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REVIEW

Review Article on Advanced Polymers Use in Gastroretentive Drug Delivery Systems

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Abstract

Conventional dosage forms could not manage release of active substances resulting in reduced bioavailability and side reactions. Being retained in a certain site in the gastrointestinal tract (GIT) could achieve further bioavailability particularly regarding drugs having low gastric absorption and low solubilization or less stability at elevated pH. Therefore, Gastroretentive drug delivery systems (GDDS) are unique approaches with gastric retention and controlling the release rate for maximizing the efficacy. The polymers broadly applied in GDDS are mainly of two sorts, natural and synthetic, according to their nature. Synthetic polymers such as Hydroxypropylmethyl cellulose (HPMC), Eudragit and Ethylcellulose while natural polymers such as natural gums, sodium alginate and Chitosan.

Keywords: Synthetic polymers, Natural polymers, GDDS, HPMC, Chitosan

1. Introduction

Oral delivery is broadly applied route to medicines comparing to other routes. Several variables may affect absorption of drug, such as unwanted physical and chemical characteristics, site of absorption, gastric emptying, and GIT transit time. The primary drug absorption sites are stomach and upper small intestine. It is essential to prolong the time of residence at or prior to the location of absorption for optimization of bioavailability, reduction of doses, and achieving patient compliance [1]. GDDS are novel methods invented to overcome obstacles by keeping away from the first pass to maximize bioavailability. The continuous release of the drug conserves the therapeutic level constant. Drugs having shorter half-lives can perform relatively higher therapeutic response when formulated in GDDS. The prevalent GDDS systems such as the floating and pulsating drug delivery system (FDDS/PDDS) that enhance efficacy by extending the GRT (gastric retention time) either effervescent or non-effervescent [2–4]. Furthermore, GDDS can achieve the controlled delivery of drugs by keeping steady release for a prolonged time at the wanted rate and to the wanted location of

absorption until the drug is totally free from the pills [5–7]. Many polymers are used in GDDS that can be categorized into two types according to their origin.

1.1. Synthetic polymers

The synthetic polymers perform a chief role in the pharmaceuticals employing as binders, film coating agent, etc. They may be either 100% synthetic or manufactured from a natural one. For instance, HPMC, ethyl cellulose and Eudragit. They have some drawbacks like high cost, pollution, low biocompatibility and sensitivity [8].

1.1.1. Hydroxypropyl methyl cellulose (HPMC, hypromellose)

HPMC is white, water soluble powder. It is semi synthetic, inert, viscoelastic polymer, applied in pharmaceuticals as an excipient and controlled-delivery component. They solubilize in cold water, composing a viscous colloid but it is characterized by insolubility in hot water, and ethyl alcohol (95%). Nevertheless, certain sorts may swell in ethyl alcohol [9]. They are used as bioadhesive, film composing and sustained release materials. Grades having high viscosity are utilized to sustain the release of active

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materials at percent 10–80% w/w. The HPMC is utilized in oral syrups at 2–5% as suspending and/or thickening substances. Percent from 2 to 20% w/w depending on the viscosity is utilized in film coating tablets such as pharmacoat [10].

Rahamathulla et al. prepared losartan potassium effervescent floating GDDS employing HPMC 15,000 and karaya gum. Losartan potassium is less soluble at high pH resulting in reduced bioavailability. Therefore, GDDS were invented to extend GRT and enhancing its bioavailability. The tablets exhibited acceptable floating for 24 h, and extended release for 24 h. The optimized formula F3 containing HPMC released 100% drug in 24 h. Moreover, its floating was continuous in the stomach of rabbit as the GRT exceeded 12 h. Its bioavailability was maximized comparing to losartan potassium oral solution [11].

1.1.2. Eudragit (polymeric methacrylates)

Eudragits are marketed as dry powders and emulsions. Acetone and isopropanol(60:40) mixed solution is employed to dissolve Eudragit. 95% acetone and alcohol are used to dissolve Eudragit S 100 that is exist as a powder utilizing for enteric coating to withstand eroding in stomach and allow release in enteric fluid of pH 7. They can solubilize immediately in neutral to weak basic and, can form membrane sheaths that are tolerant to the juice of stomach and erodible in the fluid of intestine [12].

Eudragits are mainly utilized in oral capsules and tablets as coating. According to the type of polymer used, films melting differs. Eudragit S 100 dissolves in acetone and ethyl alcohol. Eudragit species are utilized to enteric coating due to their tolerance to gastric fluid. Eudragit RL, RS, NE 30D, NE 40D and NM30D could create water insoluble film coating in extended release dosage forms. Eudragit RL produces permeable films more than those of Eudragit RS, mixing them allow variable permeability. Larger amounts (5–20%) of the dried Eudragit are employed to manage the dissolution from the tablets. In percentage range (10–50%), dried polymers are employed in direct compression. Eudragits were also employed for transdermal route and new gel to use rectally. Eudragit E are utilized in microparticles, nanoparticles, ophthalmic liquids and GDDS [12].

Many studies included using of Eudragit in GDDS such as Gupta et al. introduced famotidine GDDS to target stomach to treat ulcer using Eudragit S100. Results indicating good floating and SEM studies confirmed floating cavity and porous surface of microsphere [13]. Also, Tort et al. produced pramipexole nanofibers GDDS made from Eudragit RL and RS. The nanofiber formulae showed floating lag

time lower than 1 s and provided sustained release [14].

1.1.3. Ethyl cellulose

Ethocel (Ethylcellulose) is employed in pharmaceuticals for numerous purposes like masking the bitter taste of some drugs, moisture protection, stabilizing, extended-release multi-particle coating, precision packaging, and prolonged release. Ethocel is water insoluble. And it does not solubilize in the acidity of the stomach; however, it swells in the stomach and becoming permeable to water, allowing the extended release [15].

Ethocel is rarely applied in wet extrusion due to having great elasticity; however, it is applied successfully in corporation with some plasticizer. The fine and coarse Ethocel are utilized in extrusion and water may be employed in wet granulation when using fine one. A few kinds of Ethocel has been permitted to be used in extended-release solid dosage and GDDS. There are several types of ethylcellulose that are dissimilar in the viscosity and length of the chains [16].

El-masry MS et al. prepared GDDS of cefditoren pivoxil to enhance its solubility and increase its bioavailability. Cefditoren solid dispersions (SDs) were formulated by polyvinylpyrrolidone (PVP) and Poloxamer 188. The formulated SDs improved cefditoren release when comparing with pure substance. SDs PVP were chosen to compose GDDS. Polymers including HPMC K15M or ethyl acetate were applied using gas-generating substances (citric acid and sodium bicarbonate). The optimized formula exhibits excellent sustained release profile [17].

1.2. Natural polymers

They are originated from plants. Moreover, they are hydrophilic carbohydrate polymers. They are insoluble in organic solvents and were discussed below:

1.2.1. Chitosan

It is natural polymer manufactured from chitin. It is characterized by desirable biological characteristics like non toxicity, biodegradability, and biocompatibility. Due to having bioadhesive ability, it is appropriate for site delivery and FDDS. In neutral and acidic circumstances, it shows buoyancy and extends release. Enlarging thickness of chitosan film reduce release rate. As the film of chitosan thickened more, the dissolution is reduced that decreases influence of GIT transit time. Hollow microparticles float for 12 h in stomach. Kulkarni et al., prepared

glipizide GDDS using chitosan/xanthan gum mixtures to obtain dense particles. The study results revealed that the chitosan/xanthan gum ratio affected the mucoadhesive characteristics [18,19]. Kaewkroek K et al. developed starch – chitosan film to deliver ginger GDDS in controlling release of 90% of 6-gingerol after 8 h [20].

1.2.2. Natural gums

Xanthan gum is a polysaccharide obtained from fermentation of carbohydrates. It dissolves in acidic and alkaline solutions. It can either enlarge or reduce the drug release rate. It is soluble in water. It has elevated viscosity at low percent and this is a great advantage for drug release. Moreover, it has been proven that some tablets containing xanthan gum in corporation with citric acid were able to float for 24 h. Gellan gum is a polysaccharide after fermentation of *spingomonas elodea*. It is characterized by astonishing release, high strength, stability, flexibility, high clarity, good film composer and reversible gelling. On addition of positively charged ions, it undergoes gelling [21].

Guar gum is polysaccharide. It is characterized by solubility in water and insolubility in organic solvents. Guar gum undergoes hydration and swelling in cold water composing viscous colloid. Its ability of gelling delays the release and act as an ideal carrier for GDDS. It is applied as a softener and as a polymer in a FDDS. Guar gum is advantageous GDDS due to the swelling of the polymer. Other types of gum are used such as okra gum, karaya gum, fenugreek gum and mimosa gum.

A lot of studies investigated using natural gums. For instance, Sabale et al. developed famotidine gastroretentive tablets applying guar gum to invent controlled release tablets by increasing GRT of famotidine. Six formulae exhibit good physico-chemical properties. GDDS containing natural polymer revealed extended drug release. The optimized formula had good floating and the release was controlled [22]. Moreover, Lad G.C et al. designed metformin hydrochloride floating tablets to investigate natural polymers effect on dissolution including okra gum and fenugreek gum. Addition of sodium bicarbonate to generate gases that releases carbon dioxide in to preserve the buoyancy. Metformin hydrochloride is not totally absorbed from GI tract, its absorption window referred to the upper GI tract, having short half-life (2 h) and bad bioavailability (50–60%). Side effects of metformin hydrochloride happened in 30% patients, particularly in first weeks. To increase patient compliance, the sustained release (SR) floating trials achieved good bioavailability and efficacy [23].

1.2.3. Sodium alginate

Sodium alginate is practically insoluble in ethanol (95%), and acidic solutions. It solubilizes in aqua, turns into a gel, therefore, it can to be applied in GDDS. It has various marketed sorts. Viscosity differs affected by some factors like percent and the existence of some ions. Moreover, it reduces at an elevated pH [24].

Some researchers investigated role of sodium alginate in GDDS. For example, Srinivas L invented and assessed Lafutidine GDDS formulae applying Box–Behnken design. The buoyancy lag time of formulae was from 14 to 25 s, the time of gelling exceeded 12 h, and the release was 86.86–99.34% in 12 h. The optimized formula (sodium alginate, HPMC K4M, xanthan gum) exhibited the best characteristics [25]. Furthermore, Palanivelu M et al. formulated ranitidine hydrochloride GDDS microsphere using sodium alginate, Carbomer and Chitosan. The microspheres were evaluated including the percentage yield ranged from 58% to 90% and the in-vitro buoyancy of the microspheres ranged from 67% to 81% [26].

2. Conclusion

The inability to maintain some active substances in stomach or upper small intestine may lead to insufficient bioavailability to many active materials that are less soluble in or degraded in higher pH of intestinal fluid or drugs with difficulty to be absorbed. Therefore, GDDS are essential approach for prolonging keeping of drugs in site, performing controlled release and enhancing bioavailability. Polymeric substances perform a crucial role in keeping of the dosage form of many active substances in stomach either by floating or by any other mechanisms. Polymers used types and their role were discussed in details.

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