pH. Thus, pH plays an important role in the swelling and drug release characteristics of hydrogels [41].

3.2. Delayed or Time-Controlled Release Drug Delivery Systems

In these systems, the drug is released after a programmed duration of time. These systems are very promising but have poor availability in the colon due to erratic gastric emptying time and inability to accurately predict the colon arrival time. Gastric emptying time and GI movements such as peristalsis or contraction greatly affect the release of drugs. Time-dependent systems alone are not effective. When pH-sensitive systems are integrated with time-dependent systems, an improvement in the site-specific delivery to the colon was observed [10, 36].

There are certain challenges associated with the delayed release systems. Because of the wide variation in the gastric retention time in different individuals, the release of the drug may occur erratically when it was not programmed. Also, the transit time in diseases such as diarrhea, inflammatory bowel disease, and ulcerative colitis is increased [36].

3.3. Microbially Targeted Colonic Delivery

It consists of two approaches; prodrug approach, and polysaccharide-based delivery systems.

(i) Prodrugs

Prodrugs are pharmaceutically inactive derivatives of drug that upon enzyme hydrolysis release the pharmaceutically active drug in the colon. The extent of enzyme hydrolysis should be greater in the colon. Azo conjugates are widely employed in prodrug systems, which are metabolized by the intestinal bacteria. These systems depend upon the functional group of the drug, and thus have limited scope. Metronidazole was formulated using this approach [10].

(ii) Polysaccharide-based delivery systems

Naturally occurring polysaccharides are used widely for colon targeting because of their abundance, low cost, and varied properties. They can be modified very easily. In addition to this, they are biodegradable and hence fall into the "generally regarded as safe" category. Examples of polysaccharides include guar gum that is obtained from a plant, chitosan and chondroitin sulfate obtained from animals, alginates obtained from algae, and dextran obtained from microbes. Solid oral dosage form prepared with these polymers will provide colon-specific drug release and control the rate of drug release from delivery systems. Colonic microflora break the polysaccharide's coating or matrix into simple saccharides. As these microflora are localized in the colon, this appears to be a promising approach for colon-specific drug delivery [36].

3.4. Integrated Approaches for Colon-Targeted Delivery Systems

(a) Pressure-controlled delivery

These systems utilize the colonic luminal pressure generated as a result of peristalsis for site-specific delivery. However, reabsorption of water in the colon causes the contents of small intestine to be highly viscous, which may become a hurdle in the site-specific delivery [10].

(b) Osmotic-controlled delivery

The osmotic controlled-release oral delivery system (OROS-CT) is a system controlled by osmotic pressure. It comprises a hard gelatin capsule. The capsule starts dissolving in the small intestine and allows water to enter. Because of this, the system swells and the drug is forced out [10].

(c) Pulsincap systems

A pulsincap system utilizes the pH-dependent and time-dependent approach. It consists of a capsule body that is water insoluble, which contains the drug and a water-soluble cap covering a hydrogel plug. The capsule is then coated with a film coating that is acid insoluble, which will prevent the drug release in the stomach. The plug composed of hydrogel starts swelling when the enteric coating will dissolve in the small intestine. Metronidazole was formulated as a pulsincap system (Table 2) [10].

Integrated systems incorporating dual mechanism have received great attention recently. Of particular importance is the combination of pH-sensitive polymer and bacteria-aided biomaterials coating that can deliver small, organic molecules to the colon. The pH-sensitive polymer delays the release in the upper part of the GIT.

TABLE 2
Various polymers used in enteric coating and their dissolution pH (Saiful [42]).

S. No.	Enteric polymers	Dissolution pH
1.	Cellulose Acetate Trimellate (CAT)	5.0
2.	Hydroxy Propyl Methyl Cellulose Phthalate (HPMCP)	5.0–5.5
3.	Polyvinyl Acetate Phthalate (PVAP)	4.5–5.0
4.	Cellulose Acetate Phthalate (CAP)	6.2
5.	Hydroxy Propyl Methyl Cellulose Acetate Succinate (HPMCAS)	5.8–7.0
6.	Methacrylic Acid Copolymers (Eudragit)	5.5–7.0
7.	Shellac (esters of aleurtic acid)	7.0