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Formulation and *in-vitro* evaluation of pantoprazole loaded pH-sensitive polymeric nanoparticles

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ABSTRACT

The pH-sensitive polymeric nanoparticles are very efficient delivery systems for acid labile drugs. The main aim of the study was to formulate pantoprazole loaded pH-sensitive polymeric nanoparticles using pH-sensitive polymers to prevent degradation of acid labile drug and evaluate the effect of formation conditions on both nanoparticles characteristics and drug release patterns.

Pantoprazole loaded nanoparticles were prepared using nanopercipitation method using pH-sensitive polymers Eudragit S100 or HPMC phthalate HP55. Nanoparticles were characterized for their micromeritic and crystallographic properties, drug content, *in-vitro* release and the ability to delay pantoprazole release in acidic medium to prevent its degradation.

Physicochemical properties of nanoparticles, including particle size, loading capacity (LC), encapsulation efficiency (EE) and *in-vitro* drug release were significantly affected by formulation conditions. All formulas showed sub micronized size ranging from 299.3 ± 4.62 to 639.7 ± 9.71 nm and achieved delayed release to protect pantoprazole from degradation with different degrees, but generally Hydroxypropyl methyl cellulose phthalate HP55 loaded nanoparticles showed slower drug release than that of Eudragit S100 loaded nanoparticles. Release kinetics and morphological properties of nanoparticles with most delayed release pattern were investigated by Transmission Electron Microscope (TEM) and Compatibility between pantoprazole and polymer was proved by Fourier Transmission Infra Red (FT-IR) and Differential Scanning calorimetry (DSC). The formula stability was evaluated by measuring zeta potential value.

Our results suggested that nanoprecipitation method is effective to produce pH-sensitive polymeric nanoparticles, which can be used as a delivery system for acid labile drug (Pantoprazole) to avoid its degradation in acidic medium of the stomach.

1. Introduction

Pantoprazole is widely used proton pump inhibitor and it is a significant drug in the treatment of acid-related disorders [1] and it is also useful against Helicobacter biliary infections either alone or in combination with other drugs, such as metronidazole, clarithromycin or amoxicillin [2,3].

This drug was the first water soluble benzimidazole, 5-(difluoromethoxy)-2-[[(3, 4-dimethoxy-2-pyridinyl) methyl] sulfinyl]-benzimidazole sodium sesquihydrate [4]. A molecule with benzimidazole substitution exhibits effective and long-lasting inhibition of gastric acid secretion by selectively interacting with the gastric proton pump (K/H-ATPase) in the parietal cell secretory membrane [5].

Pantoprazole (PAN) has several advantages compared to its analogues (e.g., omeprazole) such as a specific site of binding, greater stability in a neutral pH environment, and longer duration of action [6]. Besides, it presents no potential to induce or inhibit the CYP 450 [1,2,7]. It is a more selective inhibitor of acid secretion than other proton pump inhibitors [8].

Abbreviations: PAN, Pantoprazole sodium sesquihydrate; PNPs, Polymeric nanoparticles; HPMCP HP55, Hydroxypropyl methyl cellulose; ES100, Eudragit S100; PI, polydispersity index; LC, Loading capacity; EE, Encapsulation efficiency; SAA, Surface active agent.

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The mechanism of action of pantoprazole includes that, pantoprazole turns into cationic sulfenamide in low pH values, which is its active form [2,9], this drug accumulates in the highly acidic environment of the parietal-cell canalicular lumen and it is activated. The active form, tetracyclic cationic sulfonamide, reacts with the thiol group of cysteines 813 and 822 of transmembranal H+/K + ATPase [1,10]. This conversion must occur beside the gastric parietal cells, so pantoprazole must be absorbed intact from the gastrointestinal tract [2].

Pantoprazole undergoes degradation in the stomach since; it is an acid labile drug [11–13]. Therefore, the drug should be targeted to its absorption site; to avoid the effect of acidic medium in stomach. The gastro resistant drug delivery system is developed for acid labile drugs due to the necessity to pass intact through the stomach for reaching the duodenum for absorption. The dosage form is formulated to bypass the stomach either by formulating a solution for intravenous administration (lyophilized powder for reconstitution) or as gastric-resistant (oral delayed-release) dosage form [14]. In the case of oral administration, the enteric coating prevents the degradation of the acid labile drug in the gastric juice [15,16].

The advantages of pH-sensitive nanoparticles over conventional nanoparticles include (**a**) most carriers have been used as enteric-coating materials for a long time, and their safety has been approved. (**b**) The carriers dissolve rapidly at specific pH and specific sites, which result in quick drug release and high drug concentration gradient. The phenomenon is helpful for the drug absorption. (**c**) The pH sensitive nanoparticles enhance the bioadhesion of the carrier to mucosa and facilitate the drug absorption comparing to the conventional nanoparticles due to that, they turn from the solid state to hydrogel state at the dissolution pH. (**d**) The pH sensitive nanoparticles can improve the drug stability more effectively.

The aim of this study is formulation of pH-sensitive polymeric nanoparticles (PNPs) loaded with pantoprazole using Hydroxypropyl methyl cellulose phthalate (HPMCP) HP55 or Eudragit® S100 (ES100) via nanoprecipitation (solvent displacement/interfacial precipitation) method [17–22]. Morphological properties, effect of formulation conditions on drug loading and encapsulation efficiency, ability of produced nanoparticles to delay release of acid labile drug (Pantoprazole) and hence, protect the drug from degradation in acidic medium of the stomach were also determined.

2. Materials and methods

2.1. Materials

Pantoprazole Sodium Sesquihydrate was supplied from (Arch Pharmalabs Ltd., Mumbai, India). Eudragit® S100 was a generous gift from Heinrich's Commercial Agency, Egypt. HPMC phthalate HP55 was supplied from shin- Etsu Chemical Company (Chiyoda, Tokyo, Japan). Acetone was supplied from El Nasr for chemical pharmaceutical (ADWIC) company (Qalyub, Egypt). Tween 80 was supplied from Kolb distribution Ltd. (Hedingen, Switzerland). Poloxamer 407 was supplied from BASF (Cairo, Egypt).

2.2. Methods

2.2.1. Preparation of polymeric nanoparticles loaded with pantoprazole

Nanoparticles were prepared by nanoprecipitation according to the method developed by Fessi and his colleague's [23]. PH- sensitive polymer either ES100 or HPMCP HP55 and pantoprazole sodium Sesquihydrate were dissolved in acetone to form an organic phase with polymer concentration (0.2 gm %) and different polymer: drug ratio (1:1, 1:2 and 2:1), then organic phase was added drop wise to aqueous phase containing (0.5 and 1% w/v) of surfactant (Tween 80, Poloxamer 407) under magnetic stirring at room temperature with the various ratio of organic: aqueous phase (1:4 and 1:8) as shown in Table 1. Nanoparticles were formed spontaneously and acetone was removed by continuing stirring for overnight at room temperature [24].

2.2.2. Particle size analysis

Measurement of the mean particle size of the nanoparticles dispersion was conducted with the use of laser diffraction particle size analyzer (Master seizer Hydro MU 2000 S, Malvern MU

Table 1
Composition of prepared formulae.

Code	Polymer:Drug	Polymer type	Polymer conc.	Surfactant type	Surfactant conc.	Organic:aqueous phase
T11-1	1:1	Eudragit S100	0.2 gm%	Tween 80	1%	1:04
T12-1					1%	1:08
T3-1					0.5%	1:08
T15-1			0.4 gm%		1%	1:08
P11-1			0.2 gm%	Poloxamer 407	1%	1:04
P3-1					0.5%	1:08
P12-1					1%	1:08
T39-1		HPMCP HP55		Tween 80	1%	1:08
T11-2	1:2	Eudragit S100	0.2 gm%	Tween 80	1%	1:04
T12-2					1%	1:08
T3-2					0.5%	1:08
T15-2			0.4 gm%		1%	1:08
P11-2			0.2 gm%	Poloxamer 407	1%	1:04
P3-2					0.5%	1:08
P12-2					1%	1:08
T39-2		HPMCP HP55		Tween 80	1%	1:08
T11-3	2:1	Eudragit S100	0.2 gm%	Tween 80	1%	1:04
T12-3					1%	1:08
T3-3					0.5%	1:08
T15-3			0.4 gm%		1%	1:08
P11-3			0.2 gm%	Poloxamer 407	1%	1:04
P3-3					0.5%	1:08
P12-3					1%	1:08
T39-3		HPMCP HP55		Tween 80	1%	1:08

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