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Controlled buccal patches of Zaleplon using melt granulation technique: An approach to overcome early morning awakening

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ABSTRACT

This study deals with the incorporation of melt granules in buccoadhesive patches prepared using polymers of opposing solubilities. Zaleplon (ZLP) is a Non-Benzodiazepine Hypnotic (NBZH) that suffers from extensive first pass hepatic metabolism and very short elimination half-life. The aim of this study was to develop a reliable dosage form that was capable of extending the release of ZLP to avoid early morning awakening so to improve sleep quality and also increase its bioavailability. ZLP was incorporated into Precirol-based melt granules and then further formulated into buccal patches prepared using HPMC, PVA and Ethyl cellulose. A Box-Behnken Design was adopted to statistically optimize the formulation variables, HPMC solution/PVA solution weight ratio, Precirol/ZLP ratio and percentage Ethyl cellulose. Fifteen formulae were prepared and evaluated regarding drug content uniformity, thickness uniformity, moisture loss, water sorption, mucoadhesion strength, surface pH, DSC and in-vitro release. The best achieved formula (composed of 5:1 Precirol:ZLP, 3:1 HPMC:PVA and 7.5% Ethyl cellulose) was able to control the release, where 87.24% of ZLP was released after 12 h and the patch showed acceptable mucoadhesion properties. The results revealed the ability of the developed ZLP buccal patches to be a candidate for overcoming early morning awakening.

1. Introduction

Many people face every now and then psychological tensions, job pressures or emotional disturbances distorting their biological clock leading to unusual sleeping pattern [1]. Insomnia is commonly seen among 30–35% of adults, about 10% of cases become chronic [2]. It can be diagnosed by frequent awakening, early morning awakenings, poor sleep quality and difficulty in falling asleep [3]. It is not just a primary reason for mental impairment but it can impair human effective dealing with every day's activity even it can compromise the immune system [4]. Major depressive disorders e.g. bipolar depression is associated with difficulty in maintaining sleep, early morning awakenings and poor sleep quality [5]. Unsurprisingly it can be associated with increased mortality [6].

Zaleplon (ZLP) is a NBZH indicated for the short term −2 to 4 weeks-management of insomnia [7], it binds mainly to α1 subunit located on $GABA_A$ receptor in the brain. It enhances the action of GABA more selectively than benzodiazepines. ZLP undergoes an extensive hepatic first pass metabolism leaving only 30% systemically available, its terminal elimination half-life is 1 h so it is mainly used for sleep induction [8]. Also it has shown efficacy in treatment of middle of night insomnia without hangover effects [9].

Since the birth of pharmaceutical sciences, an emerging challenge has been raised for the formulation of drugs suffering from extensive first pass metabolism into more bioavailable form. Buccal delivery has always been an appealing choice as it offers a shortcut to systemic circulation, bypassing the devastating metabolism suffered by other conventional oral routes and leading to enhanced bioavailability [10]. For drugs with short half-life, extending their release would reduce frequent dosing and in our case would prevent early morning awakening without middle of night dosing.

Two main techniques were generally adopted for the preparation of buccoadhesive patches either hot melt extrusion or solvent casting. The latter was generally preferred as it offers low cost in addition to ease of processing [11]. Emulsification/casting/solvent evaporation technique is a modification of solvent casting technique for preparation of patches using polymers of opposing solubilities with the ultimate aim of controlling the release [12]. Further control can be applied by incorporating the drug into melt granules using melt-granulation technique prior to its inclusion into the patches. This approach might take buccal delivery to a whole new level in the field of controlled delivery.

Melting method includes melting of a physical mixture of the drug and the carrier, followed by sudden cooling of the molten mass over ice bath with continuous stirring, and then the final solidified mass is

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pulverized and sieved. Melting method is also called melt-granulation technique [13,14]. Precirol is a mixture of 40% tri-, 45% di- and 14% monoglycerides of palmitic and stearic acids. It provides a matrix to sustain drug release and taste masking which make it ideal retardant to control drug release [15,16].

The aim of this study was to formulate ZLP into a buccoadhesive patch, in order to avoid the extensive first pass effect and improve its bioavailability. Concerning the control of ZLP release, we prepared Precirol-based ZLP melt-granules prior to its inclusion into the patch prepared with polymers of opposing solubilities. A Box-Behnken design was adopted to study the effect of formulation variables and to reach an optimized formula with the ultimate aim of preventing early morning awakening without middle of the night dose administration.

2. Materials and methods

2.1. Materials

Zaleplon (ZLP) was received as a kind gift from October Pharma, Egypt. Poly vinyl alcohol (PVA), Mwt 13,000–23,000; triethyl citrate (TEC); were purchased from Acros organics, Belgium. Precirol ATO 5 (Glyceryl distearate); was purchased from Gattefosse Co., St-Priest, France. Hydroxypropyl Methylcellulose K4M (HPMC); was purchased from Colorcon, Midland, USA. Ethyl cellulose (EC), viscosity 300 cps, 49% ethoxyl; Dibutyl phthalate (DBP); and mucin from porcine stomach; were purchased from Sigma-Aldrich Co., St. Louis, USA. Eudragit® RS 100; was purchased from Degussa, Rohm GmbH and Co. KG, pharma polymer, Germany. All other reagents and chemicals used were of analytical reagent grade.

2.2. Preparation of ZLP Precirol-based melt-granules

Precirol was melted in porcelain evaporating dish over a hot plate at 90 °C. ZLP was added with continuous stirring for 15 min to get a homogeneous dispersion. Then, the molten mass was rapidly cooled down over an ice bath and allowed to solidify. Subsequently, the solidified mass was ground and pulverized in a glass mortar. The solid was sieved through 0.5 μm sieve [17,18].

2.3. Preparation of buccoadhesive patches of ZLP Precirol-based melt-granules by emulsification/casting/solvent evaporation process [11,12]

An aqueous solution of PVA (30%w/v) and a hydro-alcoholic solution (3:2) of HPMC (2%w/v) were prepared and plasticized with propylene glycol (20%w/w) of total polymeric content. Also an ethanolic solution of ethyl cellulose (5–10%w/v) was prepared and plasticized with dibutyl phthalate (50%w/w) of the polymer content. Then a predetermined weights of each solution was added along with a weight of ZLP Precirol-based melt-granules equivalent to 5 mg of ZLP.

The whole mixture was homogenized at 9500 rpm for 5 min using a homogenizer (Wisemix HG-15D Daihan scientific, Korea) at 25 °C to obtain finely divided melt-granules dispersed in an o/w emulsion. The o/w emulsion was maintained under stirring by a vortex mixer, 50 vibrations/min, at 25 °C for 2 min. The solution was then casted into cylindrical molds (diameter: 1.3 cm, thickness: 0.3 cm). A weight of the solution, containing melt-granules equivalent to 5 mg ZLP, was casted into each well. The patches were left to dry in air under an inverted funnel to prevent sudden evaporation.

The patches were dip-coated as an extra barrier for further control of the release. This was done by dipping the dried patches in the prepared coating solution of Eudragit RS 100 in acetone (10 %w/w) -plasticized with TEC (30%w/w) based on polymeric content-for 5 min. The resulting patches were air-dried, then stored at ambient temperature and humidity till use.

Table 1
Levels of independent variables investigated in the Box-Behnken design and constraints for optimization.

Variables	Levels		
	(-1)	0	(+1)
A: Precirol/Zaleplon ratio in melt-granules	1	3	5
B: HPMC K_4M/PVA solution ratio (w/w)[a]	1	2	3
C: Percentage ethyl cellulose (%w/w)	5	7.5	10

Responses	Constraints
Y_1 = % Drug released after 3 h	minimize
Y_2 = % Drug released after 12 h	maximize
Y_3 = Mucoadhesion strength	maximize

[a] 2% HPMC solution: 30% PVA solution.

2.4. Experimental design

For the preparation of ZLP buccoadhesive patches a three factor, three level Box-Behnken design was adopted using the Design Expert® software (Version 7, Stat-Ease Inc., Minneapolis, MN). Three factors namely, A: Precirol: ZLP ratio, B: HPMC solution: PVA solution ratio and C: Ethyl cellulose % were investigated as independent variables. The levels for these three parameters are shown in Table 1. According to the followed Box-Behnken design, 15 runs were tried. The preparation and release studies of the suggested formulae were done in random order. The 15 runs listed in standard order are shown in Table 2.

The response surface methodology (RSM) and multiple response optimization utilizing the fitted polynomial equations were used to search for the optimal formulation with a specific release rate at different time intervals and mucoadhesion strength. The drug release percentages at 3 h (Y1), 12 h (Y2) and the mucoadhesion strength (Y3) were the target responses. These dependent variables were chosen as shown Table 1.

2.5. Patches characterization

2.5.1. Drug content

Each patch was digested in 50 ml 10% methanol solution in a volumetric flask for 48 h, to make sure the drug was completely dissolved. The solution was filtered and an aliquot was used to assay for drug content spectrophotometrically at the predetermined λ_{max} of ZLP

Table 2
Composition of different buccal patches according to Box-Behnken design.

Number of runs	Precirol: Drug[a]	HPMC: PVA[b]	%EC[c]
FM 1	5: 1	1: 1	7.5
FM 2	3: 1	1: 1	5
FM 3	1: 1	1: 1	7.5
FM 4	3: 1	2: 1	7.5
FM 5	5: 1	3: 1	7.5
FM 6	5: 1	2: 1	10
FM 7	1: 1	2: 1	10
FM 8	3: 1	1: 1	10
FM 9	1: 1	2: 1	5
FM 10	5: 1	2: 1	5
FM 11	3: 1	3: 1	10
FM 12	3: 1	2: 1	7.5
FM 13	3: 1	2: 1	7.5
FM 14	3: 1	3: 1	5
FM 15	1: 1	3: 1	7.5

[a] A weight equivalent to 5 mg of ZLP is added in each individual patch.
[b] 2% HPMC solution: 30% PVA solution (both are plasticized by propylene glycol 20% w/w of solid content), 0.66 g of the solution mixture was added in each individual patch.
[c] The solution is plasticized by dibutyl phthalate 50% w/w of the solid content, 0.33 g of the solution was added in each individual patch.