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Formulation of clarithromycin floating microspheres for eradication of *Helicobacter pylori*

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ABSTRACT

The aim of this study was to develop floating microspheres for gastroretentive delivery of clarithromycin for eradication of *Helicobacter pylori*. The microspheres were prepared by solvent evaporation using ethyl cellulose (EC) at different weight ratio with clarithromycin with hydroxypropyl methyl cellulose (HPMC E5) acting as secondary polymer. The emulsifier employed either polyvinylpyrrolidone (PVP) or polyvinyl alcohol (PVA). The microspheres were evaluated for floatation, drug entrapment and release, particle size, shape and surface morphology. The physical form of clarithromycin was monitored using FTIR, DSC and X-ray diffraction. The microspheres were in micron range with particle size reducing when replacing PVP with PVA. Further size reduction was recorded in presence of HPMC. The entrapment efficiency increased at high EC concentration especially in presence of HPMC. Immediate floatation was seen with at least 56% of the particles remaining on the surface after 8 h. Physical characterization reflected amorphousization or solubilization of clarithromycin after entrapment in the microspheres. The release pattern followed Higuchi matrix kinetic model in most formulations except those containing low concentration of EC or those containing high HPMC content with HPMC increasing the rate of drug release. The study presented floating microspheres with different release pattern depending on the composition.
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1. Introduction

Development of gastroretentive dosage forms has gained much attention recently [1]. Gastric residence time (GRT) is considered as one of the important factors affecting the bioavailability of drugs after oral administration [2]. Variable and/or rapid gastric emptying rate may result in incomplete drug release with subsequent reduction in drug absorption. This is specifically manifested with drugs having narrow absorption window in the upper part of the gastrointestinal tract [3]. The oral bioavailability of such drugs can be sufficiently increased by prolonging GRT through gastroretentive dosage form [4]. Gastroretentive drug delivery systems have high potential for improving local action in the upper part of the GIT. Alternative strategies have been utilized to develop gastroretentive drug delivery systems. These include preparation of mucoadhesive systems, swelling and expanding systems and floating drug delivery systems [5]. The former type has many problems including aggravation of the stomach ulceration. In addition, there is a high possibility for failure of mucoadhesion. Floating drug delivery systems are those that remain buoyant over gastric contents. These systems can employ either single solid dosage form or multiparticulate drug delivery formulations. The later type has gained much interest due to reduced inter and intra-subject variability and lower probability of dose accumulation [6–8].

Helicobacter pylori (H. pylori) is a microorganism which survive in the upper part of the GIT. It is one of the most important reasons for gastric ulceration. Eradication of such organism requires high local concentration of the antibacterial agent in the upper part of the GIT. This can be achieved only through gastroretentive formulation [9]. Clarithromycin is one of the most widely used agents for eradication of *H. pylori*. It showed high potential for application as a monotherapy in vivo [9]. Clarithromycin is acid stable and is well absorbed from the gastrointestinal tract, irrespective of the presence of food with oral bioavailability of 55% [10]. The objective of this work was to develop and evaluate a multiparticulate gastroretentive formulation for clarithromycin.

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2. Materials and method

2.1. Materials

Clarithromycin, Ethyl cellulose, Hydroxypropyl methylcellulose, were obtained as gift samples from Sigma for Pharmaceutical Industries, Quesna, Egypt. Polyvinylpyrrolidone (PVP) was procured from Sigma Chemical Company, St Louis, MO, USA. Methanol, dichloromethane (pharmaceutical grade) were obtained from El Nasr Pharmaceutical Chemicals Company, Cairo, Egypt. All other chemicals used were of analytical grade.

2.2. Preparation of microspheres

Microspheres containing clarithromycin as the core material were prepared by solvent diffusion evaporation technique with slight modification [11]. Table 1 presents the composition of the tested formulations. The drug and polymers were dissolved in a mixture of methanol and dichloromethane (1:2 v/v). This solution was slowly introduced into 200 ml of aqueous solution of either polyvinylpyrrolidone (0.13% w/v) or polyvinyl alcohol (PVA) (0.9% w/v) as emulsifiers. The organic solvent was evaporated under continuous mechanical stirring using paddle mixer for 3 h at ambient temperature. The resultant microspheres were washed 4 times with distilled water before being collected using mesh screen. The microcapsules were dried at ambient temperature [12].

2.3. Assay of drug

Drug analysis employed colourimetric determination after derivatization reaction using p-dimethyl amino benzaldhyde (PDMAB) and sulfuric acid. The reagent was prepared by dissolving 2 g of PDMAB in 100 ml concentrated sulfuric acid. Stock solution of clarithromycin was prepared by dissolving 50 mg of drug in 50 ml methanol to produce a solution containing 1000 μg/ml. This stock was used to prepare drug solutions containing 30, 40, 50, 60, 70, 80, 90 and 100 μg/ml. These were prepared by adding the required amounts of the stock solution in 10 ml volumetric flasks followed by addition of PDMAB (1.5 ml) and completing to the volume with concentrated sulfuric acid. This produces green coloured species which is quantified by colourimetric determination at 600 nm using a blank which is similarly treated in absence of drug. The recorded absorbance values were plotted as a function of drug concentration to construct the calibration curve [13]. The method was validated for linearity, accuracy, range, precision, lower limit of detection (LOD) and lower limit of quantification (LOQ). This was conducted according to the ICH guidelines [14].

Table 1
The composition of floating microspheres.

Formula	Drug(g)	Ethyl cellulose (g)	HPMC (mg)	Emulsifier
F1	1	1	–	PVP
F2	1	2	–	PVP
F3	1	3	–	PVP
F4	1	2	25	PVP
F5	1	2	50	PVP
F6	1	2	100	PVP
F7	1	3	100	PVP
F8	1	1	–	PVA
F9	1	2	–	PVA
F10	1	3	–	PVA
F11	1	2	25	PVA
F12	1	2	50	PVA
F13	1	2	100	PVA
F14	1	3	100	PVA

2.4. Characterization of floating microspheres

2.4.1. Surface morphology and particle size

The surface morphology and particle size were determined using scanning electron microscope (SEM). The samples were dried in a critical point drying machine using liquid carbon dioxide. The dry samples were mounted on aluminum stubs and were coated with gold in a SPI-MODULE™ VAC/Sputter before scanning and photography using SEM (JEOL- JSM-5200 LV, Japan) which was adjusted to 25 KV.

2.4.2. Drug entrapment efficiency (EE)

Known weight of the dry floating microspheres (50 mg) was taken and crushed before addition of methanol (50 ml) under magnetic stirring. The solution was then filtered using syringe filter 0.45μ before determination of the drug concentration using the developed colorimetric method. The percent drug entrapped was calculated as using the following equation [9]:

$$EE\ (\%) = (\text{Calculated drug content/ Theoretical drug content}) \times 100$$

2.4.3. In vitro evaluation of floating ability

Known weight of the floating microspheres (100 mg) was added to dissolution vessel containing 200 ml of simulated gastric fluid (0.1 N hydrochloric acid, pH 1.2) maintained at 37 °C. The paddle was adjusted to a stirring rate of 100 rpm for 8 h at the end of which the buoyant microparticles were collected by sieving. The settled microspheres were harvested as well. The collected microparticles were left to dry at ambient temperature before recording the weight of each fraction. The floating ability was calculated as the percent buoyancy which was estimated according to the following equation in which WF represents the weight of the floating fraction and WS is the weight of the settled fraction [12].

$$\text{Buoyancy}\ (\%) = WF/(WF + WS)*100$$

2.4.4. Differential scanning calorimetry (DSC)

Thermal analysis of the drug, the polymers and the medicated microspheres was performed using a differential scanning calorimeter (Shimadzu, DSC 60, Japan). Known weight of the test sample was loaded in aluminum pans which were crimped and mounted on the DSC. The thermal events were recorded while heating from 30 to 400 °C at a heating rate of 10 °C/minutes. This was performed under continuous stream of nitrogen gas. The recorded data were analyzed using thermal analysis software (TA-60WS). The equipment was calibrated using indium.

2.4.5. Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of the unprocessed drug, polymers and the microsphers were recorded using a Bruker Tensor 27 FTIR spectrophotometer (Ettingen, Germany) equipped with a deuterated L-alanine dopedtriglycine sulfate (DLaTGS) detector. Samples were mixed with potassium bromide (spectroscopic grade) and compresed into disks using hydraulic press. These disks were subjected to FTIR scanning in the range of 4000 to 400 cm^{-1}.

2.4.6. Powder X-ray diffraction (PXRD)

The crystalline nature of the drug in pure state and after encapsulation into microspheres was monitored using X-ray diffractometry. This employed GNR APD 2000 pro-X-ray diffractometer with Cu Ka radiation (1.54056 Å) (Italy). The diffractometer

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