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Stability of metronidazole, tetracycline HCl and famotidine alone and in combination

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Abstract

Metronidazole, tetracycline HCl and famotidine are commonly used for the treatment of *Helicobacter pylori*-associated peptic ulcer. In this paper, stabilities of these drugs and their combinations in solid and liquid states were studied as part of preformulation in the development of a combination drug delivery system. Solubility studies of metronidazole and tetracycline HCl were investigated, which indicated that both metronidazole and tetracycline HCl have high solubilities at and around pH 2.0. Metronidazole is relatively stable with little degradation in liquid phase. Tetracycline HCl in the dry state is stable when stored at room temperature regardless of exposure to light or humidity in the range of 20–65%. Enhanced temperature associated humidity effect was responsible for the instabilities of tetracycline HCl and famotidine to different extents. Elevated temperature accelerated the degradation of all the drugs in liquid phase but light exposure was not a factor for the degradation. The degradation processes of tetracycline HCl and famotidine were highly dependent on the pH of the solution, and relatively stable profiles were achieved at pH 4.0. No potential incompatibility between the drugs under storage conditions was observed in the development of a new multi-drug delivery tablet.

Keywords: Stability; Compatibility; pH-solubility; Metronidazole; Tetracycline HCl; Famotidine; Drug combinations

1. Introduction

Helicobacter pylori is identified as the dominant factor in the causes of peptic ulcer (Malfertheiner and Freston, 1997). Approximately 90–100% of patients with duodenal ulcers and 70–90% of patients with gastric ulcers have been infected by *H. pylori* (Balaban and Peura, 1997; Faigel and Melnyk, 1999). Antibiotics have been strongly recommended by the National Institute of Health (NIH) (Malfertheiner and Freston, 1997) and several antibiotics-based combination regimens for the treatment of *H. pylori*-related peptic ulcers

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have been approved by the Food and Drug Administration (FDA) because of their effectiveness (Balaban and Peura, 1997).

Metronidazole and tetracycline HCl are two antibiotics used along with bismuth in a triple therapy that is believed to be one of the most effective regimens in the eradication of *H. pylori* and is used as a "gold standard therapy" (Balaban and Peura, 1997). However, poor patient compliance significantly reduces the healing rate, and the frequency of dosing, side effects and large number of tablets to be taken daily (e.g. 16 tablets/day) are some of the main concerns (Malferteiner, 1996; Unge, 1996; Howden, 1997).

To overcome these deficiencies, a three-layered matrix tablet based on the gold standard triple therapy with a supplement of an H_2 receptor anatagonist has been developed in our laboratory utilizing the principle of geometrical modification of monolithic matrix along with gastroretentive delivery strategies. This novel formulation approach provides for simultaneous delivery of the four actives with different release rates to potentially improve the therapeutic outcome and enhance patient compliance by overcoming the aforementioned limitations. However, one major concern in design of such delivery system from preformulation point of view is the possible incompatibilities between metronidazole and tetracycline HCl when combined in a single layer of three-layered matrix tablet.

The stability and compatibility of the active ingredients are an important concern in the preformulation studies that are conducted during the early stages of dosage form development. Drug substances can undergo the decomposition processes via hydrolysis, oxidation, photolysis, etc. Furthermore, isomerization, including epimerization, is also grouped into this category of decomposition in terms of pharmaceutical instability. For instance, the formation of epitetracycline HCl is the indication of decomposition of its parent drug tetracycline HCl.

The physicochemical characteristics, as well as the pharmacological and pharmacokinetic parameters of the drugs of interest, i.e. metronidazole (Wearley and Anthony, 1984; Moreau, 1995; Erah et al., 1997; Jones et al., 1997; Scheibel and Dyke, 1997; Yao and Moellering, 1999; The Merck Index, 2001; Van der Wouden et al., 2001; Bakshi and Singh, 2003), tetracycline HCl (Ali, 1976; Moreau, 1995; Corrall, 1997; Jones et al., 1997; Murray et al., 1998; Yao and Moellering, 1999), and famotidine (Cooper et al., 1990; Piper et al., 1997; Karalliedde and Henry, 1998; Lacy et al., 2001; Schrefer and Nissen, 2001; The Merck Index, 2001), have been well investigated. In addition, owing to the commercial availability of these dosage forms as single tablets or capsules they appear to be relatively safe and can be given as combination product.

However, when combinations of drugs are used in one formulation, chemical incompatibility issues become one of the most important factors influencing drug stability. Interaction may take place either among different active ingredients or active ingredient and excipients within the formulation, and can be classified as physical or chemical incompatibility according to the mechanism of interaction. The former is always shown as precipitation, complexation, color change, etc., while the latter is chemical reactions, including decomposition.

In view of the stability of the pharmaceutical substances, an adequate stability study is necessary and a requirement prior to submission to the Food and Drug Administration (FDA). In addition, the United State Pharmacopoeia (USP) requirements and the International Conference on Harmonization (ICH) guidelines all provide various techniques that are widely used to monitor the possible decomposition pathways and degradation products. Understanding of the nature of active compounds in a combination formulation is the essential component of a successful product development.

More importantly the stability, physical and chemical compatibility is the primary concern when facing complicated combinations of drugs in the design of the three-layered matrix tablet. Therefore, the stabilities of different drugs and their combinations in solid and liquid states, normal and accelerated conditions were studied in this work. The solubility studies of metronidazole and tetracycline HCl were initially investigated, as this drives the formulation and dissolution studies of the proposed three-layered matrix tablet.

Furthermore, evaluation of the stabilities of combined granulation of metronidazole and tetracycline HCl, and the granulation of colloidal bismuth subcitrate (CBS) and famotidine was performed by the developed and validated HPLC method.