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A Review on Enteric Coating Technology

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Abstract

Oral drug delivery remains the most preferred option for the administration of various drugs. As very few drugs are coming out of research and development and the existing drugs are suffering from the problem of resistance and side-effects as well, there is an ever-growing need to focus more on alternate methods of drug delivery. Recently, extended release and enteric-release technology has become a very useful tool in the medical practice as they overcome the problems of conventional oral therapy and offer numerous advantages as well. The delivery of drug to the intestinal region can be achieved by applying coating of enteric polymers on the solid dosage form. Colon-specific drug delivery is being evaluated as a promising option not only for colonic pathologies but for systemic absorption of drugs as well. Various semi-synthetic and synthetic polymers are being used for producing an enteric coated drug product to provide the desired site-specific effect. Enteric coating increases the stability of drugs in gastric fluids and dissolves in the intestinal pH to release the drug for absorption.

Keywords: Enteric coating, colon-specific delivery, systemic absorption, enteric coating polymers.

Contents

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1. Introduction

Oral site-specific drug delivery systems have attracted a great deal of interest recently for the treatment of a variety of bowel diseases and also for improving systemic absorption of drugs, which are unstable in the stomach. However, the micro-environment in the gastrointestinal tract and varying absorption mechanisms generally cause hindrance for the formulation scientist in the development and optimization of oral drug delivery. Delivery of therapeutic agent into the intestinal region could be accomplished by the application of an enteric coating on a solid dosage form. Several approaches have been attempted and reported during the last decade to develop new methodologies for site-specific drug release, including pH sensitive drug release and time controlled drug release. Among these, the time controlled release systems such as sustained or delayed-release dosage forms are very promising. Nevertheless, due to the potentially large variation of gastric emptying time of dosage forms in human, these dosage forms may show high inter-patient variability in the site of drug delivery. On the other hand, pH sensitive delivery systems such as

enteric coating dosage forms offer a simple and practical means for intestinal drug delivery[1]. Colon is being evaluated as a promising site for the drug delivery, not only for local colonic pathologies but also for the systemic drug delivery of protein and peptide drugs. This site may also be useful in the treatment of diseases susceptible to diurnal rhythm such as asthma, arthritis, etc[2,3]. As a site for drug delivery, colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and an increased responsiveness to absorption enhancers. This has led to the development of various systems for targeting drugs to the colon. These include pH-controlled release systems, enzyme-controlled delivery systems (including prodrugs and polysaccharides based delivery systems), time-controlled release systems and pressure/ osmotically controlled release systems,[4,5,6].

Enteric coated systems are designed to provide protection to tablets in the stomach. Application of a thicker coat causes a delay in the drug release in the small intestine and slows down drug release, which is both pH and time-controlled. This ensures drug delivery to be colon specific. For the preparation of such tailor-made formulations, the selection of a polymer with a suitable coat level is crucial[7].

Most of the commercially available systems for colon specific drug delivery utilize Eudragit (L-100/ S-100) or cellulose acetate phthalate (CAP). Other coating polymers such as shellac (SH) and ethyl cellulose (EC) may provide an alternative polymer for the development of these systems. Eudragit S-100 (ES) is a methacrylic acid methyl methacrylate co-polymer, which is soluble at a pH of 7. CAP is also an effective enteric coating material as it dissolves at a pH of 6. It is used at a concentration of 0.5-0.9%[8].

For a formulation to acts as an effective colon specific drug delivery system, the primary condition is that a minimum amount of drug should be released in the environment of the upper GIT, i.e. in stomach and small intestine. The normal transit time in the stomach is 2 hours (though this may vary); while in intestine it is relatively constant and is around 3 hours[2]. The usual colonic transit time varies from 20-30 hours. Thus, for a dosage form to be effective as a colon drug delivery system, the drug release is required to be retarded in the upper GIT conditions. Thereafter, the drug release should be complete within the next 20-30 hours [5].

2. Coating of Solid Dosage Forms

Film coating of solid dosage forms is a highly sophisticated process, first described in 1930[9]. Its obvious advantages resulted soon in replacement of the traditional sugar coating by the emerging technology. Thus the first film-coated tablet became commercially available in 1954. The technology advanced with the introduction of the semi-synthetic cellulose derivatives and the synthetic acrylic polymers in the early 1950s[10,11].

Film coatings are applied for several reasons[9,12,13]:

a. Taste masking and moisture/light protective coatings
b. Improved product appearance
c. Improved mechanical resistance (reduced friability)
d. Modified drug release (e.g. Gastric resistant or extended release coatings)

The properties and performance of the final coat is strongly affected by the polymer properties and the formulation parameters. The coating formulation may contain other major components besides the polymer such as solvent, plasticizer or pigments which can affect the performance of the coat by changing e.g. the mechanical properties [9, 14].

Based on their origin or preparation:

a. Natural polymers
b. Semi-synthetic polymers
c. Synthetic polymers

Natural polymers are mostly subjected to several purification steps, but without chemical modification. Usually, related to their origin, they are mixture of different compounds, subjected to a certain variability of their composition and thus the variability in the resulting performance [9,15].

Semi-synthetic polymers are derivd from a natural substance, receiving its specific property after certain chemical modifications. E.g. the cellulose derivatives.

Synthetic polymers are fully chemically synthesized, e.g. methacrylic acid copolymers.

Protective coatings:

Sometimes, thin films of water soluble polymers are often applied for masking the unpalatable taste or odor, to improve the stability of moisture sensitive products or for better mechanical resistance of the coated product during handling 16]. Such protective coatings need to remain intact for the short time of swallowing the dosage form. Thereafter, they should dissolve instantaneously to assure immediate drug release without retardation. Polymers employed for this purpose are mostly water soluble, such as cellulose ethers (e.g. HPMC, PVA, PVP)[17].

Functional coatings:

Film coatings applied to achieve a certain desired release profile of the incorporated drug are generally called functional or modified-release coatings. Those, intended to protect the drug from the acidic environment of the

gastric medium or to prevent the drug release in this part of GIT, are commonly called enteric coatings. Extended-release coatings, in contrast, are required to control the release of the drug over a prolonged period of time [14].

Extended release coatings:

The patient compliance is strongly decreasing in cases where multiple daily administrations are necessary to maintain constant blood levels of the drug. Thus, extended release polymers were developed to provide a sustained action by releasing the drug in a controlled manner over a period of time. Waxes and some natural polymers were already discovered earlier to be useful for this purpose. Their mechanism of drug release is based on slow degradation or erosion[10,14].

Enteric coatings:

An enteric coating is a barrier applied to oral medication that controls the location in the digestive tract where it is absorbed. Enteric refers to the small intestine; therefore enteric coating on the dosage form prevents the release of drug before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable to highly acidic pH of stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. Enteric coating is suitable for drugs that have irritant effect in stomach (like aspirin), drugs which are unstable in acidic pH of stomach. Thus, enteric coating is aimed to prevent the formulations from gastric fluid in the stomach and release the drug component in the intestinal region or once it has passed into the duodenum.

Some of the most important reasons for the application of enteric coating to the dosage form are as follows:

1. To protect the acid-labile drugs from the acidic pH of gastric fluid. Example: enzymes and certain antibiotics.
2. To prevent gastric distress or nausea due to irritation caused by certain drugs. Example: Sodium salicylate.
3. To deliver drugs intended for the local action in intestines. Example: intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach.
4. To deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
5. To provide a delayed release component to repeat action tablets.

Enteric coating polymers:

a. An ideal enteric coating material should possess the following properties:
b. Resistance to gastric fluids.
c. Ready susceptibility to or permeability to intestinal fluids.
d. Compatibility with most of the coating solution components and the drug substances.
e. Stability alone and in the coating solutions i.e. the film should not change upon aging.
f. Formation of a continuous film on the dosage form.
g. Non-toxic and non-irritant.
h. Low cost.
i. Ability to be readily printed or to allow film to be applied to debossed tablets.

With an acid-resistant property, enteric coating polymers are primarily weak acids containing free carboxylic acid groups on the polymer backbone, thus are capable of ionization at elevated pH. In the low pH of stomach, these polymers are unionized and therefore, insoluble in acidic media but these functional groups ionize and the polymer becomes soluble in basic media as the pH increases in the intestinal tract (pH >5). Solubility of the polymers depends on the number of carboxylic groups varied in the composition. Thus, an enteric polymeric film coating allows the coated solid to pass intact through stomach to the small intestine, where the drug is finally released for absorption through the intestinal mucosa into the systemic circulation where it is intended to exert its pharmacological action.

Enteric coating polymers can be classified into 3 groups based on chemical compositions as listed below:

1. Polymethacrylates

- Methacrylic acid / Ethyl acrylate

2. Cellulose esters

a. Cellulose acetate phthalate (CAP)
b. Cellulose acetate trimellitate (CAT)
c. Cellulose acetate succinate
d. Hydroxyl propyl methyl cellulose acetate succinate (HPMCAS)
e. Hydroxyl propyl methyl cellulose phthalate

3. Polyvinyl derivatives

- Polyvinyl acetate phthalate (PVAP)

Commercial enteric polymers are available as powder, aqueous dispersions and organic solution.

Cellulose acetate phthalate (CAP):

Cellulose acetate phthalate was synthesized in 1940 by Hiatt and was one of the first polymers used for its enteric properties1. The CAP polymer exhibits rapid dissolution at a pH > 6 and is relatively permeable to moisture and gastric juices. Due to its high moisture permeability, CAP is susceptible to hydrolytic decomposition. Phthalic and acetic acid molecules may hydrolyze during storage and significantly compromise the degree of enteric protection

that the film coating provides. The addition of a plasticizing agent has been shown to improve the water resistance of CAP films[18].

This cellulose derivative has half OH groups acetylated and one quarter esterified with phthalic acid. It is practically insoluble in water and ethanol; soluble in acetone. Diethyl phthalate triacetin can be used as plasticizer. These days, colloidal latex dispersion of CAP (10-30% solids) that can be diluted prior to application, is the most widely used in enteric film coating. CAP concentrations in oral formulations are typically limited to 0.5-0.9% of the tablet core weight. It is practically insoluble in water, alcohols and chlorinated and non-chlorinated hydrocarbons but demonstrates good solubility in acetone, methanol, ethanol and several solvent mixtures. The glass transition temperature of CAP is 175°C but is reportedly compatible with various plasticizers including acetylated monoglyceride, butyl phthalyl butyl glycolate, dibutyl tartarate, diethyl phthalate, dimethyl phthalate, glycerin, triacetin and propylene glycol. A 20% w/w addition of triacetin, diethyl phthalate reduces the glass transition temperature to 95°C and 100°C respectively. Like other phthalates, CAP is susceptible to hydrolysis under high temperature and high humidity [19].

Cellulose acetate trimellitate (CAT):

This cellulose derivative contains part of OH groups acetylated and part esterified with mellosic acid. It is practically insoluble in water and ethanol; soluble in acetone. Diethyl phthalate triacetin can be used as plasticizer. Cellulose esters (CAP, CAT, HPMCP) can be modified as aqueous film formers by partially or completely neutralizing the free acid groups of the polymer. Enteric film is formed as the coating comes in contact with the acidic medium in the stomach (salt _ free acid groups). As adjuvants triacetin (plasticizer) and magnesium carbonate (stabilizing agent) can be used. Acid resistance and stability of the neutralized enteric film coatings can be varied[20].

Hydroxyl propyl methyl cellulose acetate succinate (HPMCASs):

HPMCASs are synthetically modified mixtures of acetic acid and monosuccinic acid esters of hypromellose. These are available in three grades (L, M & H), which correspond to pH dependent release profiles of low pH (5), medium (5.5) and high (6.5) pH. These synthetically modified natural products are traditionally used as controlled-release agents, enteric coating agents, film-forming agents, sustained-release agents and more recently as solubility enhancing agents. HPMCASs are incompatible with acids, peroxides and other oxidizing materials18. HPMCASs are practically insoluble in all organic solvents, but they can form a turbid viscous solution with the addition of acetone, or a mixture of ethanol and dichloromethane. These polymers have glass transition temperature ranging between 120^{o}C -135 ^{o}C[21].

Hydroxyl propyl methyl cellulose phthalate:

These are natural cellulose synthetically modified to produce partly methyl ethers, 2-hydroxy propyl ethers and phthalyl esters. These polymers are typically used in oral pharmaceutical formulations as enteric coating materials for tablets, beads or granules. These polymers are characteristically insoluble in gastric fluids but are swellable and rapidly soluble in the upper intestine. These can be used as coating agents because they do not require the addition of plasticizer or other film formers to produce coatings for oral formulations[18].

Hypromellose phthalates are insoluble in dichloromethane, methanol, isopropanol, ethyl acetate and ethanol but demonstrates desired solubility in acetone, tetrahydrofuran, mixtures of dichloromethane and methanol, mixtures of DCM and ethanol and mixtures of acetone and methanol. The insolubility of this polymer in single-solvent system makes it challenging to conduct simple drug-compatibility studies and spray drying applications. However, solvent mixtures can be effectively prepared for commercial spray-drying by using proper spray-drying optimization. These polymers remain chemically and physically stable at room temperatures for several years but are susceptible to hydrolysis under elevated temperatures and humidity conditions[18].

Polyvinyl acetate phthalate (PVAP):

This is another enteric polymer commonly used to coat solid dosage forms. This polymer is structurally similar to CAP containing the dicarboxylic phthalic acid ina partially esterified form. Faster release of drug components occurs with PVAP because its dissolution occurs at a pH of approximately 5.0. Due to its lower moisture permeability, PVAP is relatively more stable to hydrolysis than CAP.

Polymethacrylates:

In the mid 1960s, Lehmann and Dreher developed copolymers of methyl methacrylate and ethyl acrylate as ester components with methacrylic acid for use as enteric polymers. These polymers are produced by an emulsion-polymerization process and are commercially available in several forms. The dissolution properties of these polymers are dependent on the content of carboxyl groups in the polymer[22]. They are synthetic cationic and anionic polymers of dimethyl aminoethyl methacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Polymethacrylates are commercially available for use as film forming agents, tablet binders and tablet diluents. e.g. cationic methacrylate, methacrylic acid copolymer Type A, Type B and Type C[18].

3. Conclusion

By the above discussion, it can be easily concluded that enteric coated drug products are helpful in increasing the efficiency of the dosage form and overcoming theproblems of patient compliance and conventional therapy. The market for enteric coated products has come a long way and will continue to grow in future with further advancements in the technology. At present there remains a scarcity of new polymeric materials but one unique approach is to use the combinatorial methods to design arrays of new polymeric materials. Thus, colon specific drug delivery offers a wide scope for drug targeting techniques and improved bioavailability of active drug molecule as well.

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