A PHARMACEUTICAL STUDY ON MODIFIED RELEASE OF CERTAIN PROTON PUMP INHIBITORS

Thesis
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CAIRO UNIVERSITY
(2012)
Acknowledgement

All words of thanks to "ALLAH", the source of all knowledge, by whose abundant grace this work was accomplished.

I believe that acknowledgements should be heartfelt to express my deep everlasting thanks and profound gratitude to Prof. DR. Ahmed Abd El-Bary Abd El-Rahman, Professor of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, for his kind and inspiring supervision, endless co-operation, fruitful advice and valuable guidance.

I wish to express my appreciation and sincere gratitude to Associate Prof. Ehab Rasmy, Associate Professor of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, for his kind help, constructive comments, instructive advice and valuable time that he sacrificed for me during the exhaustive process of organization, revising and proof reading this thesis which made this work possible.

I am deeply thankful to all members of "EPICO" Company for facilitating the usage of laboratory facilities and tablet machine, without whom the work could not be accomplished specially Dr. Akram Farid and Dr. wael Ali.

I really appreciate the efforts of all my colleagues and all staff members of Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), I am deeply thankful to Prof. Dr. M. Seif El Din Ashour and Dr. khaled Abu Zeid with very special consideration to Sarah Salah, Ahmed Samir and Reham Mohsen, teaching assistants in Analytical Chemistry Department, and Mrs. Manal Ali Research lab Chemist, for their unlimited co-operation, encouragement and great support.
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List of Abbreviations

ANOVA.................................................................Analysis of Variance
BP..........................................................................British Pharmacopoeia
DCP.................................................................Dibasic Calcium Phosphate Dihydrate
DSC..........................................................................Differential Scanning Calorimetry
FDA...............................................................................Food and Drug Administration
FT-IR.................................................................Fourier-Transform Infrared Spectroscopy
HPLC.................................................................High Performance Liquid Chromatography
HPMCP...............................................................Hydroxypropylmethylcellulose Acetate Phathalate
ICH.................................................................International Conference on Harmonisation
LSD............................................................................Least Significant Difference
NSAID..............................................................Non-Steroidal Anti-inflammatory Drugs
PPIs.................................................................Proton Pump Inhibitor
PVAP.................................................................Polyvinyl Acetate Phathalate
RH...........................................................................Relative Humidity
SPSS.................................................................Statistical Package for Social Sciences
USP.................................................................United States Pharmacopoeia
RA .................................................................Rabeprazole sodium
Abstract

Rabeprazole sodium belongs to Proton pump inhibitors (PPIs), which act by blocking the enzyme system responsible for active transport of protons into the gastrointestinal lumen, namely the hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) of the gastric parietal cell, also known as the 'proton pump'

PPIs are very sensitive to acidic environments where they are chemically degraded. As pH decreases, the rate of degradation increases; that is why the acidic environment of the stomach causes serious decomposition of PPIs, leading to reduced bioavailability for these drugs. Consequently, most oral dosage forms of PPIs are formulated as delayed release systems, commonly in the form of enteric coated granules and tablets. The purpose of enteric film coating of an oral solid dosage form is to impart delayed drug release.

The objective of this work was to obtain a stable delayed release oral dosage form by preparing and comparing between different tablet and capsule formulae and also comparing between different enteric coatings representing different classes.
Accordingly, the work in this thesis is divided into three chapters:

Chapter 1: Preparation and Evaluation of Delayed release Rabeprazole Sodium tablets.

Chapter 2: Preparation and Evaluation of Delayed release Rabeprazole Sodium capsules.

Chapter 3: Stability Studies of the selected Delayed release Rabeprazole Sodium tablets and capsules.
Chapter 1

Preparation and Evaluation of Delayed release Rabeprazole Sodium tablets.

Six different formulae of Rabeprazole Sodium tablets were prepared as delayed release tablets to protect the drug content from the acidic environment of the gastric media, hence, improving the stability and bioavailability. Rabeprazole Sodium is one of the proton pump inhibitors which belongs to Antisecretory drugs used in the treatment and prophylaxis of peptic ulcer disease. The method in this chapter included preparing two formulae, which were chosen from six suggested formulae for the core tablet, by direct compression and each formula was coated by three different enteric coating polymers in a pan coater, these enteric coating polymers were Hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP) and Eudragit L100-55 representing three different classes which are cellulosics, vinyls and acrylics respectively. The final dosage forms were evaluated by subjecting them to quality control tests as well as in vitro drug release study in both compendial acid phase, 0.1N HCl (pH 1.2), followed by borate buffer, pH 9. The results of this study revealed that all dosage forms demonstrated excellent enteric protection in the acid phase, followed by rapid release in their respective buffer media.
Chapter 2

Preparation and Evaluation of Delayed release Rabeprazole Sodium capsules.

Rabeprazole sodium was subjected to microencapsulation with three different enteric coating polymers by dipping technique, these enteric coating polymers were Hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP) and Eudragit L100-55 representing three different classes which are cellulosics, vinyls and acrylics respectively. An experimental design (factorial design) was conducted and results were analyzed by Statgraphics software, but the results were not satisfactory. Hence six different formulae of Rabeprazole Sodium capsules were prepared as delayed release capsules to protect the drug content from the acidic environment of the gastric media, hence, improving the drug stability and bioavailability. The method in this chapter included preparing two formulae for the core powder mixture, filled into hard gelatin capsule and each formula was coated by three different enteric coating polymers by dipping technique, these enteric coating polymers were Hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP) and Eudragit L100-55. The final dosage forms were evaluated by subjecting them to quality control tests as well as in vitro drug release study in both compendial acid phase, 0.1N HCl (pH 1.2), followed by borate buffer, pH 9. Results: All dosage forms demonstrated
Abstract

excellent enteric protection in the acid phase, followed by rapid release in their respective buffer media.
Chapter 3

Stability Studies of the selected Delayed release Rabeprazole Sodium tablets and capsules.

The stability of the six delayed release tablet formulation and the six delayed release capsule formulations were investigated by storage in accelerated conditions [40°C/75% relative humidity] for 6 months. The results showed that all dosage forms demonstrated excellent enteric protection in the in vitro drug release study through the acid phase, 0.1N HCl (pH 1.2) followed by rapid release in their respective buffer media during the six months period of the study. But there were significant decrease in the drug content in the formulations containing Avicel PH102 as a diluent. The results also showed that Hydroxypropyl methylcellulose phthalate (HPMCP) enteric coating system provide excellent performance together with the core tablet formula containing sprayed dried mannitol as a filler and magnesium hydroxide as alkalinizing agent. On the other hand, the best results of the capsule formulations were achieved using sprayed dried mannitol as a filler and magnesium hydroxide as alkalinizing agent and Eudragit L100-55 who showed good physical properties concerning the softness of the capsule in contrast to Hydroxypropyl methylcellulose phthalate (HPMCP) and polyvinyl acetate phthalate (PVAP) which made the capsule hard and brittle causing it to be broken easily.
Introduction

Gastrointestinal disorders

Peptic ulceration is a common condition consisting of a distinctive break in the gastrointestinal mucosa, usually of the stomach or duodenum [1].

Treatment is aimed at eradicating *H. pylori* with antibacterials and neutralizing or inhibiting acid activity with antisecretory drugs, and a number of guidelines are available [2-5]. Surgical treatment is used in patients with acute complications such as perforation, hemorrhage, obstruction, or pyloric stenosis, or in patients with recurrent or intractable ulcer disease, or where there is suspicion of malignancy [1]. The best eradication regimen has not yet been established, and the number of regimens being tried is large [6-8]. The most widely used regimens comprise so-called 'triple therapy' with a proton pump inhibitor and two antibacterials.

NSAID-induced ulceration, has been attributed to inhibition of prostaglandin synthesis and mucosal cell proliferation, and the ulcers they cause may differ from non-iatrogenic ulcers in their pathology and prognosis [9, 10]. In particular, they are not directly related to *H. pylori* infection [11]. If peptic ulceration develops during treatment with an NSAID the drug should be withdrawn if possible. If this can be done, the ulcer may be treated with an antisecretory drug such as an H$_2$-
antagonist or proton pump inhibitor given for 4 to 8 weeks. If NSAIDS have to be continued, *treatment* is with antisecretory drugs or the prostaglandin analogue misoprostol [9, 10]. Ulcers tend to heal more slowly with H$_2$-antagonists if NSAIDs are continued, whereas the rate of ulcer healing with proton pump inhibitors appears not to be affected.

Stress ulceration, may occur in the stomach or the duodenum following major physical trauma such as burns or surgery, or after severe sepsis or illness.

Peptic ulceration is responsible for about 50% of all cases of upper gastrointestinal bleeding. Although many patients cease to bleed without a specific intervention, the condition is potentially life-threatening and in severe cases prompt resuscitation with intravenous fluids and blood may be required. Endoscopic therapy has substantially improved management of patients with severe bleeding or at high risk of re-bleeding [12, 13].

Once hemorrhage has been controlled, long-term treatment with an antisecretory drug to promote healing and reduce the risk of re-bleeding is often given, particularly in weak and elderly patients. Eradication of *H. pylori* is generally recommended, using an appropriate regimen [12].

Gastro-oesophageal reflux disease, results from the reflux of gastric or duodenal contents into the esophagus. Symptoms include heartburn, acid regurgitation, and