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Research Article

**FORMULATION AND DEVELOPMENT OF ZOLPIDEM
TARTRATE FAST DISSOLVING FILMS BY USING
SODIUM CMC****Pamula Reddy Bhavanam***Department of Pharmaceutics, KVK College of Pharmacy, R R Dist, Telangana-501512,
India.**Abstract:**

Drug 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 tartrate by the incorporation of suitable polymer in the oral dissolving films (OTF) for use in specific populations viz. geriatrics and patients experiencing difficulty in swallowing. The oral dissolving films loaded with zolpidem tartrate were prepared by solvent evaporation method using sodium CMC by adding suitable plasticizer 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 parameters of 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). Effective drug release was achieved for zolpidem tartrate by way of preparation of oral dissolving films by solvent evaporation method. ZOL7 showed the highest drug release at the 10 min time point. The ZOL7 oral dissolving film with higher amount of superdisintegrant CCS and SSG showed fastest onset of drug release.

Keywords: Zolpidem tartrate oral dissolving films, solvent evaporation method and Dissolution rate.**Corresponding author:****Pamula Reddy Bhavanam***,Department of Pharmaceutics,
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INTRODUCTION:

Novel drug delivery system in the recent years was developed to enhance safety and efficacy of drug molecules by designing a suitable dosage form for administration¹. The oral route is the most acceptable and preferred route for drug delivery, has its own merits and demerits². There is a need for development of dosage form with better therapeutic efficacy and fewer side effects³. Various bioadhesive mucosal dosage forms include mucoadhesive tablets, gels, ointments, patches have been developed⁴. Recently, fast dissolving drug delivery systems has become one of the popular and acceptable drug delivery systems, because of their ease of administration and better patient compliance. This novel drug delivery system can also be beneficial for meeting the current needs of the industry for improved solubility, stability, biological half life and bioavailability enhancement of drugs⁵. Fast dissolving films (FDFs) have attracted interest as an excellent dosage form, not only for oral care, but also for patients with aphasia or dysphasia^{6,7}. They can be taken with ease at any time by the patient without requiring any water for swallowing⁸⁻¹⁰. The oral strip technology delivery system consists of very thin oral strips which are postage stamp-sized rectangular shape polymeric films, which is placed on the patient's tongue or along the inside of the cheek. The hydration of the film by the saliva gets adhered onto the site of application. Then it disintegrates rapidly and dissolves to release the medication for absorption onto the oral mucosa as well as gastro intestinal tract producing faster onset of action. These flexible films are suitable for oral, topical and enteral use where they can be applied to mucosal membrane areas of the mouth, rectum, vagina, nose and ear.

EXPERIMENTAL:

Materials

Drug used in this study was purchased from Vijaya Scientifics limited, Hyderabad. HPMC (3cps and 5cps) was gifted from RA Chem Pharma Limited, Hyderabad. All the other materials and reagents used were of analytical grade.

Preparation of mouth dissolving films

The mouth dissolving film of ZOL 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 plasticizer like 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 4cm² 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°C. 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. Three 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 4cm² 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 a UV spectrophotometer at a wavelength of 295nm. 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,

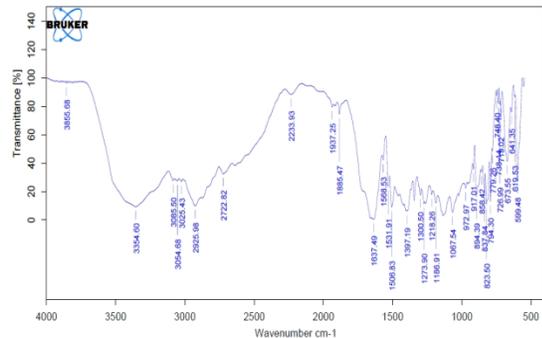


Fig.1:FT-IR spectrum of Zolpidem

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.

Variation of Mass

When manufacturing the oral films the film solutions were cast into sheets and then cut into smaller strips of $4\text{ cm}^2(2\text{ cm} \times 2\text{ cm})$. Oral films were cut from different sheets and the variability between the sheets of the respective polymer was investigated. The variation of mass of Sodium CMC oral thin films showed the highest variation in mass with an average mass of 293 mg. Thus the mass was either lower or higher than the nominal value which can have consequences on the content uniformity. In conclusion, a homogenous distribution of pure drug and, if possible, prevention of recrystallization of pure drug reduces mass variation and enhance the content uniformity.

Film Thickness

The determination of film thickness is the most common method to characterize the produced oral thin films. The micrometer screw gauge method was used to determine the thickness of the ZOL polymeric oral thin films. The thickness of the films was determined by using the screw gauge. Oral thin films made from Sodium CMC showed an average film thickness of $633\mu\text{m}$.

pH value

The pH value was determined by dissolving one oral film in 2ml of distilled water and measuring the pH of the obtained solution. Differences were expected because various polymers were used. The pH value of ZOL polymeric oral films was measured by electrometric pH meter.

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.

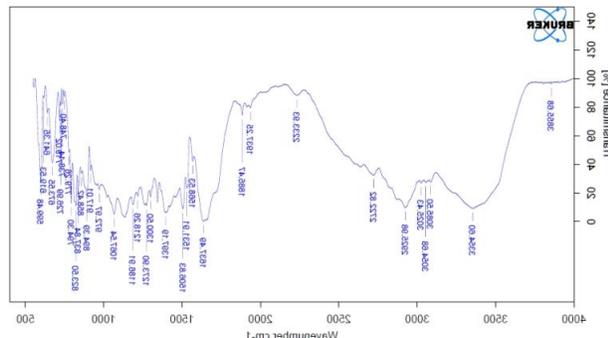


Fig.2: FT-IR spectrum of oral thin film

Folding endurance

Folding endurance was determined by repeatedly folding the film ($2\text{ cm} \times 2\text{ cm}$) at the same place until it breaks at the place of folding. The an average folding endurance of ZOL polymeric thin films. The film strips of Sodium CMC exhibited an average folding endurance of 17.3

In Vitro 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 $0.45\mu\text{m}$ 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 ZOL₁, ZOL₂ and ZOL₄ shows the slowest and lowest drug release prepared with Sodium CMC compared to the Pure ZOL at 15 min time point. The film ZOL₃ showed the highest drug release at the 15 min time point. In the case of ZOL₃ 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 ZOL₃ with super disintegrant dissolved completely 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 (ZOL₃) oral dissolving films leads to faster dissolution.

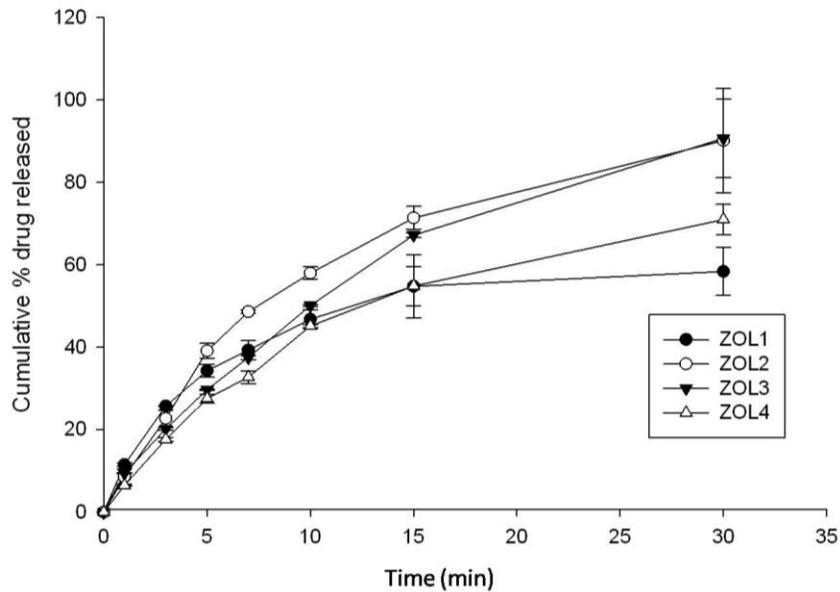


Fig.3: Comparative dissolution profiles of ZOL from oral thin films of ZOL -Blanose containing varying concentrations of Blanose

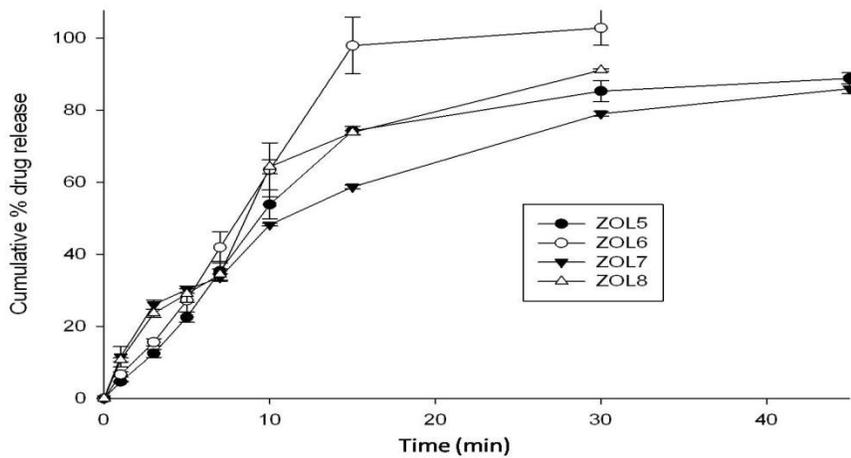


Fig.4: Comparative dissolution profiles of ZOL from oral thin films of ZOL -Blanose containing varying concentrations of Blanose

The films prepared with Sodium CMC are ZOL₅, ZOL₆ and ZOL₈ showed the similar drug release at the 30 min time point. When the ZOL pure drug and

ZOL₇ were compared, the ZOL₇ showed the highest drug release 99.73% at the 10 min time point.

Comparative Dissolution Profiles

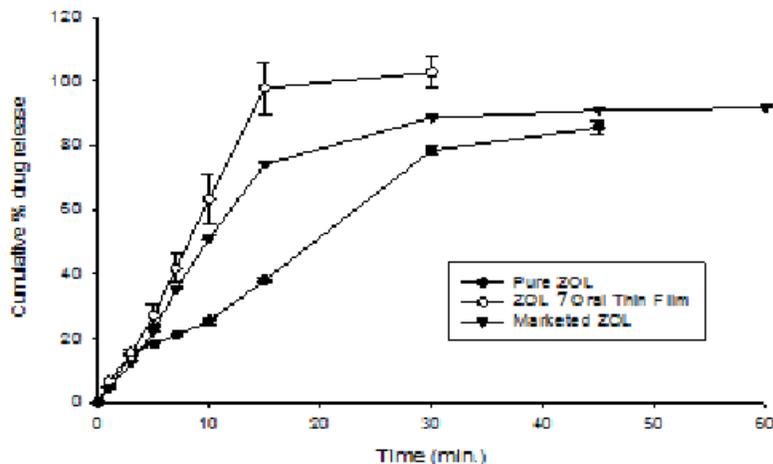


Fig.5: Comparative dissolution profiles of ZOL from pure ZOL, ZOL 7 and marketed ZOL branded formulation

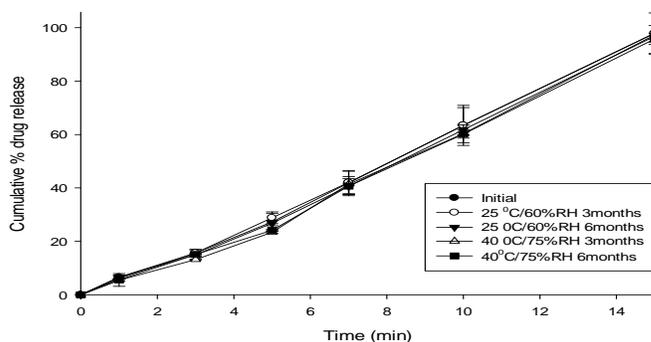


Fig.6: Comparative dissolution profiles of ZOL from oral thin films of ZOL 7 before and after stored at 25°C/60% RH and 40°C/75% RH for 6 months. (Mean \pm S.D)

Stability studies of promising oral thin films as per ICH guidelines

Hence, ZOL 7 was selected for stability studies and stored 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 (DSC, XRD and 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 7 and the aged ZOL7 stored 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-Sodium CMC containing polymeric thin film (ZOL 7) is a fairly stable and promising film for improving the dissolution rate of the drug ZOL.

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: Sodium CMC weight ratio is 1:6. 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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