Colonic enzymes digest the polysaccharides facilitating the release of the drug [43].

In a study, colon-targeted delivery was designed for acetylharpagide using integrated approaches of delayed release and pH-sensitivity. The acetylharpagide tablet core was coated with ethyl cellulose for delayed release and pH-dependent polyacrylic resin II and III. The evaluation demonstrated that the optimized tablets increased apparent V_d, delayed t_{max}, and prolonged absorption time [44].

In spite of all these advances, development of an efficacious colon-targeted drug delivery remains a challenge due to the complicated colon targeting, difficulty in access of the colon, wide range of pH values, variety of enzymes involved, and the resident microflora. In the future, exploration of nanotechnology along with the combined approaches seems to be an area of research.

4. FEEDBACK-REGULATED SYSTEMS

Rate-controlled delivery systems have been introduced since mid 1970s. Feedback-regulated system is a type of rate-controlled system. In the feedback-regulated systems, the drug release is activated from the system by a triggering agent. The concentration of the triggering agent regulates the drug release through various feedback mechanisms. The rate of drug release is detected by the sensor. Bioresponsive systems and self-regulating systems are the two types of feedback-regulated systems [11].

4.1. Bioresponsive Systems

In the bioresponsive systems, the feedback mechanism uses the bioresponsive mode to activate and regulate the drug release. It is composed of a bioresponsive polymer membrane that encloses the drug reservoir. The drug permeability of the membrane is regulated by the concentration of endogenous chemical in the tissue. Insulin implant is a typical example of bioresponsive system. It consists of an amine hydrogel membrane that encloses the insulin reservoir. Glucose acts as a triggering agent. Glucose penetrates through the membrane and is oxidized to gluconic acid by the oxidase enzyme present in the membrane. Because of the production of gluconic acid, the amine polymer chains are acidified, causing the hydrogel membrane to swell. This leads to the release of insulin. Thus, insulin delivery is bioresponsive to the glucose concentration [11].

4.2. Self-Regulating Systems

In the self-regulating systems, the feedback mechanism uses the self-regulating mode to activate and regulate the drug release. A permeable polymer membrane enclosing the drug complex acts as the drug reservoir. The drug release is activated by the permeation of an endogenous agent into the membrane. An injectable insulin is a typical example of self-regulating system. It consists of a polymer membrane that encloses glycosylated insulin–concanavalin A complex. Glucose acts as a triggering agent. Upon penetration into the system, glycosylated insulin is released from the complex. Hence, the concentration of the glucose entering the system will self-regulate the amount of insulin delivered [11].

5. ENTERIC DRUG DELIVERY SYSTEMS

In targeted drug delivery systems, enteric coating has emerged as a versatile step in controlling the drug release. They produce a pH-dependent effect bestowing location-specific drug release. They are named as enteric referring to the intestine and having a coat that is designed specifically to pass through the stomach unaltered, without disintegrating in the intestine [12].

Because of their nature of exerting pH-dependent effect to facilitate the drug release, they are used in various delivery systems. They are expressed as gastroresistant, entero-soluble, delayed release, and pH-sensitive enteric dosage forms. The polymers used in enteric coating protect the drug inside by remaining unionised in a lower pH. When they come in contact with high pH in the intestine, the acid functional groups of the polymers ionise, leading to swelling of the polymer or solubilization of the coating, followed by the contact of the drug with intestinal fluids and its release (Singh Deep [45, 46]).

5.1. Reasons for Enteric Coating

Enteric coating has become significant in today's formulations because it acts as a barrier to control the drug release location. The major reasons for enteric coating are as follows:

- To provide protection to active pharmaceutical ingredients that are sensitive to acidic environment caused by gastric acids or enzymes. The examples of active pharmaceutical ingredients to be protected include flurouracil, doxorubicin, and duloxetine [47].
- To avoid nausea and gastric distress due to irritation caused by drugs. For example aspirin, naproxen, bisphosphates, and diclofenac.
- To facilitate delayed release mechanisms. For example sulfasalazine for Crohn's disease and hydrocortisone, valsartan for chronotherapy.
- To minimize the first-pass metabolism of drugs. For example nicotine and bleomycin.
- Drug targeting at specific region in most concentrated form such as colon delivery system that is just