European Journal of Pharmaceutics and Biopharmaceutics xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

Orally disintegrating tablet of novel salt of antiepileptic drug: Formulation strategy and evaluation

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ARTICLE INFO

Article history:
Received 5 March 2013
Accepted in revised form 4 June 2013
Available online xxxx

Keywords:
Lamotrigine-cyclamate salt
Orally disintegrating tablet
Disintegration time
Electronic tongue
Near infrared chemical imaging
Dissolution

ABSTRACT

The aim of present research was to design and evaluate orally disintegrating tablet (ODT) of novel lamotrigine-cyclamate salt. Box–Behnken response surface methodology was selected to design the optimized formulation. The independent factors selected were tablet hardness (X_1), disintegrant (X_2) and lubricant (X_3) levels, and responses chosen were disintegration time (DT, Y_1), friability (Y_2), T_{50} (Y_3), and T_{90} (Y_4). The tablets were also characterized for drug uniformity by near infrared chemical imaging (NIR-CI) and taste masking evaluation by electronic tongue. All the selected independent variables were statistically ($p < 0.05$) effect the Y_1 while Y_2, Y_3, and Y_4 affected only by X_2. The optimized ODT was found to meet the regulatory requirement of DT and friability specification. The NIR-CI images indicated uniform distribution of active and inactive ingredients within the tablets. The electronic tongue results were analyzed by principle component analysis (PCA). It indicated that novel salt of lamotrigine and its ODT formulation have a taste similar to cyclamic acid which is indicated by close proximity on PCA score plot, lower Euclidean distance, and high discrimination index values. Furthermore, these parameters were very close to ODT placebo formulation. On the other hand, lamotrigine, its ODT, and placebo formulation were far from each other. In summary, lamotrigine salt provides another avenue for pediatric friendly formulation for children and will enhance patience compliance.

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1. Introduction

About 50% of patients with chronic illness do not comply with medication [1,2]. Compliance is the key factor for the success of all pharmacological therapy but critical in chronic conditions. About one third of hospitalization in United States is due to non-complaint to medication related [3]. Poor compliance in taking medication can lead to morbidity, death, and increase the cost of health care in the Unites States. Factors responsible for poor compliance are patients, physician, health system [4], and formulation palatability [5]. Unpleasant medication taste and unpleasant palatability are the formulation related factors that plays a major role in medication compliance especially in pediatric population [6]. Unpalatability can be masked/reduced by formulation techniques and some of them reported in the literature are complexation with ion exchange resins [7] and cyclodextrins [8], coating with polymer [9], prodrug [10], solid dispersions [11], and salts [12].

Type of dosage also increases patient's compliance to dosage regimen. For example, transdermal drug delivery system improves patients' compliance by decreasing frequency of administration and ease of administration [13]. Similarly, if the patients have difficulty in swallowing because of pathological condition or size of the dosage form, orally disintegrating tablet (ODT) will help in such scenario in improving patients' compliance [14,15]. This is especially useful for pediatric population that cannot easily swallow intact tablets. According to FDA, an ODT is "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." Usually dissolution and absorption occurs simultaneously with disintegration of medication. It can be administered with or without water and thus eradicating the need of water for oral drug administration. FDA drafted the guidelines for the development of ODT for the pharmaceutical industry to meet the quality standard. Ideally, ODT tablet weight should be less than 500 mg to maintain ease of administration and it should disintegrate in less than 30 s in United States Pharmacopeia (USP) disintegration test method or alternative [16].

Lamotrigine (LMT) is a broad spectrum antiepileptic drug first approved in Ireland in 1990 and 1994 in the United States. It is also approved by FDA for the treatment of epilepsy in children 2 years and older and for bipolar disorder in adults [17]. It belongs to BCS class II meaning dissolution is the rate limiting factor for its oral bioavailability [18]. It is also bitter in taste [19] and this factor may hinder in achieving the compliance. Masking the bitter taste

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0939-6411/$ - see front matter Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.ejpb.2013.06.006

may improve patient compliance. In our previously published research, we reported the novel salt of LMT with cyclamic acid (CYA), a commonly used sweetener that has increased the aqueous solubility and dissolution rate of LMT by many folds [20]. We anticipated this salt would mask and improve the bitter taste of LMT because of sweet taste of CYA. The focus of the current study was to develop ODT of LMT–CYA salt by Box–Behnken design of experiment (DOE) approach for ease of administration and its physicochemical characterization. Another aim was to compare the taste characteristics of LMT, LMT–CYA salt and their ODT formulation by electronic tongue method.

2. Materials and methods

2.1. Materials

LMT and CYA were obtained from Hangzhou Starshine Pharmaceuticals (Hongzhou, China) and Acros Organics USA (Morris Plains, NJ, USA), respectively. Methanol, ethanol, acetone, potassium hydrogen phosphate, potassium chloride, and sodium hydroxide were obtained from Fisher Scientific (Norcross, GA, USA). Following chemicals were obtained and were used as received: Pearlitol® (Roquette America, Keokuk, IA, USA), Polyplasdone™ XL (ISP Technologies, NJ, USA), and magnesium stearate (Sigma–Aldrich, St. Louis, MO, USA). All other chemicals and reagents used were of analytical grade or better.

2.2. Methods

2.2.1. Salt preparation

The salt was prepared by method described by Rahman et al. [20]. Briefly, equimolar quantities of LMT (93.75 g, 0.366 mol) and CYA (65.63 g, 0.366 mol) were dissolved in 600 ml ethanol in 1000 ml round bottom flask attached to a condenser at 70 °C and refluxed for 30 min with stirring. The solution was cooled to room temperature by itself and salts crystals precipitated in the reaction vessel during the cooling process. Collected salts were air-dried for 24 h and vacuum oven-dried at 30 °C for 48 h. Dried salts were passed through a sieve#80 mesh ASTM kept in desiccator until the characterization studies.

2.2.2. Physicochemical characterization

The salt, individual components, their equimolar physical mixture, and ODT formulation were characterized by Fourier transform infrared (FTIR) (Tensor 27, Bruker, Billerica, MA, USA) and Raman spectroscopy (MultiRAM, Bruker, Billerica, MA USA). Crystalline nature was investigated by powder X-ray diffraction (PXRD, D8 Advance, Bruker AXS, Madison, WI, USA). DSC thermograms were collected with a SDT 2960 Simultaneous DSC/TGA system (TA Instruments, New Castle, DE, USA). Morphology was studied by scanning electron microscopy (SEM, JSM-6390 LV, JEOL, Tokyo, Japan).

2.2.3. Experimental design

ODT formulations were optimized by Box–Behnken [21] quadratic response surface experimental design by running 15 experiments. These experiments represent middle point of each edge and center point of multidimensional cube. The center point experiment was run in triplicate and DOE was constructed using JMP version 7.0.1 (SAS, NC, USA). The model could be described by following equation:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_12X_1X_2 + B_{23}X_2X_3 + B_{13}X_1X_3 + B_{11}X_1^2 + B_{22}X_2^2 + B_{33}X_3^2$$

where Y is the measured response of selected factors level combination, B_0 is the intercept, B_1–B_{33} is the regression coefficient calculated from observed value of Y, X_1, X_2 and X_3 are the independent factors, X_iX_j (i = 1, 2 or 3 and j = 1, 2 or 3) is the interaction terms, and X_i^2 (i = 1, 2 or 3) is the quadratic terms.

The independent factors selected were hardness (X_1), disintegrant (X_2), and lubricant (X_3) level. Their low, medium, and high levels are shown in Table 1. The independent factors and their level selection were based on the preliminary studies and literature. The dependent factors selected were disintegration time (DT, Y_3), friability (Y_2), T_{50} (Y_3), and T_{90} (Y_4) (time require to release 50% and 90% of the drug, respectively).

2.2.4. Tablet compression

Fifteen ODT formulations were prepared as per the generated Box–Behnken design and their compositions are given in Table 2. Tablet weight was 75 mg and kept constant for all the formulations. All formulation contained LMT–CYA salt equivalent to 25 mg LMT while Pearlitol® level in the formulation range from 23.5 to 28 mg depending upon the contribution of magnesium stearate and Polyplasdone™ XL according to DOE. The ingredients of the formulation (except lubricant) were passed through sieve 30 and blended in MINIBLEND™ (Globe Pharma, New Brunswick, NJ, USA) for 5 min at 10 rpm. Magnesium stearate were passed through sieve #60 and added to ingredients blend and mix with them for another 5 min in the blender. The final blend were compressed into tablets using Mini Press-1 (Globe Pharma, NewBrunswick, NJ, USA) 10-station tableting machine and 5 mm flat die and punches (Natoli Engineering Company, Saint Charles, MO, USA). ODT formulations were tested for quality control test such as hardness (VK 200 Tablet hardness tester, Varian, Palo Alto, CA), friability (EF-2 Friabilator, Electrolab, Mumbai, India as per US pharmacopeia), and disintegration (in water at 37 °C as per US pharmacopeia, ED-2 Disintegrator testor, Electrolab, Mumbai, India).

2.2.5. Assay and uniformity of dosage unit

Twenty tablets were powdered in mortar and pestle, and the powder sample equivalent to 25 mg LMT was transferred into 100 ml volumetric flask and volume was made up with mobile phase. The flasks were stirred at 100 rpm and sonicated for 10 min at 25 °C. The samples were filtered through 0.22 μm nylon filter and injected into HPLC system. 10 tablets were individually transferred into 100 ml volumetric flask for uniformity of dosage unit testing and followed the same procedure as used in the assay test. The calculation for uniformity of dosage unit was made as per US Pharmacopeia [22].

2.2.6. Dissolution

ODT formulations were tested for dissolution test in USP apparatus 2 in 500 ml water at 50 rpm and 37 °C. 1.5 ml sample was withdrawn at 5, 7, 10, 13, 18, and 22 min and amount of lamotrigine released was determined by HPLC method described by Rahman et al. [20], and experiment was performed in triplicate.

2.2.7. Electronic tongue

LMT, CYA, LMT–CYA salt, their ODT, and placebo formulations were evaluated for taste characteristics by α-Astree liquid and taste analyzer (e-Tongue). The taste testing system consist of seven

Table 1
Experimental factors and their level.

Factor	Low (−)	Middle (0)	High (+)
Hardness (Kp), X_1	1	2.5	4
Disintegrant (%), X_2	5	7.5	10
Lubricant (%), X_3	1	1.5	2

Please cite this article in press as: Z. Rahman et al., Orally disintegrating tablet of novel salt of antiepileptic drug: Formulation strategy and evaluation, Eur. J. Pharm. Biopharm. (2013), http://dx.doi.org/10.1016/j.ejpb.2013.06.006