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Stomach specific polymeric low density microballoons as a vector for extended delivery of rabeprazole and amoxicillin for treatment of peptic ulcer

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ABSTRACT

The study was intended to develop a new intra-gastric floating in situ microballoons system for controlled delivery of rabeprazole sodium and amoxicillin trihydrate for the treatment of peptic ulcer disease. Eudragit S-100 and hydroxypropyl methyl cellulose based low density microballoons systems were fabricated by employing varying concentrations of Eudragit S-100 and hydroxypropyl methyl cellulose, to which varying concentrations of drug was added, and formulated by stirring at various speed and time to optimize the process and formulation variable. The formulation variables like concentration and ratio of polymers significantly affected the in vitro drug release from the prepared floating device. The validation of the gastro-retentive potential of the prepared microballoons was carried out in rabbits by orally administration of microballoons formulation containing radio opaque material. The developed formulations showed improved buoyancy and lower ulcer index as compared to that seen with plain drugs. Ulcer protective efficacies were confirmed in ulcer-bearing mouse model. In conclusion, greater compatibility, higher gastro-retention and higher anti-ulcer activity of the presently fabricated formulations to improve potential of formulation for redefining ulcer treatment are presented here. These learning exposed a targeted and sustained drug delivery potential of prepared microballoons in gastric region for ulcer therapeutic intervention as corroborated by in vitro and in vivo findings and, thus, deserves further attention for improved ulcer treatment.

1. Introduction

Peptic ulcer is pathological lesions present on the inside of the mucosal lining of the gastrointestinal tract that specially transpire in the stomach (gastric ulcer) and duodenum (duodenal ulcer) [1]. The main violent factors which may contribute to peptic ulcer are gastric acid, bile salts, abnormal motility, pepsin, alcohol and non-steroidal anti- inflammatory drugs (NSAID), over and above infection with *Helicobacter pylori*. The foremost strategies that are proposed for the prevention of peptic ulcer disease are reducing gastric acid formation and escalating gastric mucosal protection [2]. Ethanol-induced gastric injury is a frequently used technique in the valuation of therapeutic efficacy against peptic ulcer [3,4].

The gastrointestinal route of drug administration is most popular and convenient route of drug administration despite some known disadvantages. The current trend in the development of oral drug delivery system is to explore possibilities for targeted drug delivery within the various parts of GIT and maximizing the drug utilization [5,6]. The absorption window of drugs in the upper gastro intestinal track (GIT) is usually inadequate with conventional pharmaceutical dosage forms. The gastric residence time (GRT) of these dosage forms and, as a consequence, of their drug release into the stomach and upper intestine is habitually short [7]. The essential physiologic parameters which effect the GRT, have to be looked upon, to make possible to understand the realistic difficulty of increasing the GRT of a dosage form [8]. Various approaches

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such as low density, gas generating, mucoadhesion, swelling, raft forming, expandable, and super porous hydrogels have been investigated to achieve prolonged residence times of the system in the upper part of the GIT [5,9–12].

Microballoons are multiple-unit intragastric floating device consisting hollow space within it with admirable buoyancy in vitro and prolonged the GRT [13,14]. Microballoons can be distributed extensively throughout the gastrointestinal tract, providing the opportunity of achieving a longer-lasting and more consistent release of drugs, has been sought. This gastrointestinal transit-controlled formulation is intended to float on gastric juice with a specific density of less than 1. This property results in delayed transit through the stomach [15,16]. Encapsulation of drug within the microballoons ensures the stability during processing and storage against atmospheric condition, prevent detrimental reactions within the dosing device. Encapsulation also safeguard the core materials from the adverse environment of the gastrointestinal tract and to allow a site specific controlled release of core material [17]. These result in increasing the oral bioavailability. Thus it can increase the contact time between the antimicrobial agents and the bacterium. Therefore it can be expected that local delivery of antibiotics through a floating drug delivery system may result in complete removal of the organism in the fundal area of the gastric mucosa due to bactericidal drug levels being reached in this area, and might lead to better treatment of peptic ulcer disease [15].

Rabeprazole sodium (RBZ) is an effective proton pump inhibitor (PPIs) that controls the gastric acid secretion [18,19] and so, used in the treatment of erosive gastro-esophageal reflux. RBZ is chemically known as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole sodium salt. RBZ is an extremely water soluble drug and exhibits a higher degradation rate as the pH decreases. The drug has a bioavailability of about 52% [20,21]. Of all PPIs tested, rabeprazole was the most potent acid inhibitor during the first day of dosing [22]. Amoxicillin (AMX) is semi synthetic, orally absorbed, extensively employed broad-spectrum β-lactam antibiotic drug. AMX is a semi-synthetic analogue of penicillin's family. Chemical structure of AMX is consisting of D-4-hydroxyphenylglycine side chain attached to 6-aminopenicillanic acid (6-APA) moiety [23,24]. Its wide spectrum bactericidal activity, safety and efficacy established broad spread utility in medicaments in the form of tablets, capsules, powder and injections for oral suspension [25] and for treatment of humans and animals [26]. It is widely used in a standard eradication treatment of gastric *H. pylori* infection combined with a second antibiotic and an acid-suppressing agent [27,28]. An anionic polymer, Eudragit S 100 (S100), which is composed of methacrylic acid and methyl methacrylate monomer units, was used as a microballoon carrier. Eudragit® S100 required a higher pH medium and/or longer time for solubilisation therefore stabilized the system in upper GIT [29]. Hydroxypropyl methylcellulose (HPMC), which is commonly used in hydrophilic matrix drug delivery systems, is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. HPMC is a semisynthetic, low density, inert, viscoelastic polymer used as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products [30].

The foremost aims of this exercise were to fabricate and characterize microballoons systems incorporating RBZ and AMX. Optimum ratios of polymers were selected to develop microballoons with higher formulation yield and buoyancy. The drug polymer ratio and process variables were also optimize. The developed formulations were characterized in term of particle size, % yield, % buoyancy and in vitro drug release property. Drug loaded microballoon formulations were also evaluated for buoyancy in rabbit's stomach using radiographic technique. Finally, treatment in rats was assessed in terms of the ulcer index (mm^2), preventive ratio compared with standard drug solutions.

Table 1
Optimization of parameters and different process.

Optimization parameters	Variables	Remark
ES 100:HPMC (mg)	1.5:1 4:1 7:1 9:1	Drug:polymer 33:100 Emulsifier 0.75% Temperature 40 °C Stirring speed 300 rpm Stirring time 1 h
Drug:polymer (mg)	20:100 25:100 33:100 50:100	Emulsifier 0.75% Temperature 40 °C Stirring speed 300 rpm Stirring time 1 h ES 100:HPMC (mg) 9:1
Temperature (°C)	20 30 40 50	Emulsifier 0.75% Stirring speed 300 rpm Stirring time 1 h ES100:HPMC (mg) 9:1 Drug:polymer 33:100
Emulsifier (PVA)	0.5 0.75 1.0 1.25	Stirring speed 300 rpm Stirring time 1 h ES 100:HPMC (mg) 9:1 Drug:polymer 33:100 Temperature 40 °C
Stirring speed	100 300 600 900	Stirring time 1 h ES 100:HPMC (mg) 9:1 Drug:polymer 33:100 Temperature 40 °C Emulsifier 0.75%
Stirring time (h)	0.5 1 2 3	ES 100:HPMC (mg) 9:1 Drug:polymer 33:100 Temperature 40 °C Emulsifier 0.75% Stirring speed 300 rpm

2. Materials and methods

2.1. Materials

Eudragit S-100 (ES-100) was procured from Rohm Pharma Gmbh, Essen, Germany and hydroxypropyl methyl cellulose (HPMC) was obtained from G.S. chemical testing Laboratories, New Delhi, India. Dichloromethane, methanol, polyvinyl alcohol (PVA) and tween 80 were procured from CDH, Mumbai, India. Rabeprazole sodium (RBZ) and Amoxicillin trihydrate (AMX) were obtained as gift samples from Khandelwal Labs, Mumbai, India. All other chemicals used were of analytical grade.

2.2. Fabrication of microballoons of RBZ and AMX

Microballoons were prepared using emulsion solvent diffusion method as reported by Kawashima et al., [16]. Eudragit S-100 and HPMC in a ratio of 9:1 were dissolved in a mixture of dichloromethane and methanol (1:1) at room temperature (25 ± 1 °C). Then RBZ was consistently dispersed in this polymer solution. This polymer solution containing dispersed drug was poured drop wise into 200 ml aqueous solution of polyvinyl alcohol (0.75%w/v) containing 0.2w/v of tween 80 at 40 °C. Resultant emulsion was stirred continuously with the help of a mechanical stirrer (Remi, India) at 300 rpm (Fig. 1). The resulting microballoons were collected, washed with distilled water, dried and kept in vacuum desiccators. Same protocol was followed to formulate the microballoons of AMX by keeping all the parameter constant (AMX was used instead of RBZ). Various process variables for the preparation of microballoons of RBZ and AMX (Table 1) were optimized