International Journal of Pharmaceutics 542 (2018) 117–124

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Zaleplon loaded bi-layered chronopatch: A novel buccal chronodelivery approach to overcome circadian rhythm related sleep disorder

Michael M. Farag*, Nevine S. Abd El Malak, Soad A. Yehia

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Egypt

ARTICLE INFO

Keywords:
Zaleplon
Pulsatile release
Double casting technique
Early morning awakening
Lyophilisation
LC–MS/MS

ABSTRACT

The aim of this study was to develop a novel buccal bi-layered chronopatch capable of eliciting pulsatile release pattern of drugs treating diseases with circadian rhythm related manifestation. Zaleplon (ZLP) was used as a model drug intended to induce sleep and to treat middle of night insomnia. The chronopatch was prepared adopting double casting technique. The first layer was composed of a controlled release patch containing ZLP-Precirol melt granules intended to release ZLP in a sustained manner to maintain sleep and to prevent early morning awakening. The second layer was composed of a fast release lyophilized buccal disc containing ZLP loaded SNEDDS (Z-SNEDDS) intended for rapid sleep induction. Pharmacokinetic parameters of ZLP from the chronopatch were compared to those of the immediate release capsule, Siesta®, as reference in Mongrel dogs using a randomized crossover design. The appearance of two peaks having two C_{max} and T_{max} proved the pulsatile release pattern. The increase in relative bioavailability of ZLP from the chronopatch was 2.63 folds. The results revealed the ability of the developed ZLP loaded bi-layered chronopatch to be a candidate for overcoming early morning awakening without middle of night dose administration.

1. Introduction

The concept of ideal drug delivery has changed significantly over the last few decades, this was mainly due to a better understanding of the underlying causes and pathophysiological factors related to the diseases. Therefore making the drug immediately available following administration or constant drug delivery will not provide such idealized delivery in many cases (Wilson and Crowley, 2011). A shifted paradigm namely 'chronodelivery' has emerged adopting the concept of adapting drug delivery to the body's circadian rhythm.

The relation between many body functions as well as many diseases with the circadian rhythm is well established. Therefore in order to maximize the therapeutic outcome, it is better to adjust the maximum drug release to coincide the manifestation of clinical symptoms based on circadian timing. This could preferably be used for the management of diseases with time dependant manifestation such as bronchial asthma, myocardial infarction, rheumatic disease, angina pectoris and sleep disorders (Maroni et al., 2010).

Many successful devices applied the concept of chronodelivery, among them we could mention ChronoCap® adopting injection molding of hydroxypropyl cellulose to obtain swellable/erodible shells, capable of drug release after a required lag time (Gazzaniga et al., 2009). While the ChronoCap® was based on hydrophilic release-controlling polymer, the Time-Clock® system was depending on an erodible layer composed of natural waxes and surfactants (Pozzi et al., 1994). Another device is Pulsincap™ which depended on a release plug composed of cross-linked PEG 8000 hydrogel, the lag phase was determined by the time needed for plug removal (Stevens et al., 2002). It is worthy to mention that none of the above systems was intended for the buccal route which make them unsuitable for highly metabolized drugs, which highlight the need for a novel device such as the bi-layered chronopatch intended for the buccal route to bypass the first pass hepatic metabolism.

Sleep is a primary need for all human beings just as food and shelter, being in a stressful world people may occasionally face psychological pressures distorting their biological clock leading to unsatisfactory sleeping pattern. Almost 25% of adults may suffer from insomnia, 10% of cases become chronic (Summers et al., 2006). Insomnia can be classified into four main types: frequent awakening, early morning awakenings, poor sleep quality and difficulty in falling asleep (Cricco et al., 2001).

Zaleplon (ZLP) is a non-benzodiazepine hypnotic used for short term management of insomnia mainly for sleep induction (Dooley and Plosker, 2000), it has a great affinity to α1 subunit located on $GABA_A$ receptor in the brain, therefore it enhances the action of GABA more selectively than benzodiazepines. ZLP suffers mainly from extensive hepatic first pass metabolism leaving only 30% systemically available

* Corresponding author at: Department of Pharmaceutics and Industrial pharmacy, Faculty of Pharmacy, Cairo University, Kasr El-Aini Street, Cairo 11562, Egypt.
E-mail address: michael.farag@pharma.cu.edu.eg (M.M. Farag).

https://doi.org/10.1016/j.ijpharm.2018.03.014
Received 16 February 2018; Received in revised form 3 March 2018; Accepted 7 March 2018
Available online 08 March 2018
0378-5173/

and short elimination half-life (1 h) (Drover, 2004). Also it has shown efficacy in treatment of middle of night insomnia without hangover effects (Verster et al., 2004). Formulation of ZLP into buccal bi-layered chronopatch could avoid these problems. Literature search revealed that no previous studies were carried out to formulate bi-layered chronopatch containing ZLP.

The aim of this study was to formulate ZLP into bi-layered chronopatch to allow the pulsatile release of ZLP through the buccal route in order to avoid its extensive hepatic metabolism, enhance its bioavailability and prevent early morning awakening. This work mainly focus on the preparation and characterization of the second layer consisting of the lyophilized buccal disc containing ZLP loaded SNEDDS, also the preparation, characterization and in vivo evaluation of the chronopatch to estimate the pharmacokinetics of the drug following buccal administration of the chronopatch to Mongrel dogs compared to marketed product.

2. Materials and methods

2.1. Materials

Zaleplon (ZLP) was received as a kind gift from October Pharma, Egypt. Methanol and Acetonitrile (HPLC grade); were purchased from Sigma-Aldrich Co., St. Louis, USA. Capryol™ 90 [Propylene Glycol Monocaprylate (Type II)]; Labrafil® M 1944 CS (Oleoyl Polyoxyl-6 Glycerides NF); Labrafac® PG (Propylene Glycol Dicaprylate/Dicaprate); Labrasol® (Caprylocaproyl Polyoxylglycerides); Transcutol™ HP (Diethyleneglycol Monoethyl Ether), Lauroglycol™ 90 [Propylene Glycol Monolaurate (Type II)], were received as a kind gift from Gattefosse Co., St-Priest, France. Polyethylene Glycol (PEG) 200, was purchased from Fluka, Switzerland. Cremophore® RH 40 (Polyoxyl 40 Hydrogenated Castor Oil USP/NF), Cremophore® EL (Polyoxyl 35 Hydrogenated Castor Oil USP/NF), Solutol® HS 15 (Polyoxyl 15 Hydroxystearate USP/NF) were purchased from BASF, Germany. Miglyol® 840 (Propylene glycol dicaprylocaprate), was purchased from Sasol Hamburg, Germany. Syloid® FP 244 (silicone dioxide, NF) was purchased from Grace Davison (Grace GmbH and Co. KG, Germany). Gelatin, El Nasr pharmaceuticals co., Egypt. Torsemide (internal standard) was supplied and certified by Multi-Apex Pharma, Egypt. Siesta® capsule, containing 10 mg ZLP (AlAndalous, Cairo, Egypt, Batch No.: 140151). All other reagents and chemicals used were of analytical reagent grade.

2.2. Solubility studies of ZLP in different components of self-nanoemulsifying drug delivery systems (SNEDDS)

The equilibrium solubility of ZLP in various oils, surfactants and co-surfactants was determined using the method described by Dixit and Nagarsenker (2008)). In brief, known excess amount of the drug (100 mg) was added to 3 mL of the investigated component in a vial and shaken for 72 h at 30 ± 0.5 °C in a thermostatically controlled shaking water bath to attain equilibrium. The contents of the vials were then centrifuged at 3000 rpm for 10 min using an ultracentrifuge to precipitate the undissolved ZLP. Aliquots (0.1 mL) from the supernatants were then withdrawn and filtered through a cellulose filter (Millipore® filter 0.22 µm) and measured spectrophotometrically at (λ_{max} = 236.6 nm) using UV/VIS spectrophotometer (UV-1601 PC), (Shimadzu, Kyoto, Japan) after appropriate dilution with methylene chloride (1:5000).

2.3. Construction of ternary phase diagram and effect of drug loading

The selected components -based on the solubility studies- comprising of Capryol™ 90 as the oily phase together with either Cremophore® RH 40 or Cremophore® RH 40:Labrasol® 1:1 as surfactant and Transcutol™ HP as co-surfactant. Thirty-six points of self-emulsifying systems were prepared in each phase with varying concentrations of oil, surfactant and co-surfactant till reaching a final concentration of 100% w/w (Abdelbary et al., 2013; Basalious et al., 2010). Phase diagrams were constructed by weighing appropriate amounts of surfactant and co-surfactant first into small vials, mixed by vortex mixing for 5 min, then appropriate amount of oil is then added to prepare 300 mg system.

From each mixture point on the phase diagram, 300 mg was diluted 100 times with distilled water and the mixture was stirred using a magnetic stirrer with a rotation speed of 125 rpm at 37 °C. Visual observation of the diluted nanoemulsions was carried out immediately for investigating self-emulsification ability, phase separation and presence of any precipitate. The diluted nanoemulsions were left for 24 h for stability assessment. Clear or slight bluish dispersions and translucent nanoemulsions were used to draw the ternary phase diagram. The percentage transmittance of each point was measured to confirm the clarity. To determine the effect of drug addition on the nano-emulsion boundary and the self-emulsifying performance of the prepared SNEDDS, the phase diagrams were also constructed in the presence of ZLP with constant drug loading of 5 mg drug in 300 mg system for all the prepared SNEDDS.

2.4. Characterization of the selected Z-SNEDDS

2.4.1. Globule size and polydispersity index (PDI) determination

Z-SNEDDS (1–6) were diluted 100 times with phosphate buffer saline (pH = 6.8) and were subjected to constant stirring on a magnetic stirrer with 125 rpm at 37 °C. Then each sample was placed directly in the module and analyzed by diffraction light scattering at 25 °C and a scattering angle of 173° using Zetasizer Nano ZS (model MAM 5000, Malvern instrument limited, Worcestershire, UK). This experiment was done in triplicates and the average results (± SD) were recorded (Kaur et al., 2013).

2.4.2. Transmission electron microscopy (TEM)

The morphology of (Z-SNEDDS2) as a representative sample was investigated using Jeol (JEM-1230) transmission electron microscope (Tokyo, Japan) to confirm the morphology and size of globules. Briefly, an aliquot of the prepared system was diluted 100 times with distilled water and filtered with Millipore® filter 0.2 µm, then adequate amount of 1% phosphotungstic acid was added and gently mixed. One drop of the mixture was placed on the carbon-coated grid, drained off the excess and left to dry to be observed under TEM.

2.4.3. Preparation of lyophilized Z-SNEDDS buccal discs (Mahmoud and Salah, 2012)

Lyophilization of liquid Z-SNEDDS is difficult as the components of the isotropic mixture are not volatile. To overcome this problem, the selected SNEDDS were adsorbed to Syloid® FP 244 as a solid carrier with a constant ratio 2.6:1 (w/w) which was selected upon previous preliminary studies where different ratios were studied and was found to be the optimum ratio to obtain free flowing powder. Then, the solidified Z-SNEDDS were mixed with 5% mannitol as a cryoprotectant and dispersed in 3% gelatin solution as inner support. The dispersion was then homogenized for 3 min using SilentCrusher S homogenizer (Heidolph, Germany) at 15000 rpm to ensure homogenized dispersion.

The dispersion is then individually casted in a special mold so that a specific weight of dispersion containing the desired dose is casted in each well. The mold is then frozen at −20 °C overnight and then freeze-dried for 24 h using a Novalyphe-NL 500 Freeze-dryer, (Savant Instruments, Halprook, NY).

2.5. Characterization of the prepared lyophilized Z-SNEDDS buccal discs

2.5.1. Weight uniformity

Ten discs, from each formula, were individually weighed and the