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ORIGINAL ARTICLE

Design of a novel bilayered gastric mucoadhesive system for localized and unidirectional release of lamotrigine

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KEYWORDS

Lamotrigine;
Bilayered gastric mucoadhesive tablets;
2^3 full factorial design;
Methacrylic polymers;

Abstract Lamotrigine is a BCS class II drug with pH dependent solubility. The bilayered gastric mucoadhesive tablets of lamotrigine were designed such that the drug and controlled release polymers were incorporated in the upper layer and the lower layer had the mucoadhesive polymers. The major ingredients selected for the upper layer were the drug and control release polymer (either HPMC K15M or polyox) while the lower MA layer predominantly comprised of Carbopol 974P. A 2^3 full factorial design was constructed for this study and the tablets were optimized for parameters like tablet size, shape, *ex vivo* mucoadhesive properties and unidirectional drug release.

Abbreviations: %, percentage; BCS, biopharmaceutical classification system; API, active pharmaceutical ingredient; cms, centimetres; h, hours; °C, degrees centigrade; Mg, milligrams; G, grams; mL, millilitre; nm, nanometre; mm, millimetre; min, minute; sec, seconds; MDT, mean dissolution time; rpm, revolution per minute; #, sieve number; USP, United States pharmacopoeia; HCl, hydrochloric acid; UV, ultra violet; f_2, similarity factor; f_1, difference factor; ≈, approximately equivalent to; r^2, correlation coefficient; n, release exponent (power law Korsmeyer Peppas equation); MA layer, mucoadhesive layer; CR layer, control release layer; BGMT, bilayered gastric mucoadhesive tablets.

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Modified basket dissolution model;
Zero order release;
Unidirectional drug release

Oval tablets with an average size of 14 mm diameter were set optimum. Maximum mucoadhesive bond strength of 79.3 ± 0.91 * 10^3 dyn/cm^2 was achieved with carbopol when used in combination with a synergistic resin polymer. All the tested formulations presented a mucoadhesion time of greater than 12 h. The incorporation of methacrylic polymers in the lower layer ensured unidirectional drug release from the bilayered tablets. The unidirectional drug release was confirmed after comparing the dissolution results of paddle method with those of a modified basket method. Model independent similarity and dissimilarity factor methods were used for the comparison of dissolution results. Controlled drug release profiles with zero order kinetics were obtained with polyox and HPMC K15M which reported $t_{90\%}$ at 6th and 12th hours, respectively. The "*n*" value with polyox was 0.992 and that with HPMC K15M was 0.946 indicating an approximate case II transport. These two formulations showed the potential for oral administration of lamotrigine as bilayered gastric mucoadhesive tablets by yielding highest similarity factor values, 96.06 and 92.47, respectively, between the paddle and modified basket method dissolution release profiles apart from reporting the best tablet physical properties and maximum mucoadhesive strength.

1. Introduction

Lamotrigine (LM) is an antiepileptic agent used as a monotherapy and as an adjunct with other antiepileptic agents for the treatment of partial seizures and primary and secondary generalized tonic–clonic seizures. It is also used for seizures associated with the Lennox–Gastant syndrome (Brodie, 1992). LM is a BCS class II drug with pH dependent solubility (solubility in water is 0.17 mg/mL at 25 °C while that in 0.1 M HCl 4.1 mg/mL at 25 °C). LM is an amine containing compound with a good solubility in the acidic or the gastric media and its solubility decreases with increasing pH. Gastric retention of such a drug facilitates better absorption on account of its higher solubility at stomach's acidic pH. It is rapidly and completely absorbed after oral administration with negligible first pass metabolism and requires multiple dosing (2–3 times daily) for maintaining the therapeutic effect throughout the day. Existing formulations of LM provide immediate release with t_{max} ranging from 1.4 to 4.8 h and result into a release profile exhibiting cyclic peaks and troughs (Cheng et al., 2005). It is also marketed as an extended release tablet formulation which is manufactured by a special, laborious and expensive process wherein a central orifice is drilled into an enteric coated tablet to form a device called Diff-CORE™ (http://www.biospace.com/news_story.aspx?StoryID=169319 &full=1. Date: 2/1/2010, time: 7:08:36 AM). In order to overcome the limitations of the available formulations, it was proposed to develop a less laborious, economic and an industrially applicable method for the delivery of LM with improved solubility and plasma concentrations within the therapeutic window over an extended period of time. Therefore, we consider gastroretentive mucoadhesive formulation of LM as one of the most attractive routes for the oral delivery of LM.

Bilayered and gastric mucoadhesive drug delivery systems offer distinct advantages. The phenomenon of bioadhesion is related to the ability of some synthetic or biologic macromolecules and hydrocolloids adhere to biological tissues. If the biological tissue involved is mucous or mucous membrane, the phenomenon is referred as mucoadhesion (Joao, 2010). Mucoadhesion has the potential to localize the drug delivery by retaining the dosage form at the adhesion site. Gastric mucoadhesive systems can be the best formulations for the administration of drugs with good acid solubility and for those drugs which are rapidly and completely absorbed from gastro intestinal tract (Bardonnet et al., 2006). The concept of bi-layer tablet was explored in the present study to control the release of API from one layer by utilizing the functional property of the other layer since this property finds appreciation in the fabrication of novel drug delivery systems (Sivakumar et al., 2010).

This study aimed to develop a gastric mucoadhesive tablet formulation of LM using Carbopol 974P and polyox as the mucoadhesive polymers. The primary challenge had been to handle the incompatibility problem between carbopol and the amine containing LM (Rowe et al., 2009). Hence, a bilayered tablet formulation containing drug in one layer and mucoadhesive polymers in the other layer has been worked out so as to avoid any contact between carbopol and LM. Literature reported the development of several bilayered tablet formulations for the unidirectional delivery of drugs in the buccal cavity, the concept of which has been applied in the current research work. The size of the resting pylorus aperture, 12.8 ± 7 mm was also considered while designing the tablet size in the present study (Chanda et al., 2010). The unidirectional and controlled release of LM for systemic use in the form of bilayered gastric mucoadhesive tablets (BGMT) was investigated in the present paper. The aim of present study was to ascertain the feasibility of *in vitro* development of BGMT formulation of LM, understand the effect of different excipients on the ex vivo mucoadhesion and release profile of final formulation besides studying and exploring the application of a newly designed dissolution method in combination with model independent methods in characterizing the unidirectional drug release profile.

2. Materials and methods

Lamotrigine (LM), Polyox, HPMC K15M Premium, Carbopol 974P, Eudragit L100, Talc, Aerosil, Magnesium stearate, Lactose monohydrate and MCC 102 were sponsored by RA Chem Pharma Ltd. (Hyderabad, India). All chemical reagents used were of analytical grade. Goat gastric mucosa was obtained from a slaughter house.

2.1. Precompression flow properties and compressibility of bilayered gastric mucoadhesive tablets

All the precompression properties were determined independently for upper "controlled release (CR) drug layer" and