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Tamarind Seed Polysaccharide Applicable in the Formulation and Characterization of Zolpidem Tartrate Mouth Dissolving Films

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Abstract : Zolpidem is used for the treatment of insomnia and some brain disorders.The purpose of the present work is to formulate and enhance the drug release of zolpidem tartrateby the incorporation of natural and synthetic polymer in the oral dissolving films for use in patients experiencing difficulty in swallowing.The oral dissolving films loaded with zolpidem tartrate were prepared by solvent evaporation method by using tamarind sedd polysaccharide and blanose (sodium CMC) by adding suitable plasticizer PEG 400 and glycerin. The prepared oral dissolving films were evaluated for drug content, weight variation, thickness, pH, folding endurance, *In vitro* drug release and stability studies.The evaluation parametersof zolpidem tartrate were found to be satisfactory in terms of drug content, thickness and pH.Comparison of the dissolution profiles of zolpidem tartrate oral dissolving films in phosphate buffer (pH 6.8).Effectivedrug release was achieved for zolpidem tartrate by way of preparation of oral dissolving films by solvent evaporation method.The ZOL6 showed the highest drug release 99.73% at the 15 min time point.The ZOL6oral dissolving film with higher amount of superdisintegrantCCS showed fastest onset of drug release.

Keywords : Zolpidem tartrate oral dissolving films, solvent evaporation method and Dissolution rate.

Introduction

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties.Oral cavity has been considered as a site of absorption for a long period of time. Ponchel was found that nitroglycerine was absorbed from the oral cavity in 1993[1]. Since then various active substances have been studied for local or systemic use[2]. The ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug absorption and it leads to greater bioavailability[3].The outer structure of the oral cavity is a mucous membrane consisting of an epithelium, basement membrane and lamina propria overlying a submucousa containing blood vessels and nerves[4-6]. The mechanism of oral mucosal drug absorption occurs by passive diffusion of the non-ionized species through the intercellular spaces of the epithelium, a process governed primarily by a concentration gradient[7-9].The concentration of water soluble polymer is about 60-65% in the formulation of OTF [10, 11].The selection of the plasticizer will depend on compatibility with the polymer and type of solvent used in the preparation of the film. It enhances the strength of the polymer [12, 13].Some of the plasticizers commonly used in the preparation of films are glycerol, propylene glycol, low molecular weight PEG, phthalate derivatives, citrate derivatives, and castor oil. The plasticizer concentration is used in the preparation of OTF is 0-20% w/w of dry polymer weight [14-22].

Experimental

Materials

Drug used in this study was gifted from Orchid Pharma limited, Chennai. All the other materials and reagents used were of analytical grade.

Preparation of mouth dissolving films

The mouth dissolving film of ZOLby using polymers were prepared by solvent evaporation method. An aqueous solution of the polymers was prepared in distilled water. ZOL was added to the aqueous polymeric solution. This was followed by addition of plasticizers like PEG 400 and glycerin. Citric acid was also mixed with it. Taste masking can be done by palatability evaluation studies by aspartame, which is known to be 200 times sweet than sucrose. The solution was casted on a Petridish and dried at room temperature for 24hrs. The film was carefully removed from the Petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose per strip.

Weight variation

The $4cm^2$ film was cut at three different places in the cast film. The weight of each film strip was taken and then weight variation was observed.

Thickness

The thickness of each fast dissolving film formulation(2×2 cm) was measured by using a micrometer screw gauge(Fscrow, China)(accuracy up to 0.001) at five points(centre and corners) on the film to ensure the uniformity of the film thickness. The mean thickness (mm) was calculated from the five points. Three samples of each FDFs formulation were measured.

Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

In vitro Disintegration

The *in vitro* disintegration time of the ODFs (2×2 cm) was determined using a disintegration tester (Electrolab ED-2L) with distilled water at 37± 0.5^0C. The disintegration time was defined as the time taken for ODF to completely disintegrate with no solid residue remains on the screen. This test was done in triplicates and the average value was taken as DT.

*In vitro*Dissolution Studies

According to previous studies, dissolution studies were performed using USP 23 apparatus, paddle over disc method. As the paddle over disc apparatus was not available, USP apparatus 1 (basket) (Lab India Model No: DISSO-2000) was used for this study. Five hundred millilitres of phosphate buffer (pH 6.8), which is a prescribed media for zolpidem tartrate was maintained at 37±5°C while the basket was set at 50 rpm. A film sample of $4cm^2$ was cut and taken into the basket. The five millilitres of dissolution samples were withdrawn at different time intervals, and the same amount was replaced with the fresh buffer. The withdrawn samples were filtered and analysed using aUVspectrophotometer at a wavelength of 295 nm. The percentage drug release was calculated. The relationship between time and percentage release was plotted to determine when the maximum amount of drug is released. The dissolution studies were carried out in triplicate (n=3).

Results and Discussion

Characterization

Compatibility studies by FTIR

When we observe the Fig:1&2 of FTIR spectra, the drug, exhibited the peaks at 3085.50 cm^{-1}, 3054.68 cm^{-1}, 3025.43 cm^{-1} for C–H aromatic stretching, 2925.98 cm^{-1} for CH_3, C–H stretching, asymmetry, 2233.93 cm^{-1} for C -N stretching and 1637.48 cm^{-1} for C =O. The same peaks of the drug were observed in the drug-polymer physical mixture; this indicates the absence of drug-polymer interaction.

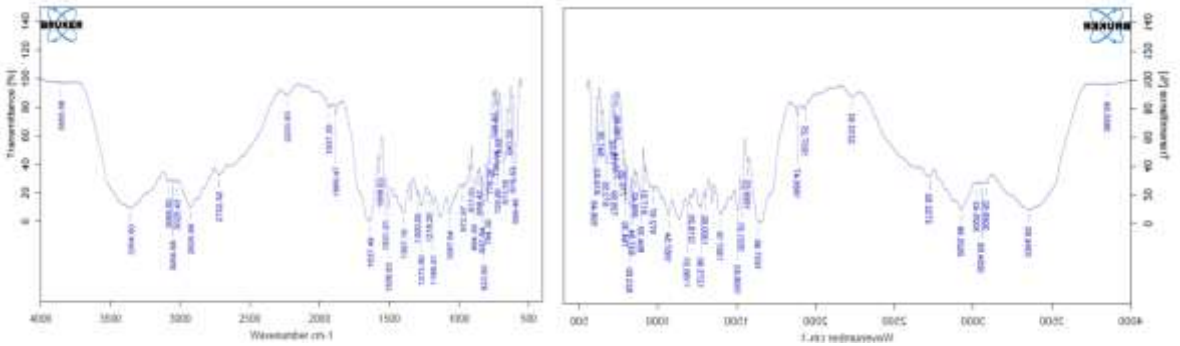

Fig.1:FT-IR spectrum of Zolpidem Fig.2: FT-IR spectrum of oral thin film

The FT-IR studies (Fig:1&2) all the spectra of drug and drug with polymer mixture at the same wave number, indicated no modifications or interaction between the drug and the excipients. From this it can be concluded that the drug has maintained its identity without losing its characteristic properties.

InVitro Dissolution studies

Dissolution rate of ZOL and its polymeric films were determined in 500 ml of pH 6.8 phosphate buffer at 37°C with a stirrer rotation speed of 50 rpm using the USP I dissolution rate test apparatus employing the basket. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals with the bulb pipette containing the prefilter. The samples were filtered through 0.45µm millipore filter. The samples were suitably diluted and assayed spectrophotometrically (Lab India) at 295 nm. Each test is repeated for three times. The percent of drug dissolved at various time intervals was calculated and plotted against time. The results are shown in **Fig.3.** The films ZOL_1, ZOL_2 and ZOL_4 shows the slowest and lowest drug release prepared with Sodium CMC compared to the Pure ZOL at 15 min time point. The film ZOL_3 showed the highest drug release at the 15 min time point. In the case of ZOL_3 the oral dissolving films with less amount of super disintegrant (SSG) showed fastest onset of drug release. However, it was evident that the oral thin films of ZOL_3 with super disintegrant dissolved rapidly within 15 min whereas the oral dissolving films with higher amount of super disintegrant with different plasticizers showed less amount of drug release. In conclusion, the addition of less amount of super disintegrant to the ZOL- Sodium CMC (ZOL_3) oral dissolving films leads to faster dissolution.

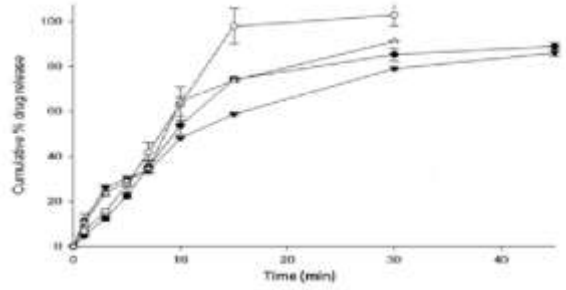

Fig.3:Comparative dissolution profiles of ZOL from oral thin films of ZOL -Blanose containing varying concentrations of blanose

The results are shown in **Fig.4** for the films developed with TSP as polymer**.** The films prepared with TSP are ZOL_5, ZOL_7 andZOL_8showed the similar drug release at the 30 min time point. When the ZOL pure drug and ZOL_6 were compared, the ZOL_6 showed the highest drug release 99.73% at the 15 min time point.

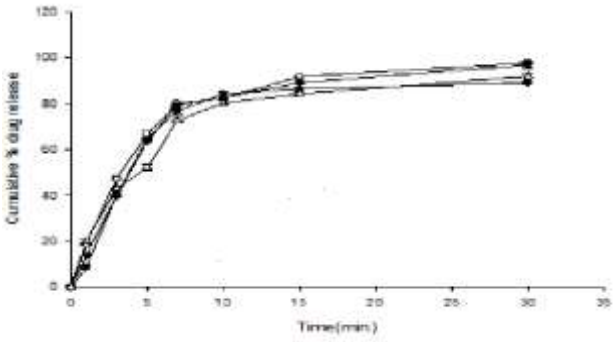

Fig.4:Comparative dissolution profiles of ZOL from oral thin films of ZOL- TSP containing varying concentrations of TSP

Comparative Dissolution Profiles

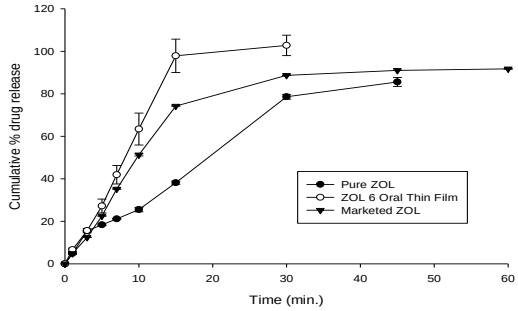

Fig.5: Comparative dissolution profiles of ZOL from pure ZOL, ZOL 6 and marketed ZOL branded formulation

Stability studies of promising oral thin films as per ICH guidelines

Hence, ZOL 6 was selected for stability studies andstored at 25°C/60 % RH and 40°C/75 % RH. The samples were withdrawn at 0, 3 and 6 months and subjected to drug content, dissolution and solid state analysis (FTIR studies).

The samples withdrawn from all the conditions (after 3 and 6 months) did not show the color change. The amounts of ZOL content (%) in the polymeric films stored under conditions according to ICH guidelines. Less than 5 % of the ZOL was lost during 6 months in the films stored at 25°C/60 % RH and 40°C/75 % RH. From the above results ZOL appeared to be stable in the storage conditions tested.

The comparative dissolution profiles of the freshly prepared ZOL 6 and the aged ZOL6stored at 25°C/ 60 % RH and 40°C/ 75 % RH for 6 months are shown in Fig.6. Reduced crystallinity and improved wettability are responsible for the faster dissolution rate. Therefore, it can be concluded that the ZOL- TSP containing polymeric thin film (ZOL 6) is a fairly stable and promising film for improving the dissolution rate of the drug ZOL.

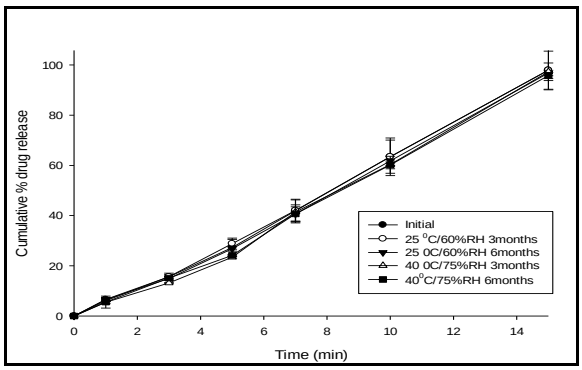

Fig.6:Comparative dissolution profiles of ZOL from oral thin films of ZOL 6 before and after stored at 25°C/ 60 % RH and 40°C/ 75 % RH for 6 months. (Mean ± S.D)

Conclusion

In conclusion, our studies showed that, hydrophilic polymers could be used as potential carriers in the dissolution rate enhancement of ZOL. The ZOL release from the pure drug and the oral thin films followed first order kinetics. The results demonstrated that the optimum ZOL: TSP (ZOL 6) weight ratio is 1:5. Since, no drug carrier interaction in the oral thin films has been evidenced, increased dispersibility and reduced crystallinity of ZOL can account for the increased dissolution rate of the films. Oral thin films were prepared by solvent evaporation method. The advantages of the solvent evaporation method are ease of preparation avoidance of organic solvents or high temperatures. This technique is easy and more convenient and economical from a practical point of view.

Declaration of the interest: The authors declare no conflict of interest. The authors are alone responsible for the content and writing of the paper.

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