailability, associated with premature drug release, limited drug solubility, and less retention period as well (Narvekar *et al.*, 2014). As a result, novel drug delivery platforms must be designed for managing drug release while simultaneously extending their gastroretentive duration. Gastroretentive drug delivery system (GRDDS) has been successfully designed to retain the dosage form localized precisely in the stomach and extend the dosing interval for stomach cancer (Nana *et al.*, 2019). The gastroretentive floating drug delivery system is particularly well suited to overcome the pharmacokinetic challenges of oral chemotherapy (Mandal *et al.*, 2016). Fabrication of a gastroretentive floating system is also needed to address several issues associated with conventional dosage forms and to maximize oral absorption of various therapeutic molecules with prolonged stomach residence duration and regulated drug delivery (Kotreka and Moji, 2011). Owing to its prolonged gastric residence time (GRT) and controlled drug release input, gastroretentive devices aid in attaining tailored drug release (Verma *et al.*, 2016). The above-described systems can also be utilized to improve the efficacy of anticancer drugs like 5-fluorouracil, with a narrow absorption window (Malik *et al.*, 2015).

### Gastroretentive drug delivery system

The oral route is the most preferred route of administration due to its various important advantages such as administration convenience, high patient compliance, cost-effectiveness, noninvasiveness, etc. (Lee and Mukherjee, 2002; Lopes *et al.*, 2016; Narayana *et al.*, 2010; Rai *et al.*, 2018; Shahiwal, 2011). Nevertheless, owing to the heterogeneity of the gastrointestinal system, the oral drug delivery system faces various limitations such as low bioavailability, gastric retention time variabilities, etc. (Lopes *et al.*, 2016). Various modern technological developments have also resulted in many novel pharmaceutical aspects, especially controlled release systems for solving these constraints (El Nabarawi *et al.*, 2017). Oral controlled release dosage forms have been broadly used for enhancing bioavailability. However, oral controlled systems may also not be able for retaining dosage forms in the stomach for a prolonged time period along with less localization in the desired

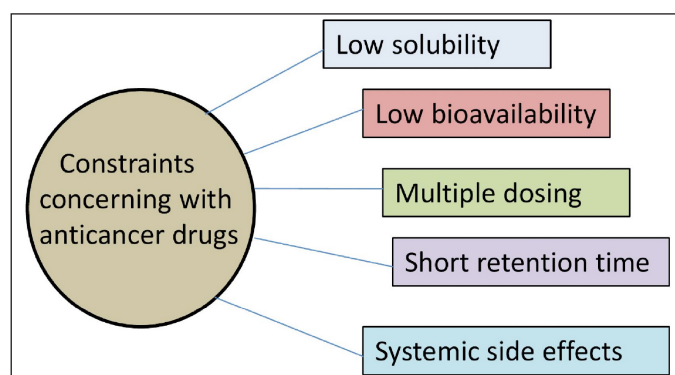


Figure 2. Numerous constraints concerning with anticancer drugs.

region of the gastrointestinal tract (Patil *et al.*, 2006). Therefore, to keep the dosage form in the stomach for the required time, GRDDS are being proposed by scientists in recent years (Awasthi *et al.*, 2014; Das *et al.*, 2020). GRDDS is a novel and advanced approach that not only displays the spatial placement of dosage form retained in the stomach but also offers temporal placement by releasing the drug in a controlled and prolonged manner (Mirani *et al.*, 2016). These systems provide several impressive and pivotal advantages, including extended GRT of dosage forms in the stomach for several hours, improved therapeutic effects of drugs through enhanced drug absorption, and suitable for specific delivery in the gastric region. Furthermore, GRDDS can improve the controlled drug delivery by constantly releasing the drug at the desired rate and at a specific absorption site for an extended period of time until the drug has been released entirely from the dosage form (Pawar *et al.*, 2011; Prajapati *et al.*, 2013; Rouge *et al.*, 1996). Prolonged residence time is highly suitable for drugs that have a narrow window of absorption in the GIT or which are unstable in the colonic and intestine environment or have low solubility in the alkaline pH (Arora *et al.*, 2005; Pahwa *et al.*, 2012b; Shah *et al.*, 2017). A gastroretentive floating system provides feasibility for site-specific delivery; also offers a reduction in a number of doses in the regimen, along with enhanced bioavailability as compared to conventional dosage forms (Chen *et al.*, 2018). Various commercialized formulations based on gastroretentive technology are depicted in Table 1 (Mandal *et al.*, 2016; Pawar *et al.*, 2012).

### Salient advantages

Following advantages of GRDDS are mentioned in the subsequent portion (Krishana *et al.*, 2021; Kumar and Philip, 2007; Pahwa *et al.*, 2011; Pahwa *et al.*, 2012a, 2013; Pahwa *et al.*, 2021). These are evidently portrayed in Figure 3.

- Increased bioavailability of drugs with a narrow window of absorption in the upper gastrointestinal tract.
- Increased patient comfort and compliance as a result of low dose frequency.
- Increased dosage retention time in the stomach.
- Gastric discomfort can be avoided by using a sustained release profile.
- Drug release is consistent, with no possibility of dumping of dose.
- Less inter and intra-subject variability.
- Site specificity.
- Maximum utilization of drugs with minimum side effects.

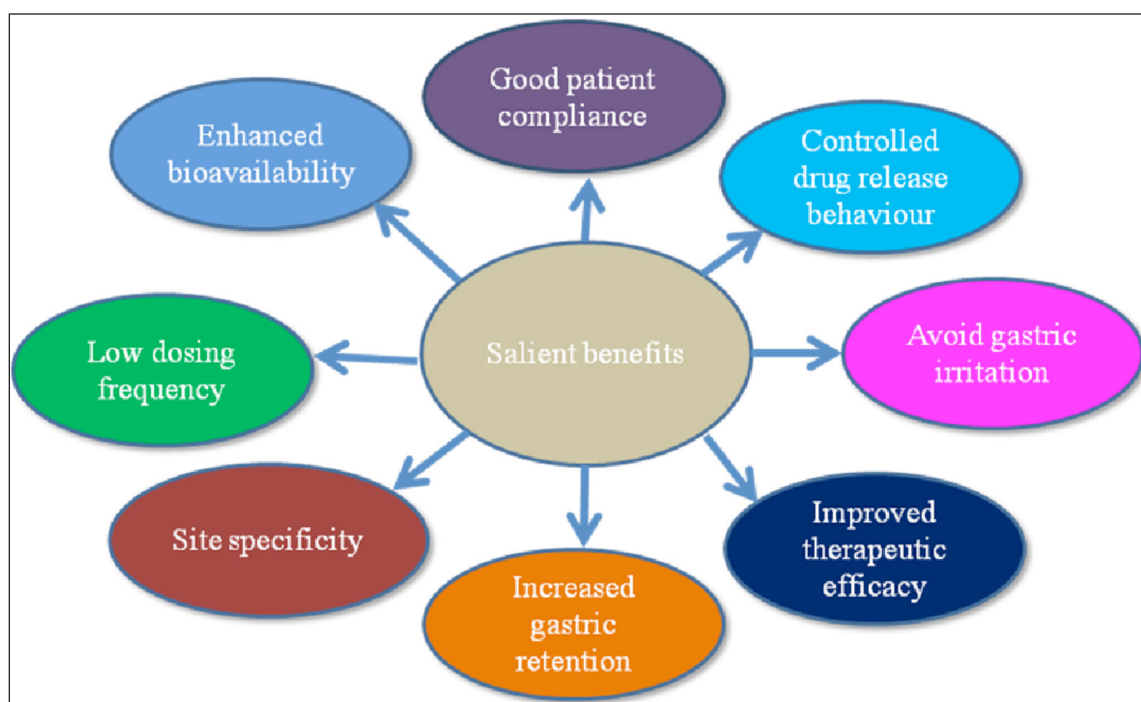
### Drawbacks aspects

However, few limitations associated with the gastroretentive system include drugs with limited solubility and stability in stomach/acidic medium that are not suitable for gastroretentive system. Also, drugs that causes irritation in the stomach cannot be developed into gastroretentive formulations (Adibkia *et al.*, 2011; Kumar and Kaushik, 2018).

The main approaches for gastric retention that have been examined include the floating system (Chen *et al.*, 2018; Mohapatra *et al.*, 2020; Vasvari *et al.*, 2019), expandable system (Zhao *et al.*, 2014), bioadhesive system (Ishak, 2015; Pawar

**Table 1.** List of commercialized gastroretentive formulations.

S. No.	Brand name	Drug	Company	Gastroretentive technology
1.	Cifran OD	Ciprofloxacin	Ranbaxy	Gas generating system
2.	Liquid gaviscon	Aluminium hydroxide and magnesium carbonate	Glaxosmithkline	Effervescent system
3.	Cytotec	Misoprostol	Pharmacia	Bilayer floating capsule
4.	Madopar	Levodopa and benserazide	Roche	Floating capsule
5.	Conviron	Ferrous sulphate	Ranbaxy	Colloidal gel forming floating system
6.	Topalkan	Aluminium and magnesium antacid	Pierre fabre drug	Floating liquid alginate preparation
7.	Valrelease	Diazepam	Roche	Floating capsule
8.	Baclofen GRS	Baclofen	Sun pharma	Coated multi-layer floating and swelling system

**Figure 3.** Salient benefits of GRDDS.

*et al.*, 2012; Raviteja *et al.*, 2014; Simons and Wagner, 2019), high-density system (Du *et al.*, 2019; Prajapati *et al.*, 2011) superporous hydrogels (Bardonnnet *et al.*, 2006; Mirani *et al.*, 2016), magnetic system (Bardonnnet *et al.*, 2006; Melocchi *et al.*, 2019), dual functioning system (Singh and Kim *et al.*, 2000; Tripathi *et al.*, 2019), etc. A floating drug delivery system helps to maintain the prolonged duration of action of drug by enhancing buoyancy over gastrointestinal contents. It aids in reducing the dosage frequency and ultimately improves patient compliance (Arora *et al.*, 2005; Mohapatra *et al.*, 2020). Also, expandable dosage forms withstand stomach transit because of their bigger size than the pyloric spincture diameter (Neumann *et al.*, 2021). Additionally, bioadhesive systems are employed to localize and adhere the delivery device within the lumen to improve absorption of the drug in site-specific manner and extend GRT (Ishak, 2015). Furthermore, high-density system utilizes their weight for gastric retention mechanism. Superporous hydrogel systems with an average pore size > 100  $\mu\text{m}$ , swell to a large size and withstand the pressure of gastric contraction resulting in

gastric retention (Hejaji and Amiji, 2002). In a magnetic system, gastrointestinal transit of dosage form can be controlled by using magnet (Melocchi *et al.*, 2019). Dual functioning system based on the combination of bioadhesion and floating principle provide enhanced bioavailability profile (Singh and Kim *et al.*, 2000). Mechanistic insight for floating system as low-density dosage form which remain buoyant in the gastric fluid for enhanced time period includes effervescent and non-effervescent approaches. Effervescent system employs matrices developed using swellable polymeric materials such as polysaccharides, methocel, etc. along with effervescent components. The system is designed in such a manner that, when it comes into contact with gastric acid, carbon dioxide is generated as a result of an effervescent reaction between organic acid and carbonate-bicarbonate salt. The buoyancy of the dosage form is ultimately maintained by the gas which entrapped inside the gellified hydrocolloids. Non-effervescent systems, comprises gel-forming, swellable, cellulosic hydrocolloids, matrix forming polymers or polysaccharides. Alginate beads, porous systems, hollow microspheres, and hydrodynamically

**Table 2.** Gastroretentive dosage forms in the management of gastric cancer.

S. No	Drug	Gastroretentive dosage forms	Salient findings	Reference(s)
1.	5-fluorouracil	Nanosponge floating tablet	High cytotoxic effect with lower IC <sub>50</sub> value, Good floating behavior and sustained release	(Jasim <i>et al.</i> , 2021)
2.	5-fluorouracil	Gastroretentive nanofibrous film	Improved pharmacokinetic profile, reduced total dose required, increased solubility	(Anothra <i>et al.</i> , 2020)
3.	<i>Brucea javanica</i> oil	Gastroretentive floating beads	Stronger antitumor activity, enhanced absorption, oral bioavailability with longer residence time	(Zhang <i>et al.</i> , 2018)
4.	Sesamol	Floating beads	Sustained curative effect, prolonged drug release profile	(Geetha <i>et al.</i> , 2015)
5.	Curcumin	Gastroretentive tablets	Superior dissolution characteristics, superior biopharmaceutical properties	(Khan <i>et al.</i> , 2015)
6.	Curcumin	Floating sponges	Higher relative bioavailability, sustained drug release at the site of action	(Arya <i>et al.</i> , 2014)
7.	5-fluorouracil	Hollow floating microspheres	Controlled drug release profile and GIT retention for prolonged period of time	(Bhardwaj <i>et al.</i> , 2014)
8.	Curcumin	Gastroretentive floating tablets	Enhanced solubility, bioavailability with better absorption and targeted action	(Goindi <i>et al.</i> , 2011)
9.	5-fluorouracil	Floating microspheres	Highly porous surface of microsphere, reduced dose and duration of therapy	(Vaghani <i>et al.</i> , 2010)
10.	Curcumin	Floating tablets	Maximum sustained release with excellent floating and swelling properties	(Shishu <i>et al.</i> , 2008)
11.	5-fluorouracil	Floating alginate beads	Sustained release profile, reduced dose and duration of therapy	(Shishu <i>et al.</i> , 2007)

**Table 3.** Some recent patents based on gastroretentive technology.

S. No.	Patent number	Title	Year	Reference(s)
1.	US 2022/0160630 A1	Expandable gastroretentive dosage form	2022	(Menachem and Zalitet <i>et al.</i> , 2022)
2.	US 2022/0110876 A1	Gastro – retentive sustained - release oral dosage form of a bile acid sequestrant	2022	(Sethuraman <i>et al.</i> , 2022)
3.	US 2022/0031604 A1	Self regulating osmotic GRDDS	2022	(Shah <i>et al.</i> , 2022)
4.	US 2022/0008334 A1	Gastroretentive devices	2022	(Zalit and Menachem <i>et al.</i> , 2022)
5.	US 2021/0236421 A1	Gastroretentive dosage forms for sustained drug delivery	2021	(Meghpara <i>et al.</i> , 2021)

balanced systems are examples of non-effervescent systems that can be developed using gel forming swellable polymers (Pahwa *et al.*, 2012b, 2013). Various research findings on anticancer drug based gastroretentive dosage forms have been reported. Table 2 summarizes various recent investigational studies of anticancer gastroretentive dosage forms.

Therefore, substantial and continual research efforts have been done globally toward designing innovative gastroretentive delivery system of anticancer drugs. Targeting gastric cancer using gastroretentive dosage forms appears to represent a promising option with site-specificity and unique drug release kinetics for achieving newer insights as per therapeutic needs. Several recent patents on gastroretentive technology are presented in Table 3.

### Future perspectives

Various research investigational studies on gastroretentive technologies have been conducted so far using single technological approaches like floating, expandable, mucoadhesive systems, etc. However, utilizing sophisticated combinatorial strategies along with versatile modifications in polymeric materials may be effective in reducing gastric retention time variability. Currently, there is an urgent need to design an array of advanced gastroretentive dosage forms of anticancer drugs having a narrow

absorption window in the GIT according to the clinical requirements. Significant research advancements are needed to achieve expected gastric retention with anticancer drugs. Future work needs to focus on gastroretentive dosage form of anticancer drugs to be retained specifically in the GIT for prolonged period of time. Moreover, using a quality by design (QbD) can also be helpful in determining the impact of formulation as well as processing factors on quality characteristics of effective gastroretentive systems. Use of QbD techniques in pharmaceutical field may be helpful in understanding and control of the manufacturing process, lowering the possibility of product failure significantly. Future directions in gastroretentive technology of anticancer drugs may need to focus on increased and controlled swelling qualities of therapeutically accessible dosage forms and optimizing buoyant behavior. Additionally, plethora of research and more intensive investigation should be developed for effective recognition of gastroretentive technology of anticancer drugs in the successful management of gastric cancer and further avoiding any side effects.

### CONCLUSION

Gastric cancer is a malignancy that has a poor prognosis. Classification and factors affecting this multifactorial disease have been elucidated in the present paper. Eradication of *H.*

*pylori*, adopting a healthy lifestyle along with precise therapeutic interventions utilizing anticancer gastroretentive dosage forms play crucial role in the management of gastric cancer with promising outcomes. Gastroretentive dosage form is a significant strategy for retaining dosage in the GIT for prolonged time period and also recognized as impressive and rational technological consideration. Substantial advancements in retention of the dosage form in the gastrointestinal region with this targeted drug delivery highlight the immense relevance of gastroretentive systems of anticancer drugs. The present article provides an overview of gastric cancer and several unique therapeutic approaches employing gastroretentive delivery. Enormous potential of encouraging gastroretentive technologies for the management of gastric cancer and for obtaining maximum therapeutic benefits from gastroretentive dosage forms of anticancer drugs are also highlighted in this paper.

### CONFLICT OF INTEREST

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### AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

### ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

### DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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