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GRDDS IN TREATMENT OF COLON CANCER: RECENT ADVANCEMENT AND FUTURE PERSPECTIVE

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ABSTRACT:

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide, with increasing incidence due to genetic, environmental, and lifestyle factors. Present treatment options are chemotherapy and surgery, which are often constrained by poor bioavailability, systemic toxicity, and resistance. Gastro retentive drug delivery systems (GRDDS) have emerged as a promising approach to enhance or increase the efficacy of anti-cancer drugs by prolonging gastric retention, improving localized drug delivery, and raising therapeutic concentration at the targeted site. This review discusses the progression of CRC, the role of *Helicobacter pylori* infection in CRC risk, and the recent advancements in GRDDS for CRC treatment. Various GRDDS technologies, such as floating, bioadhesive, expandable, osmotic-regulated, and magnetic systems, are explored for their potential to improve the therapeutic index of anticancer and antibiotic agents. The future perspective emphasizes the need for innovative gastroretentive formulations developed for CRC therapy, aiming for controlled drug release, improving patient compliance, and minimizing side effects. By integrating advanced polymeric materials and quality-by-design approaches, GRDDS holds significant potential in revolutionizing CRC treatment and overcoming current therapeutic challenges.

Keywords: Colorectal cancer (CRC), Gastro retentive drug delivery systems (GRDDS), *Helicobacter pylori*, bioadhesive, quality-by-design approaches.

1. INTRODUCTION:

The colon is an essential part of the gastrointestinal tract and is located in the lower abdomen, beneath the stomach. It is almost 150 cm long and its starting point name is Caecum, and the ending point is Anal verge. The colon is divided into five portions, namely: Caecum, Ascending colon, descending colon, sigmoid colon,

and Anal verge. These portions have different diameters; the caecum is the widest (about 7.5 cm), and the sigmoid colon is the narrowest (about 2.5 cm) [1].

The colon's main purpose is to absorb water, nutrients, and electrolytes from partly metabolized food and to further refine the residual material to form stool. Once formed, the stool is then stored in the rectum and ultimately gets expelled from the body through the anus, shown in Figure 1 [2].

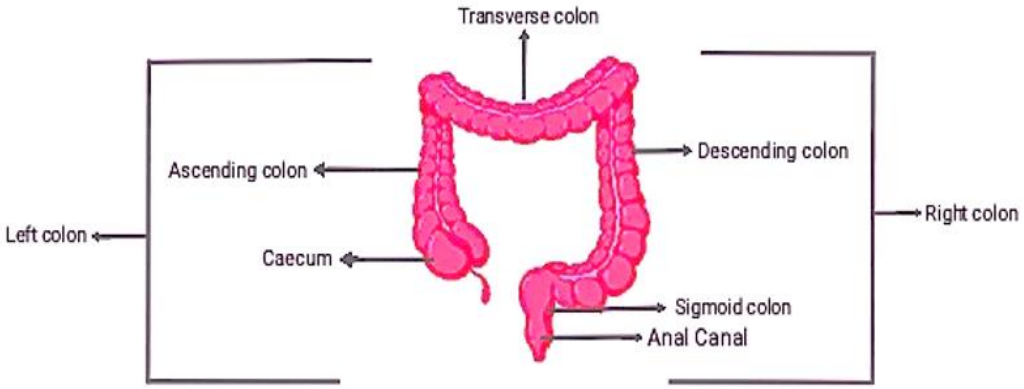

Figure 1: Anatomical description of the colon.

Colorectal cancer (CRC) is a complex disease problem and it is the third most common diagnosed cancer in the world and approximately 13 % of all cancers [3,4]. Geographical divergences were reported in incidence and mortality rates, time trends, and the future encumbrance of CRC across various countries and regions [5]. There were also alterations in the age pattern of CRC, with growing incidence in the young, particularly in developed countries [6]. CRC risk factors including genetic and environmental factors, are probably divided into modifiable and non-modifiable risk factors [7]. Modifiable risk factors include smoking, obesity, alcohol consumption, psychological stress, sedentary lifestyle, and Unhealthy Diet. Non-modifiable risk factors include genetic predisposition, age, gender, family history of CRC, and abdominopelvic radiation [8-10]. Early symptoms of the disease: (i) changes in your bowel habits (including diarrhoea or constipation or a change in the consistency of your stool for more than two weeks), (ii) bleeding in the stool, (iii) persistent abdominal pain, (iv) swelling in the colon, (v) weakness, (vi) stress, (vii) unexplained anaemia with age [11]. CRC emerges from the epithelial cells lining the colon or rectum in the gastrointestinal tract (GIT) due to the unusual growth of glandular epithelial cells [12]. The development of colorectal adenocarcinomas is caused by sequential genetic and epigenetic mutations in particular oncogenes in the epithelial cells of the GIT [13]. The normal epithelium forms into hyperproliferative mucosa and ultimately forms a benign adenoma, which can then

develop into carcinoma and metastasis in about 10 years. This process occurs through various mechanisms, including microsatellite instability (MSI) and chromosomal instability (CIN) pathways [14]. In MSI, tumors are caused by the inactivation of one of the four mismatched repair (MMR) genes: MLH1, MSH2, MSH6, and PMS2. At the time of normal DNA replication, these competent MMR genes detect errors in DNA mismatches, and the MLH1 and PMS2 heterodimer facilitates the removal of these errors and forms new corrected DNA strands [15]. The diagnosis of CRC is made using various methods and techniques with varying sensitivities: colonoscopy, sigmoidoscopy, CT colonography, and stool test [16]. The utility of sigmoidoscopy in reducing both the incidence and CRC-related death has been entrenched, as well as the integration of sigmoidoscopy and stool testing, which are cost-effective strategies but unfortunately, have not been effectively used in established guidelines [17,18].

The stomach has an important role in the GRDDS. A perfect understanding of the anatomy and physiology of the stomach area is necessary for the successful development of the gastroretentive dosage form. Anatomically, the stomach is divided into two parts: the proximal stomach, which forms the fundus and body; and the distal stomach, which forms the antrum and the pylorus as shown in Figure 2. The main principle of the stomach is to store the food for a short time, grind it, and then mildly release it into the duodenum [19].

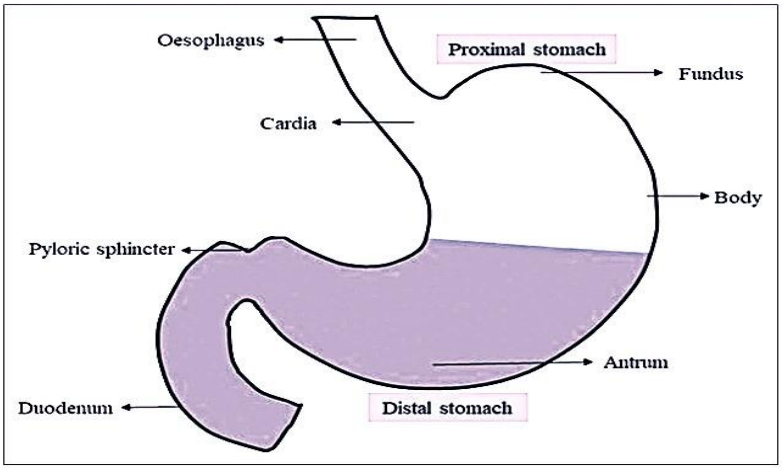

Figure 2: Schematic view of the anatomy of the stomach

Gastro retentive drug delivery system (GRDDS) is viable for medicines that have low absorption in the lower GIT, are highly unstable and have low solubility at alkaline pH have a short half-life, and have a local therapeutic effect in the upper gut for the eradication of *Helicobacter pylori*. These systems are intended to be kept in the stomach for an extended period and release their active components, allowing for sustained and prolonged release. There are various formulation techniques which include several super porous hydrogels, bio/mucoadhesive, raft-forming, magnetic, ion-exchange, expandable, low-density, and high-density systems,

which have been employed to create effective controlled-release GRDDS. Types of polymers play an important role in GRDDS formulation, polymers such as (non-ionic, cationic, and anionic polymers) [20,21].

These drugs can be delivered from the stomach to give a localized therapeutic effect at the site of action by slow release [22]. GRDDS are especially applied in the treatment of disorders like *H. pylori* infections, ulcers, colorectal cancer, gastric cancer, and reducing PH [23].

The main purpose of this review is to provide information about the progression of cancer, the recent advancement of GRDDS, how GRDDS works to treat colorectal cancer caused by *H. pylori* bacteria, and increasing PH. In addition, future perspectives on GRDDS are discussed.

2. PROGRESSION OF COLORECTAL CANCER:

CRC can be classified based on the location of the tumor in the colon and rectum. Right-sided colon cancers are developed in the transverse colon, ascending colon, and caecum, and left-sided colon carcinomas are developed in the transverse colon, descending colon, sigmoid colon, and anal canal [24,25]. Based on this categorization, the majority (about 63%) of diagnosed CRC is left-sided and mostly in younger patients [26].

Disease progression of CRC is shown in Figure 3. The prodrome and the medical condition of CRC have been shown by various studies to be related to the location of the tumor [27,28]. Prodromes related to left-side colorectal cancer include partial or total

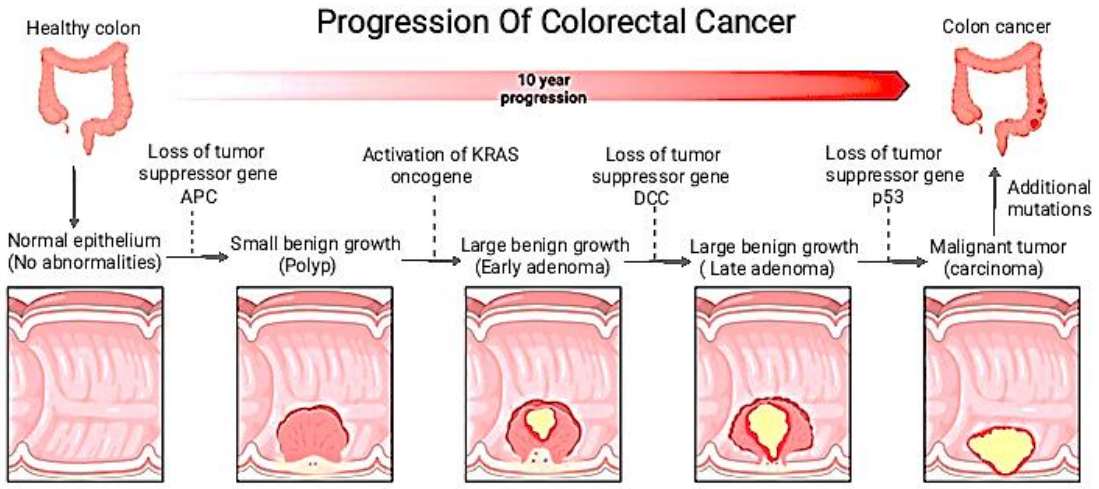

Figure 3: Disease progression of colorectal cancer.

Intestinal impediment due to the narrow lumen of the colon on this side. As a result of the hindrance, symptoms such as nausea, constipation, abdominal distention, and abdominal pain are usual. Right-sided CRC usually results in gross rectal bleeding, and the patient may face iron-deficiency anaemia [29]. Patients with right-sided CRC usually have poor medical conditions and are likely to metastasize compared to left-sided tumors [30]. The need for early diagnosis and rooting for more effective therapies is emphasized by the fact that the majority of CRC (approx. 50%) are determined at an advanced phase with resulting poor medical conditions and high mortality [31].

The colorectal tumor microenvironment (TME) is distinguished by different cell types, basically generated from the adjacent mesenchymal stroma and their interaction with tumor cells. The interactions between the surrounding stroma cells and tumor cells promote the expansion and intrusion of the tumor [32]. Tumor cells emit various signals that alter the surrounding microenvironment, turning it into a diseased entity, and continuously reshaping it as cancer progresses. This transformed TME is conveyed to affect abnormal tissue functions and significantly contribute to the development of resistance to treatment [33]. The TME is made up of Cancer Associated Fibroblast (CAF), which reflects the maximum number of cells in the TME, immune cells such as myeloid cells, mast cells, dendritic cells, and tumor-associated macrophages (TAM) [34]. CAF generates and emits factors such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), insulin-like growth factors 1 and 2 (IGF1 and IGF2), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2) and fibroblast growth factor 7 (FGF7). These factors have substantial effects on processes such as inflammation, invasion, immune evasion, and angiogenesis, all of which contribute to the progression of tumor growth [35,36]. CAF is associated with poor medical conditions and is an important marker for estimating remission in patients [37].

3. HOW DOES *H. PYLORI* INCREASE CRC RISK:

H. pylori may have both direct and indirect roles in the development of colorectal cancer. In direct effect, it involves bacterium and molecule effectors, like secreted toxins, present in the respective colon tissue. Few studies have shown the presence of *H. pylori* in colorectal cancer tissue by PCR (polymerase chain reaction) or histology studies. Two case studies found *H. pylori* around 26% of analysed colorectal cancers. A case study also found positive *H. pylori* histology in tumor tissue, whereas *H. pylori* tissue was relatively positive in the colon [38,39]. A diagnostic test detects *H. pylori* antigen in stool suggesting that the bacteria traverse the colon. Larger studies with normal tissue and tissue from all stages of carcinogenic development are required to confirm this thesis. It also needs to be illustrated if and how *H. pylori* might then be adept at eliciting cancer effects in the colon.

Under the conjecture that *H. pylori* might not be able to affect the colorectal epithelium, there are various theses as to how *H. pylori* could indirectly participate in colon cancer.

Firstly *H. pylori* infection could guide changes in the colonization of the gut with other bacteria that in turn could participate in CRC. A study by Gao and colleagues (2018), found that the gut microbiome composition did not differentiate between *H. pylori*-infected or non-infected individuals but did differentiate by *H. pylori*-related gastric lesion that between *H. pylori*-infected individuals with normal, gastritis, and metaplastic tissue [40]. As recounted above, various case studies found higher disagreement for colorectal adenoma and cancer in individuals with *H. pylori*-related gastric lesions compared with healthy controls [41-44].

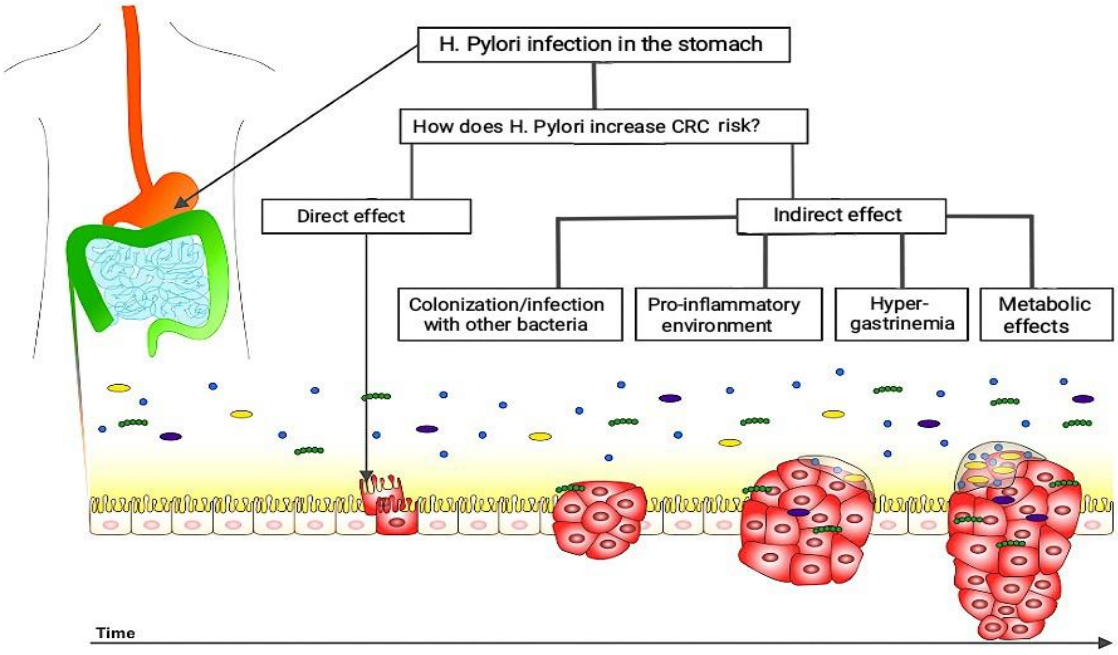

Figure 4: How does H. Pylori increases CRC risk

Secondly, *H. pylori* infection could participate in colorectal oncogenesis or carcinogenesis by increasing the discharge of gastrin which might act as a mitogen. It has been shown that *H. pylori* increases hypergastrinemia; however, it needs further investigation [45,46]. Similarly, *H. pylori* was found to be connected to metabolic diseases that in turn were also described in the risk of colorectal cancer. The analyses of a merged effect of these with *H. pylori* on colorectal cancer. We found one case study that reported significant independent associations of metabolic syndrome and *H. pylori* with colon adenoma prevalence [47], as opposed to other studies that found an increased association of *H. pylori* and diabetes with colon adenoma prevalence [48].

Finally, *H. pylori* increases chronic inflammation in the stomach mucosa, thereby also raising systemic reactions in the body [49]. Inflammation is reported to induce the risk of colon cancer, and long-term intake of aspirin as an anti-inflammatory drug was shown to guard against Colon cancer development [50]. It is unknown, whether *H. pylori* might produce a pro-inflammatory state in the GIT that might enhance the risk of colorectal cancer.

4. RECENT ADVANCEMENTS:

Helicobacter pylori is the most generic pathogenic bacteria. It is the primary known cause of gastritis, gastroduodenal infection which converts to colon cancer and gastric cancer. In addition, triple therapies, and oral site-specific drug delivery systems (mainly gastro-retentive dosage forms) enhance the gastric retention time and can induce the drug concentration at the target site, thereby progressing the therapeutic effect on colon cancer. These gastro retentive drug delivery systems include floating systems, bio-adhesive systems, and expandable systems for improving local drug delivery [51]. This review includes how much GRDDS has recently advanced in the treatment of *H. pylori* infections.

FLOATING SYSTEMS:

Davis was the first person to describe floating medicine delivery systems in 1968. Floating medicine delivery systems are low-density systems that enhance gastric retention time and increase bioavailability by floating on top of the gastric contents [52]. The desired formulation of floating systems should meet the following conditions: (1) lower density or higher buoyancy than gastric contents (1.003-1.010); (2) a protective coating to ensure the stability of the active agent in gastric acid; and (3) controlled or sustained drug release for optimal therapeutic effect.

Generally, floating systems are prepared by using hydrophilic matrices that are less thick in the case of Figure 5A or that float on top of the gastric fluid after absorption of water and swelling (Figure 5B). Low-density fatty acids are also used to increase the buoyancy and cellulose ether polymers which are used as hydrophilic matrices. Hydrodynamically balanced systems (HBSs), gas-generating systems, and low-density systems are the supereminent approaches used in designing intragastric floating systems [53].

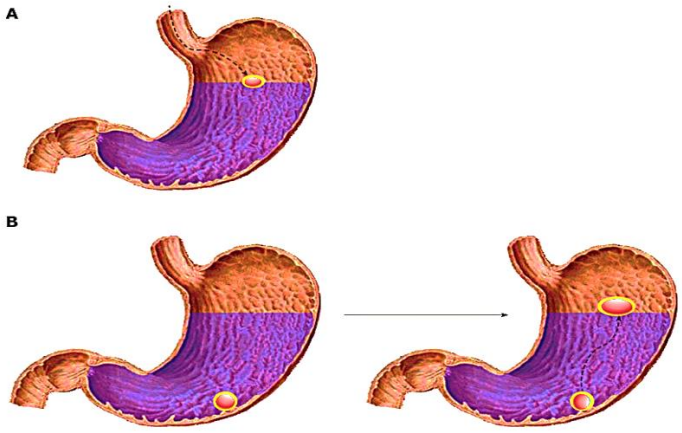

Figure 5. Floating systems: Low-density floating dosage (A) and the density of dosage can be lowered after administration (B).

Hydrodynamically balanced systems (HBSs) are dosage forms containing an admixture of medicines, a gel hedge comprising hydrophilic polymers, and other excipients. Hydroxypropyl methylcellulose, hydroxy propylcellulose, ethylcellulose, hydroxy ethyl cellulose, sodium carboxymethylcellulose, and agar are generally used excipients. After the oral administration, the hydrocolloid is dissolved by swelling and controlled at a low density, which selects for controlled drug release from the blown gel matrix (Figure 6) [54,55].

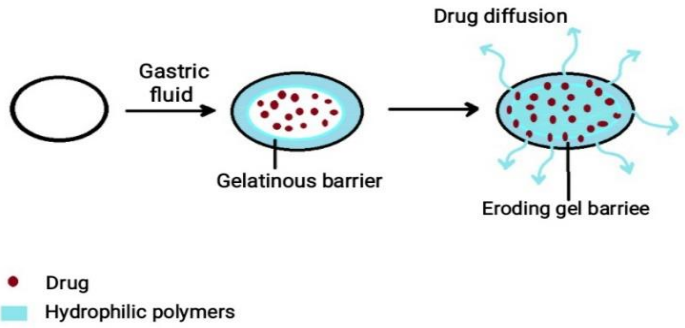

Figure 6: Hydrodynamically balanced system.

Gas- Gas-generating systems gain their buoyant characteristics by the creation of gas bubbles. Such as CO2 can be formed from sodium bicarbonate at an acidic P^H. Therefore, acids are necessary in the formulation. These systems include single-unit and multi-unit dosage forms [56,57].

Low-density systems are a form of low-density materials, enclosing air or oil. Low-density materials are generally used, including empty hard gelatin capsules, pop-rice grain, and polystyrene foams. The outer surface

of the low-density material is made up of EC and cellulose acetate phthalate coated with drug, with the trapped oil and air which provides the required buoyancy.

In the last decennary, the emulsification solvent evaporation process for the composition of low-density systems gained huge popularity. A huge number of studies have used this system, and various anti-microbial agents were encapsulated in these systems for the treatment of *H. pylori* (e.g., amoxicillin, tetracycline, and metronidazole) [58-61]. Numerous commercialized floating dosage products are present in the market, some of which target *H. pylori* bacteria, and they're listed in Table 1 [54].

Yang et al generated a triple-layer tablet which is based on Hydrodynamically balanced systems, which was made of a rate-controlling polymer matrix and a drug core [60]. The in vitro assessment stated that the sustained delivery of the antibiotics above 6- 8 hours when the tablet stayed afloat. Rajinikanth et al updated an intragastric in situ gelling system that floated for the controlled delivery of amoxicillin in the treatment of *Helicobacter pylori* infections [61]. The in vivo clearance capability of *H. pylori* was 10 times more than the effects in an in vivo gerbil model due to the prolonged GI residence time of the formulation [51,61].

Table 1: Different marketed products of Floating Drug Delivery System

Brand Name	Delivery System	Drug	Company
Valrelease	Floating capsule	Diazepam	Hoffman-LaRoche
Modopar HBS (Prolopa HBS)	Floating, CR capsule	Benserazide and L-Dopa	Roche products, USA
Topalkan	Floating Liquid alginate preparations	Al- Mg antacid	Pierre Fabre Drug, France
Conviron	Colloidal gel forming	Ferrous sulphate	Ranbaxy, India
Cifran OD	Gas-generating floating form	Ciprofloxacin	Ranbaxy, India

BIOADHESIVE SYSTEMS:

Mucoadhesive/Bioadhesive drug delivery systems are a dosage form that can adhere to the mucosal surface by various mechanisms. This formulation contains a polymer or mucous coating layer and is considered a bioadhesive material [62]. The adhesive polymers are basically used for bioadhesive materials such as

Alginate, Poly-L-lysine, Polyethylene glycol, etc. [63]. Microparticles and nanoparticles, which have greater drug delivery efficiency and mucosal permeability, are considered absolute bioadhesive carriers [64]. As this dosage form is orally administered it dissolves in the gastric juice and strongly adheres to the mucosal surface, which prolongs the residence time of the drug. Adsorption theory, diffusion theory, electronic theory, and wetting theory are referred to illustrate the adhesive mechanisms [65,66].

Despite the bioadhesive characteristics of these polymers, they are not easy to control because of gastric mucosa and gastric emptying. Despite these problems, many studies have shown considerable results.

Liu et al released a study on amoxicillin bioadhesive microspheres that use an emulsion solvent evaporation method, with Carbopol-934p as the mucoadhesive polymer and Ethyl cellulose as the matrix. The in vitro release test showed that nearly 85%-90% of the amoxicillin was dispersed in the pH 1.0 HCl solution after 4 h. In vivo and in vitro mucoadhesive tests showed that mucoadhesive microspheres adhered more firmly to the gastric mucous surface than non-adhesive amoxicillin microspheres. Amoxicillin mucoadhesive microspheres were unchanged in the gastrointestinal tract for a prolonged period [67]. Jayvadan KP and Jayant RC also produced mucoadhesive amoxicillin microspheres in the treatment of *H. pylori* infections. They produced the microspheres by applying the same method and carrier polymer. The amoxicillin microspheres showed a large potency of drug entrapment. The in vitro adhesive test displayed that mucoadhesive microspheres adhered more firmly to the gastric mucous, more than 50% of the microspheres were unchanged in the GI tract around 12 hours. In vivo, tests were performed by orally administering amoxicillin powder and mucoadhesive microspheres in *H. pylori* infection animals under fed situations at single and multiple doses. The results showed that the mucoadhesive microspheres had an excellent clearance than the powder [68].

FLOATING-BIOADHESIVE SYSTEMS:

Even though many advances have been made in both floating and bioadhesive systems, there are quite many challenges. First, gastric emptying minimizes the buoyancy of the floating systems in the stomach. Second, the floating systems are unable to discharge the drug at the located site. Third, the turnover of the gastric emptying and gastric mucosa decreases the adhesive force of bioadhesive systems. So, a dual working system would control the problems attached to floating and bioadhesive systems and would have a citable effect on progressing the therapeutic outcomes.

Zheng et al formulated floating-bioadhesive microparticles to enhance the potency of antibiotics against *H. pylori* [69]. The formulation containing clarithromycin was produced by the process of emulsification/evaporation and internal gelation with sodium alginate, ethyl cellulose, and chitosan. In vitro

buoyancy and drug release tests displayed that about 74% of the microparticles floated in an acetate buffer solution for 8 h and about 85%-90% of the clarithromycin was released in a sustained manner in 8 h. An in vivo mucoadhesive test indicates that almost 61% of the microparticles were released in the stomach after 4 h [51]. Rajinikanth et al improved stomach-specific floating-bioadhesive microspheres of clarithromycin for the treatment of *H. pylori* infections. The microspheres were made by the emulsification-solvent evaporation technique using ethyl cellulose as the polymer matrix and Carbopol-934P as the mucoadhesive material. The microspheres show high mucoadhesive characteristics and superior buoyancy during the in vitro evaluation and a citable anti *H. pylori* effect after administering orally to Mongolian gerbils infected with *H. pylori* [51,70].

EXPANDABLE SYSTEMS:

Expandable drug delivery systems are easily swallowed and expand to a larger size after contact with gastric juice in the stomach, which can enhance gastric retention time [71]. Thus, an optimal expandable dosage momentous the following properties: controlled drug release, a benefit for oral ingestion, expandable upon attachment with the gastric contents, and else a degradable nature [72,73]. Superporous hydrogels which are temperature and PH-sensitive, are fast-swelling, and have a great swelling ability are considered to be a novel material for swellable systems [74]. Chen et al prepared super porous hydrogels that used croscarmellose sodium as a composite material, and its addition resulted in a notable development in the characteristics of the super porous hydrogels [75]. Park et al formulated chitosan-based superporous hydrogels using freeze-drying and gas-blowing methods [76]. In vitro tests demonstrated that the superporous hydrogels were very sensitive to the pH of the swelling media. These swelling behaviors and degradation kinetics are necessary variables in examining gastric retention time.

This system's expansion process is swollen to the point that it cannot escape the pylorus. As a result, the dosage form is kept in the stomach for a long period. These systems are known as "plug-type systems" because it has a trend to remain blocked at the pyloric sphincter when they have enlarged diameters beyond 12–18 mm. The purpose of the formulation is gastric retention and regulated medication dispense into the stomach cavity. Even when fed, such polymeric matrices can be obtained in the GI cavity for a few hours. The degree of cross-linking between the polymeric chains controls a balance between the magnitude and time of swelling. The principle of the expandable drug delivery device was explained schematically (Figure 7) [77].

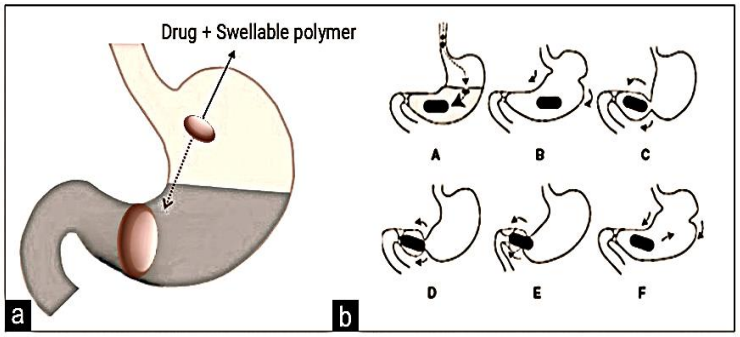

Figure 7: (a and b) GRDDS based on expandable systems and represents expandable drug delivery system. and (A) the device significantly swells on contact with gastric fluids (to a few hundred times the original volume), (B-D) the gastric contraction pushes the hydrogel to the pylorus, (E) the gastric contraction slips over the surface of the hydrogel, and (F) the hydrogel is pushed back into the body of the stomach.

OSMOTIC REGULATED SYSTEMS:

It is made up of an inflatable floating support entrapped in a bioerodible capsule and an osmotic pressure-controlled drug delivery system [78]. The osmotic controlled drug delivery system (OCDDS) is comprised of an osmotically active compartment and a drug reservoir compartment. The capsule quickly dissolves in the stomach and removes the intragastric osmotically regulated medication delivery system. Inside, the inflatable support creates a flexible hollow polymeric bag composed of a liquid that gasifies at body temperature to inflate the bag [79].

MAGNETIC SYSTEMS:

A dosage form in a magnetic system includes the active drug ingredient, excipients, and a small amount of magnetic material. As seen in Figure 8, the external magnet is positioned above the stomach to control the position of the drug formulation containing the internal magnet. GRT is determined by the external magnets' positions relative to the body and by the strength of the magnets. Previous studies have shown that magnetic drugs can increase GRT and bioavailability [80]. Groning et al. studied magnetic acyclovir tablets with and without external magnetic fields in human volunteers and the researchers also found that the presence of extracorporeal magnets improved GRT and plasma volume.

Ito et al. improved bioadhesive materials containing different ultrathin ferrites and tested them on rabbits [81]. They discovered an external magnetic field. They also found that an external magnetic field strength of

1700 G kept whole grains in the stomach for more than 2 hours. However, accurately positioning the magnet can be difficult, which may lead to low patient compliance. There have been only a limited number of studies on magnetic systems, and their therapeutic significance has yet to be determined. Therefore, future research on these systems should place greater emphasis on understanding their therapeutic value [77].

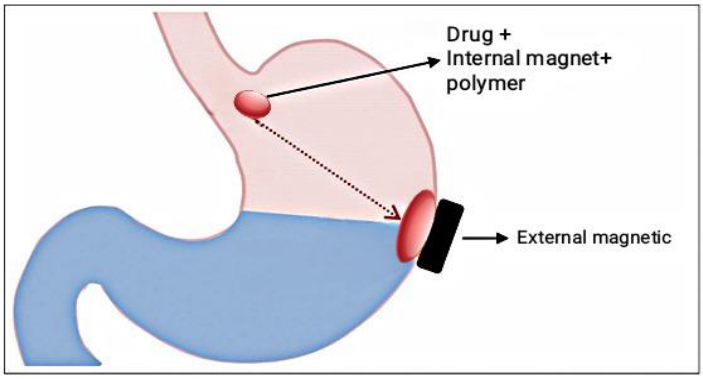

Figure 8: GRDDS based on magnetic systems

GRDDS FOR THE TREATMENT OF CRC DUE TO *H. PYLORI* INFECTION:

H. Pylori is linked with the development of serious gastrointestinal tract diseases—including ulcers, colon cancer, and gastric cancer [82]. *H. pylori* mainly remains in the gastric mucosa or at the interface between the epithelial cells and the mucous layer of the antral region of the stomach or colon.

The discovery of this bacteria has revolutionized the diagnosis and treatment of infectious diseases. Almost all antibacterial agents have low Minimum Inhibitory Concentrations (MIC) against *H. pylori* in culture. Single antibiotic therapy is ineffective for the eviction of *H. pylori* infection in vivo due to the low concentration of the antibiotic reaching the bacteria under the mucosa or targeted place. Anti-secretory agents and a combination of more than one antibiotic are required for proper eviction of *H. pylori*, but these rules are not fully effective. Side effects, bacterial resistance, and patient compliance are the other problems. Other than the multi-antibiotic therapy, various therapeutic strategies have been examined to completely evict *H. pylori* from the gastrointestinal tract [83].

One way to progress the efficacy in evicting the infection is to deliver the antibiotic locally in the lower part of the stomach. Prolonged residence time and better stability will allow more of the antibiotic to enter through the gastric mucus layer to act on *H. pylori*. The reason for the unfinished eviction of *H. pylori* is perhaps because of

the short residence time of antibiotic agents in the stomach so that effective antibacterial concentration cannot be achieved in the epithelial cell surfaces or gastric mucous layer where *H. pylori* is present [84]. Another reason may be the degradation of antibiotics in gastric acid. As conventional drug delivery systems do not stay in the stomach for a long period, they are unable to deliver the antibiotics to the site of infection in effective concentrations. So, it is important to design drug delivery systems that not only alleviate the shortcomings of conventional delivery vehicles but also deliver the antibacterials to the infected cell lines. At first, the absorption of an antibiotic into the mucus through the mucus layer (from the gastric lumen) is believed to be more efficient for *H. pylori* eviction than absorption through the basolateral membrane (from blood). Researchers have concentrated on the improvement of GRDDS which are capable of residing in the stomach for a prolonged period for more effective *H. pylori* eviction [85–87].

ANTICANCER DRUGS FOR CRC:

For the treatment of colon cancer, a variety of anticancer drugs are used, including 5-fluorouracil, irinotecan, capecitabine, carboplatin, cisplatin, paclitaxel, oxaliplatin, etc. [88]. Chemotherapy is still the most effective treatment option for colon cancer. However, traditional oral chemotherapy for colon cancer suffers because of notable limitations such as multiple doses, inadequate absorption, systemic toxicity, etc. All of which contribute to poor treatment results. Also, oral chemotherapy may engage low or variable bioavailability, linked with premature drug release, limited drug solubility, and less retention period as well [89]. As a result, novel drug delivery systems must be planned for maintaining drug release while concurrently extending their gastroretentive duration. GRDDS has been successfully designed to hold the dosage form localized exactly in the stomach and extend the dosing interval for colorectal carcinoma. The Gastro Retentive Floating Drug Delivery System (GRFDDS) is specially created to control the pharmacokinetic challenges of oral chemotherapy [90]. Formulation of a gastro retentive floating system is also needed to address different problems attached to conventional dosage forms and to maximize oral absorption of different therapeutic molecules with regulated drug delivery and prolonged stomach residence [91]. The aforementioned described systems can also be applied to upgrade the efficacy of anticancer drugs like 5-fluorouracil, docetaxel, etc., with a narrow absorption window [92].

SIDE EFFECTS AND COMPLICATIONS OF CRC TREATMENT:

Mucositis, constipation, dyspepsia, diarrhoea, nausea, and vomiting are the general gastrointestinal adverse effects of these anti-cancer agents. Incidence and intensity of adverse drug effects are attached to the therapeutic schedules, and route of administration, including dose, frequency, and co-administration of these anticancer

drugs, and depend on the duration of treatment [93]. Gastrointestinal tract toxicities are the most regarded, and they tend to impact the patient's compliance with therapeutic regulations. Infused regimens of 5-fluorouracil (5-FU) and leucovorin (LV) have shown lower toxicity than bolus regimens. Past efforts in the search for ideal 5-fluorouracil led to the invention of floxuridine and tegafur, two 5-FU derivatives with increased pharmacokinetics and pharmacological profiles resulting in bettered absorption, bioactivity, higher selectivity, metabolic stability, and less toxicity [94]. The emergence of multi-drug resistant cancer cells prepares multimodality therapy with agents that target various cancer development pathways, the hallmark of carcinoma treatment. General combination therapies work oxaliplatin and irinotecan with 5-fluorouracil and novel drugs targeting vascular endothelial growth factor (such as aflibercept, bevacizumab, ramucirumab, and regorafenib) or epidermal growth factor receptor (such as cetuximab and panitumumab) [93,95]. Adverse effects for treatment imbalance were based on the intensity of the cases, whether the patient refused treatment, necessitated subsequent dose reduction after the second reduction, adverse effect delayed medication for more than 28 days, or if the patient refused treatment due to AEs. Chemotherapy's AEs may also be confounded by tumor-attached complexity of intestinal obstruction, fistulation, perforation, and hemorrhage [96]. Kim et al. concluded that elderly patients with stage 3 colon cancer can be treated with preventative chemotherapy comprising 5-FU capecitabine or 5-fluorouracil leucovorin without significant differences in toxicity from younger patients. Further, combination chemotherapy appears to be safe in older patients with metastatic colorectal cancer, except for weak or sick elderly patients, or monotherapy may be more applicable.

5. FUTURE PERSPECTIVES:

Different examination investigational studies on gastro retentive drug delivery systems have been conducted so far using single systematic approaches like floating, expandable, mucoadhesive systems, etc. However, utilizing sophisticated conjunction strategies along with versatile improvements in polymeric materials may be useful in decreasing gastric retention time variability. Now, there is an urgent need to design an array of advanced gastroretentive dosage forms of anticancer drugs having a narrow absorption window in the gastrointestinal tract according to the clinical requirements. Major research developments are required to achieve expected gastric retention with anticancer drugs. Future work needs to focus on gastroretentive dosage forms of anticancer drugs to be retained particularly in the gastrointestinal tract for extended periods. Additionally, using quality by design can also be beneficial in determining the effect of formulation and processing factors on the quality features of effective gastroretentive systems. The use of quality by-design techniques in the pharmaceutical area may be useful in understanding and controlling the manufacturing procedure, lowering the expectation of product failure significantly. Additionally, a plethora of research and

more comprehensive investigation should be advanced for effective recognition of gastro retentive technology of anticancer drugs in the successful management of colon cancer and further avoiding any side effects. Future approaches in gastro retentive technology of anticancer drugs may need to focus on enhanced and controlled swelling qualities of therapeutically accessible dosage forms and optimizing buoyant behavior. Additionally, more research work is required where GRDDs can be improved for the targeted delivery of antibiotics and other therapeutic agents, which could increase the drug concentration at specific sites and give a good therapeutic effect with fewer adverse effects.

6. CONCLUSION:

Gastro Retentive Drug Delivery Systems (GRDDS) hold immense potential in the treatment of *H. pylori* infection, the bacteria generally associated with gastric ulcers and cancer, but also incriminate in the development of colon cancer due to its depiction in chronic inflammation and microbiome disruption. GRDDS can also improve the targeted delivery of antibiotics and other therapeutic agents, which ensure higher concentration at the site of infection, further enhancing the annihilation of *H. pylori*. By developing localized drug delivery to the stomach and the intestines, these systems can decrease the bacterial load and also reduce the inflammation that promotes neoplastic development. Moreover, the prolonged release and controlled drug delivery provided by GRDDS may help in preventing the systemic side effects generally linked with conventional treatments, such as gastrointestinal discomfort and antibiotic resistance. These systems also have the potential to associate with the gut microbiome, restoring a healthy microbial balance, which might reduce the long-term cancer risks linked to or associated with *H. pylori*. The development of GRDDS for colon cancer related to *H. pylori* poses several challenges, including formulation stability, overcoming drug resistance, and meeting regulatory requirements. By advancing GRDDS formulation and combining it with antibiotics, anti-inflammatory agents, and microbiome modulators it could provide comprehensive strategies for preventing and treating colon cancer, improving patient outcomes with fewer side effects. The Potential for more targeted and personalized medicine in this area is a key direction for future research and development.

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