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Development of gastroretentive metronidazole floating raft system for targeting *Helicobacter pylori*

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ABSTRACT

The study demonstrates the feasibility of prolonging gastric residence time and release rate of metronidazole (Mz) by preparing floating raft system (FRS) using ion-sensitive *in situ* gel forming polymers. FRSs contained 3, 4, 5 and 0.5, 0.75, 1% w/v sodium alginate (Alg) and gellan gum (G), respectively, 0.25% w/v sodium citrate and calcium carbonate (C). Lipids: glyceryl mono stearate (GMS), Precirol® and Compritol® were incorporated into G-based formulations ($G_{1\%}C_{1\%}$). Mz:lipid ratio was 1:1, except for Mz:GMS, ratios of 1:1.5 and 1:2 were also investigated. Buoyancy, gelation capacity and viscosity parameters were evaluated. Drug release and kinetics for selected formulae were examined. The selected lipid containing formula was subjected to an accelerated stability testing.

$Alg_{4\%}C_{2\%}$ FRS exhibited short gelation lag time (3 s), long duration (>24 h), floating lag time 1 min and duration >24 h, and a reliable sustained drug release (MDT 6 h). Gellan gum FRSs achieved successful floating gastroretention, but failed to achieve the required gelation capacity. Incorporation of GMS (Mz:GMS 1:1) enhanced the gelation lag time and duration (6 s and >24 h, respectively), keeping sustained drug release and formulation stability. The improved characteristics of the selected FRS make them excellent candidates for gastric targeting to eradicate *Helicobacter pylori*.

1. Introduction

Infection with *Helicobacter pylori* (*H. pylori*) is a cofactor in the development of important gastrointestinal diseases including gastritis, peptic and duodenal ulcers, gastric adenocarcinoma and colorectal neoplasm (Inoue et al., 2014; Khalifa et al., 2010). About half a million new cases/year of gastric cancer, have been linked to *H. pylori* infection, and it has been predicted to be one of the top ten leading causes of death worldwide by 2020. There are various obstacles in the eradication of *H. pylori* infections, including low antibiotic levels and poor accessibility of the drug at the site of infection (Adebisi et al., 2015). It is believed that absorption of an antibiotic through the mucus layer, is more effective for *H. pylori* eradication than absorption through the basolateral membrane (Prasanthi et al., 2011). Accordingly, preparing gastroretentive dosage forms is crucial for complete eradication of *H. pylori*.

Some approaches have been proposed to increase the gastric residence time of anti *H. pylori* drugs. They include *floating systems*, *e.g.*, tablets (Emara et al., 2014), minitablets (El-Zahaby et al., 2014a), liquid raft (Rajinikanth and Mishra, 2008; Rajinikanth et al., 2007; Dettmar and Lloyd-Jones, 1994), beads (Adebisi and Conway, 2013), microspheres (Tejaswi et al., 2011), *mucoadhesion systems* (Adebisi et al., 2015; Arora et al., 2012), and *size increasing systems* (El-Zahaby et al., 2014b). Among those systems, the floating raft system (FRS) is an advanced revolution in oral controlled drug delivery. It is a formulation of effervescent floating liquid with *in situ* gelling properties, which has been assessed for sustaining drug delivery and targeting. Moreover, the gels formed *in situ* remained intact for more than 48 h to facilitate sustained release of drugs (Ibrahim, 2009). The mechanism of the FRS involves the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called raft (Vinod et al., 2010). This layer floats on the gastric fluid because it has bulk density less than the gastric

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fluid, as low density is created by the formation of CO_2. So the system remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Pandey et al., 2012). The goal for designing this system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, decreasing the dose required or providing uniform drug delivery. Floating obtained from FRS is faster than the other floating dosage forms. The FRS also possesses some potential advantages like simple manufacturing processes, better patient compliance and ease of administration (Singh and Kim, 2000; Gaur and Saraswat, 2011; Prajapati et al., 2013). A successful FRS should fulfill some aspects, including immediate floating of the formulation to prevent rapid gastric emptying; rapid *in situ* gelling to prevent carbon dioxide escapes maintaining floating and decreasing initial burst effect; keeping intact gel patch all through the time required for drug release; providing reliable viscosity of formulation sol at administration, *i.e.*, compromise between pourable sol, and a viscous one for good gelation capacity, sustaining drug release, and ensuring reproducible dosing.

Metronidazole (MZ) is an active adjunct in treatment of *H. pylori* (Emara et al., 2014). It offers the advantage of having pH independent activity (Prasanthi et al., 2011), unlike the anti-*H. pylori* antibiotic, clarithromycin (Rajinikanth and Mishra, 2008). The problems of bacterial resistance and side effects associated with Mz could be recovered by formulating gastroretentive FRSs, since they provide adequate prolongation of drug release near the ecological niche of the bacterium (Rajinikanth et al., 2007). Few literatures had studied the Mz raft system using the traditional *stimuli*-responsive polymers (Thomas, 2014; Jamdhade et al., 2014). The use of emulsifying lipids is a novel approach that could be exploited to ameliorate the FRS characteristics. Based on our knowledge, there is scarce studies in literatures that had utilized this approach in formulating FRS, only glyceryl mono oleate was tried (Ibrahim, 2009). The aim of the present study was to prepare optimized FRSs containing the anti-*H. pylori* drug Mz using the ion-sensitive *in situ* gel forming polymers sodium alginate (Alg) and gellan gum (G). The use of amphiphillic lipids, with low HLB values, namely, glyceryl mono stearate (GMS), Precirol® (Pr) and Compritol® (Cp) to optimize both the gelation capacity and release rate of the proposed Mz FRSs was investigated.

2. Materials and methods

Metronidazole was a gift from Pharonia Pharmaceuticals Company, Alexandria, Egypt. Gellan gum (Gelrite®) was purchased from Sigma–Aldrich, Germany. High viscosity sodium alginate was purchased from Sisco Research Laboratories Pvt. Ltd., Mumbai, India. Glyceryl behenate (Compritol® 888 ATO) and glyceryl palmitostearate (Precirol® ATO 5) were kindly provided by Gattefosse', Saint Priest, France. Glyceryl monostearate was a gift from Amriya Pharmaceutical Industries, Alexandria, Egypt. Sodium citrate and calcium carbonate were purchased from Adwic Pharmaceuticals, Egypt. Other chemicals were of pharmaceutical or analytical grade.

2.1. Preparation of metronidazole floating raft system

Seventeen liquid formulations with *in situ* gelling and floating properties were prepared. The formulations were liquid sols of Alg and G, containing calcium carbonate (C) as an effervescent agent, and Mz dispersed in. Composition of the prepared *in situ* gelling sols is shown in Tables 1 and 2. Calculated amounts of each polymer, was individually dispersed in 90 ml deionized water, containing 0.25% w/v sodium citrate, and heated to 90 °C with stirring till homogenous viscous liquid was obtained, then cooled to below 40 °C. 10 ml of calcium carbonate dispersions were then added after cooling, with continuous stirring, after which the calculated amount of the drug (400 mg/10 ml formulation) was well dispersed (Rajinikanth and Mishra, 2008).

2.2. Incorporation of lipids in gellan gum based floating raft systems

Different lipids were incorporated into gellan-based formulations to improve the gelation capacity and retard the drug release rate. The amphiphillic lipids (GMS, Pr, Cp) were incorporated in $G_{1\%}C_{1\%}$ formulation, prepared as described above. Lipids were melted in a water bath adjusted at a 90 °C temperature, above their approximate melting points of 59, 56, 70 °C, respectively, and then the calculated amount of Mz was dispersed in the molten lipid. For all lipids, the Mz:lipids ratio was 1:1. As for Mz:GMS, ratios of 1:1.5 and 1:2 were also investigated. Calculated volume of the *in situ* gelling sol, containing sodium citrate 0.25% w/v was heated to same temperature of molten lipid, and then added to Mz lipid dispersion, homogenized using high speed homogenizer (Homogenizer T-25 IKA, Germany), at a speed of 4.5×10^3 rpm, for a duration ranging from 10 to 20 min, depending on the lipid emulsifying property until a homogenous stable emulsion was obtained. Calcium carbonate dispersion providing 1% w/v concentration was then added to the prepared emulsion and well mixed by homogenization (Ibrahim, 2009). Composition of the gellan gum-based FRSs is shown in Table 2.

3. Evaluation of metronidazole floating raft systems

3.1. Measurement of viscosity

Viscosity determinations of the prepared FRSs were carried out on a rotating viscometer (Brookfield DV II-RV, USA) using the appropriate spindles (Adebisi et al., 2015; Prasanthi et al., 2011; Emara et al., 2014; El-Zahaby et al., 2014a). Viscosity was measured

Table 1
Composition and physical characteristics of sodium alginate-based FRSs containing Mz as 400 mg/10 ml, and 0.25% w/v sodium citrate.

Formulation code	Sodium alginate (% w/v), calcium carbonate (% w/v)	Floating ability	Viscosity parameters		Gelation		Floating		System as FRS
			Flow index (*n*)	Consistency index (*m*)	Lag time (s)	Duration (h)	Lag time (min)	Floating (h)	
$Alg_{3\%}C_{1\%}$	3%, 1%	F	0.886	0.15*10e4	98	24	2	>24	Pass
$Alg_{4\%}C_{1\%}$	4%, 1%	F	0.862	0.35*10e4	30	>24	2	>24	Pass
$Alg_{5\%}C_{1\%}$	5%, 1%	F	0.863	0.61*10e4	10	>24	2	>24	Fail
$Alg_{4\%}C_{0\%}$	4%, 0%	NF	0.857	0.34*10e4	60	>24	Failed		Fail
$Alg_{4\%}C_{0.5\%}$	4%, 0.5%	PF	0.866	0.34*10e4	40	>24	4	>24	Pass
$Alg_{4\%}C_{2\%}$	4%, 2%	F	0.837	0.43*10e4	3	>24	1	>24	Pass

F: Floating; NF: Non Floating. PF: partial floating. All formulations were pourable except $Alg_{5\%}C_{1\%}$.