



PREPARATION AND EVALUATION OF ZALEPLON FAST DISSOLVING FILMS USING DIFFERENT FILM FORMING POLYMERS

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ABSTRACT

Orally fast dissolving films became a novel approach to oral drug delivery system as they provide convenience and ease of use over other dosage forms. The aim of this study was to formulate fast dissolving films of zaleplon (ZAL), a drug indicated for short term management of insomnia. Zaleplon solubility was increased by complexation with β -cyclodextrin. The inclusion complex was proven by differential scanning calorimetry (DSC) and fourier transformation-infrared spectroscopy (FTIR). Different film forming polymers used were instant pure-cote, HPMC E15, lycoat NG73 and kollicoate IR with propylene glycol as a plasticizer. The prepared films were evaluated for film thickness, folding endurance, drug content, disintegration time and *in vitro* dissolution. The *In vitro* drug dissolution studies were carried out in distilled water and formulation containing kollicoate IR showed a complete drug release in the first 10 minutes and an *In vitro* disintegration time of 32.9 seconds. Zaleplon, has been reported to increase melatonin secretion in healthy human beings suggesting an influence of zaleplon on chronobiology. Zaleplon fast dissolving films were found to increase the melatonin level in human serum when compared with market tablets. The Area Under the Curve for mean melatonin concentration in both zaleplon films and market tablets during the first eight hours was found to be 410.93 and 217.32 respectively.

Keywords: Zaleplon, fast dissolving films, β -cyclodextrin, melatonin, ELISA.

INTRODUCTION

Zaleplon is a pyrazolopyrimidine sedative-hypnotic drug indicated for the short term management of insomnia (1). Zaleplon has sustained hypnotic efficacy without the occurrence of rebound insomnia or withdrawal symptoms on disrupt discontinuation (2, 3). Zaleplon is a lipophilic compound with poor aqueous solubility. It's extensively metabolized into pharmacologically inactive metabolite (5), that's why it has limited oral bioavailability. An enhancement in the solubility and the dissolution rate of that drug can improve its oral bioavailability which further improves the therapeutic efficacy and patient compliance (6). Various formulation techniques can be applied to overcome the low aqueous solubility of drugs without affecting their optimized pharmacological action. Fast dissolving films dissolve in the salivary fluids of the oral cavity within a minute, releasing the active drug. This is due to the large surface area of the film that wets quickly upon contact with saliva (7). A variety of polymers are available for preparation of fast dissolving oral films. The use of film forming polymers in oral films has attracted considerable attention in medical applications. The selection of polymer, is one of the most important and critical parameter for the successful development of the film formulation.

The polymers can be used alone or in combination to obtain the desired film properties (8). Lycoat NG 73 is an excellent film forming polymer from pea starch prepared by chemical and physical treatments. Lycoat is a novel granular hydroxypropyl starch polymer that has been designed especially for orodispersible films (9). Hydroxypropyl Methyl Cellulose (HPMC E15) is known for its good film forming properties and has excellent acceptability. HPMC polymer has a high glass transition temperature and is classified according to its viscosity which affects the solubility-temperature relationship (10). Kollicoat IR, a polyvinyl alcohol - polyethylene glycol graft copolymer is a new pharmaceutical excipient that was specially developed as a coating polymer for instant release tablets. The molecule is hydrophilic and thus readily soluble in water. (11). Instant pure-cote 793 is the trademark for a new, modified pre gelatinized starch uniquely designed for film-forming applications and aqueous film coating. It is a free-flowing, granular powder with excellent dispersibility characteristics. In the present study we investigated the effect of different film forming polymers on zaleplon release from different films. Melatonin has been used as a hypnotic, at the same time; melatonin is the main hormone secreted by the pineal gland and is involved in the light-dark/wake-sleep cycle regulation (12). Zaleplon has been reported to increase nocturnal melatonin secretion in rabbits (13) as well as in healthy human beings (14) and the elevation of plasma levels of melatonin may suggest an influence of zaleplon on chronobiology.

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Thus, this study also investigated the effect of zaleplon fast dissolving films on melatonin secretion in human volunteers.

MATERIALS AND METHODS

Materials

Zaleplon (ZAL) was obtained from October Pharma S.A.E., Egypt. Lycoat NG 73 was kindly provided from Roquette, France. Hydroxypropylmethyl mellulose (HPMC E15), propylene glycol and magnesium stearate from Egyptian International Pharmaceutical Co. EIPICO. Kollicoat IR was kindly provided from BASF, the chemical company, Germany. Beta-cyclodextrin (β CD) was purchased from Acros Organic, USA. Instantpure-cote 793 from Grain Processing Corporation, USA.

Preparation of zaleplon- Beta-cyclodextrin inclusion complex

The inclusion complex formation of zaleplon with β CD has already been reported, resulting in the significant improvement of its aqueous solubility (15). For co-grinding formulations, zaleplon with beta-cyclodextrin were mixed in three geometric ratios (1:1, 1:2 and 1:3) and triturated in glass mortar pestle for 20 minutes and passed through 80 mesh screen.

Characterization of zaleplon complex Differential scanning calorimetry (DSC)

Thermal behavior of zaleplon, beta-cyclodextrin and inclusion complex were examined using thermal analyzer (Differential scanning calorimeter, model Mettler DSC60, Switzerland). The sample size was 5 mg and the temperature range was between 30 and 300°C. Nitrogen was used as carrier gas and DSC analysis was performed at heating rate of 10°C/min.

Fourier transfer Infrared spectroscopy (FTIR)

Infrared spectra of plainzaleplon, beta-cyclodextrin and inclusion complex were recorded by KBr method using pyeUnicam SP1000 IR Spectrophotometer, type pw 3710, Holland. Scanning was done from 750 -4000 cm^{-1} .

In vitro dissolution studies of zaleplon- beta-cyclodextrin complex

Dissolution of zaleplon and its inclusion complexes equivalent to 10 mg of zaleplon in three ratios (1:1, 1:2 and 1:3) was studied using a dissolution apparatus with paddles rotating at 75 rpm. The dissolution was performed in 300 mL of phosphate buffer (pH 6.8) at $37 \pm 0.5^\circ\text{C}$. At fixed time intervals, samples were withdrawn, filtered, and spectrophotometrically assayed for drug content at 232 nm.

Preparation of zaleplon films

Zaleplon fast dissolving films were prepared by solvent casting technique using different film forming polymers as shown in table 1. The polymeric solution was prepared by dissolving the determined quantities of different polymers in 10 ml distilled water, to which zaleplon complexes, propylene glycol and other ingredients were added. The suspension was stirred for 30 minutes and degassed to remove air entrapment by using ultrasonicator. The resulting solution was cast onto galas container and dried under ambient conditions. The films were then carefully removed from the container and cut into strips of dimension 3×3 cm, and stored in an air tight glass container for further investigations.

Table 1: Formulations of fast dissolving zaleplon films

| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|-----------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| ZAL: β CD | 10:37 | 10:37 | 10:37 | 10:37 | 10:37 | 10:37 | 10:37 | 10:37 |
| Instant pure-cote | 250 | | | | 250 | | | |
| HPMC E15 | | 250 | | | | 250 | | |
| Kollocoat IR | | | 250 | | | | 250 | |
| LycoatNG 73 | | | | 250 | | | | 250 |
| Propylene glycol (ml) | 1.4 | 1.4 | 1.4 | 1.4 | 1.8 | 1.8 | 1.8 | 1.8 |
| Menthol | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Water to | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

N.B. all amounts in mg.

Evaluation of fast dissolving films

The prepared films were subjected for *in vitro* evaluation tests as film thickness, folding endurance, drug content, disintegration time and *in vitro* drug release. Thickness of the film was measured by using screw gauge with a least count of 0.01 mm at different places on the film. The thickness of the film was measured at three different places and the average was measured. Folding endurance of the film was determined by repeatedly folding a small strip of the film at the same place and the

number of folds till breaking the film was recorded. The experiment was performed in triplicate and the mean was calculated. The films were tested for drug content uniformity by UV spectrophotometric method. The absorbance values were measured at a wavelength of 232 nm. The *in vitro* disintegration time of the films was determined by placing them in a glass Petri dish (6.5 cm in diameter) containing 25 ml of distilled water at 37°C, with swirling every 10 seconds. The time at which the film starts to break or disintegrates was recorded. *In vitro*

dissolution study was carried out in a 300 ml of buffer solution (pH 6.8) at 37 ± 0.5 °C at 75 rpm. At fixed time intervals, samples were withdrawn, filtered, and spectrophotometrically assayed for drug content at 232 nm. Percent drug released after 20 minutes was determined.

Effect of zaleplon on melatonin secretion in human volunteers

Twelve non-smoker drug-free healthy male volunteers, aged 33.2 ± 11.7 years (mean standard deviation), participated in the study. Women were excluded to avoid the effect of the menstrual cycle and contraceptives on melatonin secretion (16). None of the volunteers had a history of medical, neurological or psychiatric disease. The study protocol, which complied with the recommendations of the Helsinki Declaration, was fully approved and performed by Drug Research Centre (DRC, a certified center that performs bioequivalence and bio waiver studies based on Central Administration for Pharmaceutical Affairs CAPA guidelines & international regulations on Good Clinical Practice provided by benchmark regulatory bodies). Persons excluded from the test were those having made a transoceanic flight in the last month before the study; sleep problems, abnormal results in the metabolic or urine tests and having a work on night shifts. Volunteers were asked to refrain from using sun glasses, drinking coffee, tea 12 h before and for the duration of the experiment. All subjects were subjected to a randomized, double-blind and cross-over design. The first blood extraction was taken just before the ingestion of the market tablet or zaleplon film (10 mg). Blood samples were drawn after 1,2,3,4 and 8 hours, centrifuged at 3000 rpm for 10 min, and serum was separated and frozen at -30 °C until assayed for melatonin. Serum melatonin concentration was determined by an Enzyme-Linked Immunosorbent Assay (ELISA), type Reader, Tecae; model A5082, spectra classic, Austria.

RESULTS AND DISCUSSION

Characterization of zaleplon complex: Differential scanning calorimetry (DSC)

Inclusion complex between the drug and β CD was identified by DSC. Figure (1) shows the DSC thermograms for zaleplon, β CD and 1:1 inclusion complex. DSC curve of the drug shows a sharp endothermic T_{max} of 187.4 °C corresponding to the melting point of crystalline form of zaleplon, this high melting point is indicative of strong crystal lattice energy which is one of the factors responsible for lower aqueous solubility (17). DSC curve of β -Cyclodextrin showed a slightly sharp endothermic peak at 121.90°C corresponding to the melting point of β -Cyclodextrin. The drug- β CD complex DSC shows a decrease in the drug peak ensuring an interaction between them.

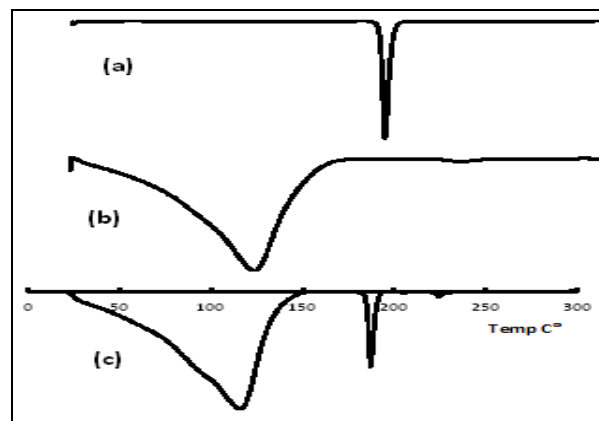


Figure 1: DSC thermogram of (a) zaleplon, (b) β -cyclodextrin and (c) inclusion complex

Fourier Infrared spectrophotometry (FTIR)

Fourier Infrared spectrophotometry (FTIR) has been employed as a useful tool to identify drug excipient interactions (18). It provides important information regarding the confirmation of inclusion complex formation of β CDs with drug molecules. IR spectrum of zaleplon (Figure 2a) is characterized by principal absorption peaks at 3088.3 cm^{-1} for C-H aromatic, 2933.7 cm^{-1} for C-H aliphatic, 1614.4 cm^{-1} for C=N, 1222.8 cm^{-1} for C-N and 15765.8 cm^{-1} for C=C aromatic. Zaleplon shows strong absorption peaks at 2231.6 cm^{-1} and 1651 cm^{-1} indicating presence of cyanide and amide carbonyl group respectively. Peaks at 684 and 801 cm^{-1} may be assigned to aromatic stretching of the phenyl group in the molecule which is m-substituted. The prominent peaks of β -CD are at 3363.2 cm^{-1} , 2926 cm^{-1} and 1001 cm^{-1} corresponding to C-H stretching, C-H stretching, and OH bending, respectively (Figure 2b). Other peaks appear are at 1647.2 cm^{-1} for C=O (amide I band), at 1417.6 cm^{-1} for CH₂ deformation, at 937.4 cm^{-1} for CH₂ stretching and at 856.3 cm^{-1} for C-H bending. The IR spectra of the inclusion complex (Figure 2c) shows that peak for cyanide bond of the drug was decreased and also C-H aromatic bond at 3008.3 cm^{-1} was disappeared indicating inter molecular hydrogen bonding between zaleplon and β -CD. Disappearances of several guest signals can be considered as a confirmation of the formations of the binary system. It was noted in the IR pattern of the complex that it was dominated by the betacyclodextrin vibrational bands. This is because, structurally, betacyclodextrin is huge in size as it is built up from seven repeating monomer units therefore, its significant control on the IR profile of the complex should be expected (19). Furthermore, this finding suggests that only part of zaleplon was encapsulated in the beta-cyclodextrin cavity (20).

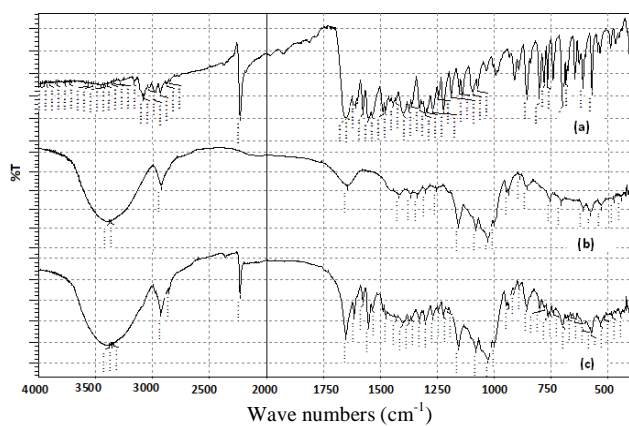


Figure 2: FT-IR spectra of a: plain zaleplon, b: β -cyclodextrin and c: inclusion complex

In vitro dissolution studies of zaleplon- beta-cyclodextrin complex

Figure (3) shows the dissolution profile of plain zaleplon compared to its inclusion complexes. It was found that 28.3% of plain drug was dissolved after 20 minutes while a complete drug release was obtained from the inclusion complex (ratio 1:1) after the same period. The increase in drug dissolution upon complexation with β CD may be due to the interactions between the hydrophobic part of the drug and the non-polar cavity of β CD that causes dehydration of the hydrophobic drug molecule and its transfer into the cavity, thereby increasing the affinity toward water and hence increasing the dissolution. The surfactant-like properties of β CD can also be another reason to explain the higher dissolution rate of the complexes. The third reason is that β CD reduces the interfacial tension between particles of drug and the dissolution medium, leading to a greater rate of dissolution (21). Other complex ratios showed higher drug release than plain drug but not more than those made by 1:1 ratio.

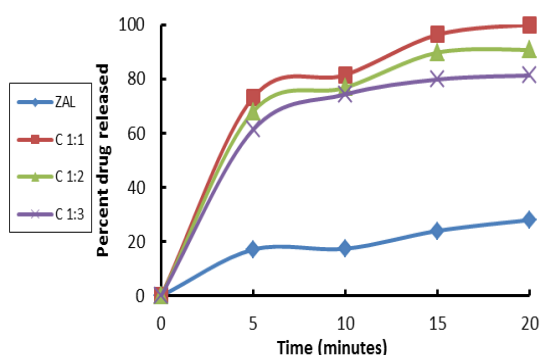


Figure 3: % Drug released from plain zaleplon and from different inclusion complexes in different ratios.

Evaluation of fast dissolving films

Fast Dissolving Films were evaluated for thickness and found to be in the range of 0.30 to 0.33mm.

The folding endurance values of the prepared films were found to be in the range from 46 to 69. The drug content values were between 98.11 to 100.91%. The disintegration time of the films was from 32.9 to 43.5 seconds (Table 2).

Table 2: Evaluation of zaleplon films

| | Drug content (%) | Folding endurance | Film thickness (mm) | Disintegration time (second) |
|-----------|------------------|-------------------|---------------------|------------------------------|
| F1 | 98.51±0.71 | 62±0.12 | 0.33±0.01 | 33.2±0.04 |
| F2 | 98.99±0.51 | 54±0.51 | 0.31±0.01 | 34.5±0.06 |
| F3 | 100.91±0.56 | 53±0.01 | 0.31±0.03 | 33.5±0.08 |
| F4 | 99.51±0.56 | 57±0.10 | 0.30±0.02 | 35.2±0.10 |
| F5 | 99.12±0.66 | 61±0.12 | 0.30±0.04 | 33.0±0.09 |
| F6 | 98.11±0.58 | 61±0.01 | 0.33±0.03 | 43.0±0.09 |
| F7 | 98.83±0.85 | 62±0.02 | 0.31±0.03 | 32.9±0.01 |
| F8 | 100.87±0.89 | 46±0.12 | 0.32±0.40 | 43.5±0.02 |

Regarding the *in vitro* release, films prepared with kollicoat IR (F₃ and F₇) showed a complete drug release after 15 minutes as shown in figure (4). This can be explained on the bases that presence of kollicoat IR causes increase in drug release due to wetting ability and conversion of crystalline form to amorphous one. Because of the formation of amorphous phases, the dissolution rate is very high since the drug simply dissolved along with the polymer (22). Also the polyvinyl alcohol moiety of kollicoat provides good film forming properties and the polyethylene glycol part acts as an internal plasticizer leading to excellent flexibility. In contrast to other film formulations, the plasticizer cannot migrate because it is covalently bound in the molecule. Instant pure-cote showed nearly complete drug release after 20 minutes (F₅), which could be due to the higher swelling ability observed for the pregelatinized starches. This higher swelling ability could lead to the absorption of large quantities of water into the film mass and the subsequent generation of a higher swelling force, which would initiate the active mechanism of disintegration. Lycoat NG 73 which is a granular hydroxylpropyl starch, showed the same dissolution pattern of instant pure-cote with the benefit of hydroxyl propyl group that increases the polarity and thus the solubility of the drug. Formulations with HPMC E15 showed 95.7% drug release (F₆), this is due to the ability of the hydrophilic polymer to absorb water, thereby promoting the dissolution, and hence the release. Moreover, the hydrophilic polymers would reach out of the film and hence, create more pores and channels for the drug to diffuse out of the films (23). Increasing the plasticizer amount increases the dissolution rate in all formulations; this is because propylene glycol which is a hydrophilic polymer will increase the partition coefficient that is a helpful property to increase the diffusion of zaleplon through the films (24).

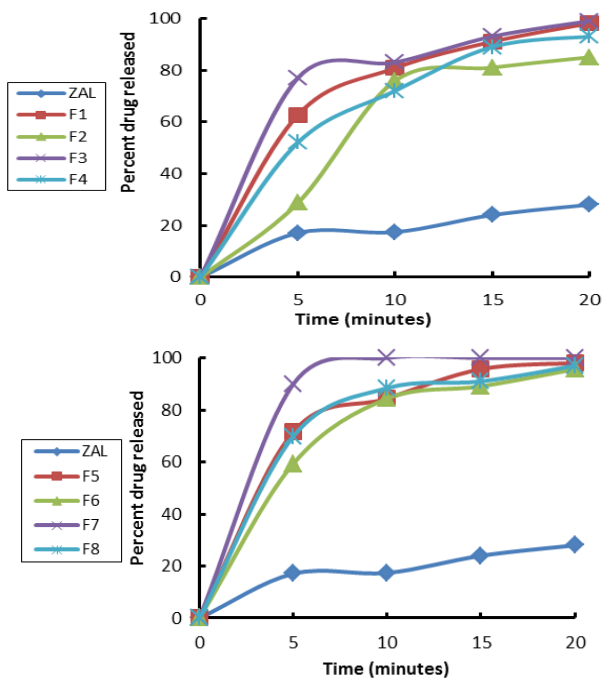


Figure 4: % Drug released from plain zaleplon (ZAL) and from different fast dissolving formulations

Effect of zaleplon on melatonin secretion in human volunteers

Zaleplon films prepared with kollicoat IR showed maximum *in vitro* release among other film forming agents, that's why it was used to study the therapeutic effect of zaleplon in human volunteers. Figure (5) shows the amount of melatonin in plasma human volunteers after administration of zaleplon fast dissolving films and market tablet. It's clear that melatonin level was slightly increased during the first three hours, while melatonin level increased significantly from zaleplon films during the next five hours.

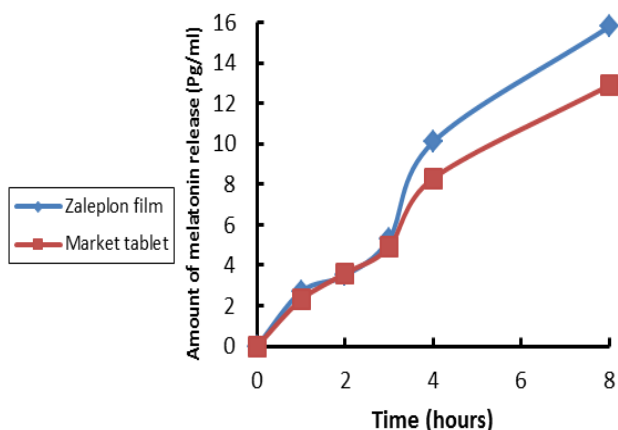


Figure 5: Amount of melatonin in serum human volunteers after administration of zaleplon fast dissolving films and market tablets.

Numerical integration using trapezoidal method was obtained to calculate the melatonin Area Under the Curve for both zaleplon films and market tablets during

the first eight hours and found to be 410.93 and 217.32 respectively. Figure (6) shows the increase in melatonin level in zaleplon films and market tablet. It's clear that the increase in melatonin level was higher in zaleplon films and the increase was clear after the fourth hour. Unpaired *t*- test was conducted with Prism Graph Pad (version 5.04), USA, to compare the mean melatonin AUC in zaleplon films and market tablets. A *P*-value < 0.0001 was defined to be extremely significant.

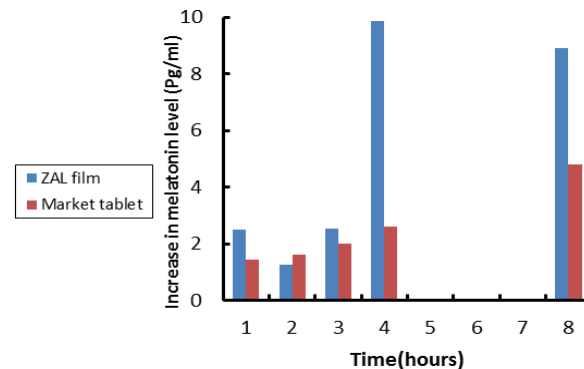


Figure 6: Increase in melatonin in level in human volunteers during 8 hours

CONCLUSION

In this study, zaleplon solubility was increased by complexation with betacyclodextrin. Zaleplon fast dissolving films were prepared using different film forming polymers and those prepared with kollicoat IR showed higher *in vitro* drug release. Zaleplon films showed higher melatonin level in human serum and higher Area under the Curve than market tablets.

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