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***RESEARCH ARTICLE***

# Design and evaluation of fast dissolving oral films of Zolpidem by solvent casting method

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## ABSTRACT:
Present research was aimed with the objective of formulation of Zolpidem fast dissolving oral films, for rapid dissolution of drug and absorption, which may produce the rapid on set off action. The fast dissolving oral films were prepared by solvent casting method using various polymers like HPMC E5, HPMC E15, HPMC K15, microcrystalline cellulose and poly vinyl alcohol. Glycerol used as plasticizer. Prepared films were evaluated for various physicochemical parameters like film thickness, tensile strength, folding endurance, content uniformity, estimation of moisture content, disintegration studies and dissolution studies. As polymer concentration increases thickness increases. Thickness directly proportion to tensile strength so as thickness increases tensile strength also increases. Folding endurance increases as polymer concentration increases. The moisture uptake studies revealed that, the film take up very little moisture (1-2%) in high humid environment, hence this may favors the stability as well as compatability. In vitro drug release studies reveals that among all formulations F7 formulation highest amount of drug release compared to other formulations, hence F7 formulation was taken as optimized formulation for further studies. Short term stability studies were conducted for optimized formulation up to 3 months at 40±2ċ 75% R.H. after stability studies films were transparent all physical parameters were favorable and drug release was satisfactory.

**KEY WORDS**: Fast dissolving films. Zolpidem, Solvent casting method, HPMC E5,E15 and K15,Oral thin films.

## INTRODUCTION:
Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration (Vaishali Y et al). It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin.

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FDOFs are useful in patients such as pediatric, geriatric, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for these who have an active life style. It is also useful whether local action desired such as local anaesthetic for toothaches, oral ulcers, cold sores or teething. (Govind Soni et al). Zolpidem Tartarate (ZT) is a prescription medication used for the treatment of insomnia and some brain disorders. It is a short-acting non benzodiazepine hypnotic of the imidazopyridine class that potentiates GABA, an inhibitory neurotransmitter, by binding to GABA-A receptors at the same location as benzodiazepines. It works quickly, usually within 15 minutes, and has a short half-life of two to three hours. ZT is used for short-term (usually about two to six weeks) treatment of insomnia.

**Table No 1: Formulation of fast dissolving oral films of Zolpidem**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| DRUG(mg) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| HPMC E15 (mg) | 10 | 20 | _ | _ | _ | _ | _ | _ |
| MCC (mg) | 10 | 10 | _ | _ | _ | _ | _ | _ |
| Pregelatinsed starch (mg) | _ | _ | 10 | _ | _ | _ | _ | _ |
| HPMC K15 (mg) | _ | _ | 10 | _ | _ | _ | _ | _ |
| HPMC E15 (mg) | _ | _ | _ | 10 | 15 | _ | _ | _ |
| PVA (mg) | _ | _ | _ | 10 | 15 | _ | _ | _ |
| HPMC E5 (mg) | _ | _ | _ | _ | _ | 200 | 400 | 600 |
| Glycerol (mg) | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| Mannitol (mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Vanilla (mg) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Water (ml) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

It has not proven effective in maintaining sleep and is more used for sleep initiation problems. The fast dissolving oral films were prepared by solvent casting method using various polymers like HPMC $E_5$, HPMC $E_{15}$, HPMC $K_{15}$, microcrystalline cellulose and poly vinyl alcohol. Glycerol used as plasticizer (Vinay Umesh Rao et al).

## MATERIALS AND METHODS:

**Materials**:

Zolpidem tartarate (EMCO industries, Hyd) HPMC E5, HPMC E 15, HPMC K15 and Poly vinyl Alcohol (PVA (Dow Chemicals, USA) Micro crystalline cellulose, Pregelatinised starch (S.D fine Chemical .Mumbai) Glycerol (Merck, India).

**Methods: solvent casting method** (Pratikkumar Joshi et al):

Accurately weighed quantities of polymers (HPME E5, E15 and k15) were dissolved in distilled water. The solution was heated and bubble free, to this plasticizer,(glycerol) and sweetener, (mannitol) were added and mixed thoroughly, drug was added to above solution and dissolve completely, now clear solution was poured into clean Petri dish. It was dried in hot air oven up to 24 hours then peeled off from the Petri dish stored in desiccators for further study.

**Evaluation of fast dissolving oral films:**

**1. Percentage elongation and tensile strength** (Buchi N et al) **:**

The films were cut into a size of 2cm x 2cm strips. One end of the strip along its length was clamped to the tensile strength testing apparatus and the other end was attached to a movable rod. The movable rod was attached to a pan with the help of a non-stretchable string through a pulley. Weights were carefully added onto the pan and the weight was gradually increased. The elongation of the patch was determined by measuring the distance moved by the pointer (on a graph paper) after the addition of the weight each time. The weights were added, until the film was cut.

Percentage elongation was determined using the formula,($L_w$ -L)

$$\textit{Percentage elongation at break point} = \frac{(Lw - L) \times 100}{L}$$

The tensile strength of the patch was determined using the formula,

$$\textit{Tensile strength} = \frac{W}{a \times b} \times \frac{l + \Delta l}{l}$$

Where,

a = width (cm), b =thickness (cm), l =length of the test patch strip (cm), $\Delta l$ = elongation at the break point (cm) and W = weight required to break the patch (g)

**2. Folding endurance**

The folding endurance was measured manually for the prepared films. A strip of film 2x2cm was cut evenly 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 gave the exact value of folding endurance.

**3. Thickness:**

Precise film thickness measurements were carried out using NIKON DigiMicro encoders/gauges (Nanowave Inc. MA 01590 USA, MF501–50 mm travel range along with TC-101) that are used in motion control systems with optical linear encoder heads with a specially developed MPM300-OEM motion processing module providing nanometer resolution. These encoder/gauge heads were used with the Nikon TC-101 interpolator-counter with digital read-out. The encoders use a 12 volt direct current (VDC) power supply. Thickness was measured at four corners and in the centre of the selected film.

**4. Determination of moisture content:**

The prepared films were weighed and kept in a vacuum desiccator containing anhydrous silica at room temperature. The patches were weighed repeatedly until they showed a constant weight. Percent moisture content was determined using the formula,

% Moisture Content =
(Initial weight of the film – Final weight of the film) x 100
Initial weight of the film

**5. Determination of moisture up take** (M.K. Patidar et al) **:**
The prepared films were weighed and kept in a desiccators containing anhydrous silica at room temperature for 24 hours. It was then taken out from the desiccator, weighed and exposed to relative humidity of 75% (saturated solution of sodium chloride) in desiccators. The film was weighed until it showed a constant weight. Percent moisture uptake was determined using the formula.

% Moisture Uptake =
(Final weight of the film – Initial weight of the film) x 100
Initial weight of the film

**6. Drug content:**
Six films of each formulation were used. Films were cut into small pieces and transferred into a glass mortar. About 10 mL of water was added and triturated for 30 min. The contents were transferred into 100 mL volumetric flask. The mortar was rinsed three times with each 15 mL of water and the rinsed portions were transferred to a volumetric flask. The solution was shaken continuously for one hour. It was then heated on a steam bath for 10 min and cooled to room temperature. Fifty milliliters of water was added and the volume was made up with water. The solution was filtered through Whatman-1 filter paper and the drug content in the resultant solution was determined by measuring the absorbance at 293 nm.

**7. Disintegration tests** (Sandeep Saini et al)**:**
Disintegration refers to the physical process by which a film dissolves into a solution. Disintegration times were measured *in vitro for six samples* by the standard United States Pharmacopeia (USP) disintegration method in artificial saliva at 37°C using the disintegration apparatus (Electrolab, ED-2L, Mumbai, INDIA). The time required for full disintegration was recorded for each film.

**8. *In vitro* dissolution studies** (S. Raju et al)**:**
*In vitro* dissolution test was carried out according to the USP II paddle dissolution apparatus. The test solution was 900 mL of 6.8p$^{H}$ phosphate buffer at 37±0.5°C and the rotation rate of 75 rpm. 5 mL sample of the dissolution medium was withdrawn at regular time intervals. After each withdrawal, an equal volume of dissolution medium was replaced. The absorbance was measured at 295 nm and the percent drug released was calculated.

**9. Stability studies:**
Stability studies on selected formulations were conducted according to International Conference on Harmonization (ICH) guidelines. Stability studies were carried out for the best films, stored in an aluminum package in a chamber (Electrolab) controlled at 40°C and 75% in humidity for 3 months. The content of ZT was then determined spectrophotometrically as described earlier. The films were also subjected to other physical and dissolution tests.

## RESULTS AND DISCUSSIONS:

### Evaluation parameters fast dissolving oral films:

### Disintegration time:

**Table No 2**: **Disintegration times of different batches of prepared oral thin films**

| Formulation codes | Disintegration time (sec) |
|---|---|
| **F1** | **49** |
| **F2** | **90** |
| **F3** | **No film** |
| **F4** | **57** |
| **F5** | **85** |
| **F6** | **No film** |
| **F7** | **23** |
| **F8** | **47** |

Totally 8 batches of films were prepared to optimize the formulation (F1 to F8). Among these F1, F4, F7 and F8 showed best formulations based on the disintegration studies. The disintegration time of the developed oral thin films are shown in Table the data reveal that all the formulations, except F2, F3, F5 and F8 disintegrated within 60 sec and hence omitted for further studies, as it did not meet the criteria of oral thin films according to which disintegration should take place in less than a minute.

### Physical parameters:

**Table No 3: Physical properties of the prepared oral thin films**

| Formulation Codes | Thickness of patch (µm) | Tensile strength, (N/m$^2$) | Elongation (%) |
|---|---|---|---|
| **FI** | 39±0.01 | 1.689±0.18 | 9.3±0.65 |
| F4 | 43±0.02 | 1.865±0.23 | 10.1±0.59 |
| F7 | 56±0.01 | 1.72±0.78 | 10.3±0.62 |
| F8 | 67±0.03 | 2.13±0.65 | 11.2±0.12 |

**Table No 4: Moisture studies and content uniformity of the prepared oral thin films**

| Formulation Codes | Moisture content (%) | Moisture uptake (%) | Drug content (%) |
|---|---|---|---|
| **FI** | 2.89±0.05 | 2.85±0.05 | 92.6±1.1 |
| F4 | 3.01±0.11 | 3.12±0.09 | 93.8±2.1 |
| F7 | 3.23±0.25 | 3.23±0.35 | 91.6±1.12 |
| F8 | 3.12±0.68 | 3.31±0.76 | 97.8±1.74 |

## DISCUSSION:

The tensile strength of each film was determined and the data obtained is given in Table no 3. The data reveal that tensile strength varies from 1.8-2.2 N/m$^2$.Addition of polymers and increase in polymer weight/ratio shows a significant increase in the tensile strength. The data indicates that as the concentration of polymer increases thickness increases. Thickness is directly proportional to tensile strength. In other words as thickness increases tensile strength also increases. The data obtained for moisture absorption are given in Table. No 4 As the concentration of polymer increases, the percent moisture absorption increases. Low moisture content ensures stability and prevents the formation of dried and brittle films. The moisture uptake of the formulations indicates that in high humid environment, the patches take up very little moisture (1-2%). This may favors the stability as well as compatibility with high humid conditions of the formulations. The drug content of the prepared films was in the range of 92-98%.

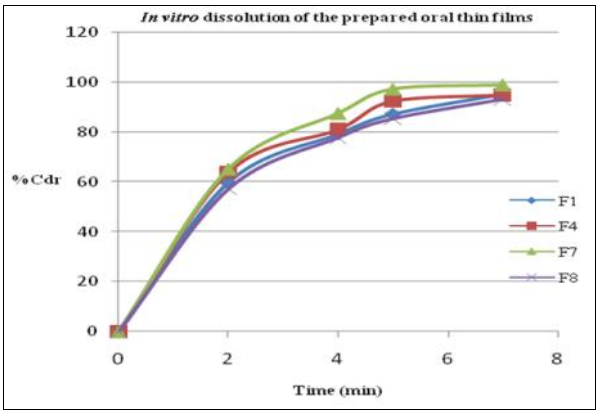


**Fig No 1: *In vitro* dissolution studies of the prepared oral thin films of Zolpidem**

## DISCUSSION:

The *in vitro* drug release data indicate that batch F7 shows highest drug release compared to all other formulations. Therefore F7 batch was studied for further studies. For F7 formulation conducted stability studies as per ICH guide lines

### Stability studies:

**Table No 5: Physical properties of the prepared oral thin film of F7 (stability studies)**

| Time (days) | Elongation (%) | Tensile strength, (N/m$^2$) | Thickness of patch (µm) |
|---|---|---|---|
| 0 | 11.2±0.11 | 1.79±0.25 | 48±0.01 |
| 30 | 11.2±0.21 | 1.783±0.33 | 48±0.02 |
| 60 | 10.9±0.78 | 1.79±0.43 | 49±0.01 |
| 90 | 10.7±1.2 | 1.778±0.56 | 48±0.01 |

**Table No 6: Moisture studies and content uniformity of the prepared oral thin films of F7 (stability studies)**

| Time (days) | Moisture content (%) | Moisture uptake (%) | Drug content (%) |
|---|---|---|---|
| 0 | 3.01±0.09 | 3.13±0.07 | 92.5±0.9 |
| 30 | 3.01±0.22 | 3.13±0.09 | 91.8±1.2 |
| 60 | 3.01±0.1 | 3.13±0.05 | 91.5±1.5 |
| 90 | 3.01±0.13 | 3.13±0.03 | 92.1±1.3 |

From the investigation it was found that the formulations were satisfactorily stable up to 3 months at 40ºC ±2ºC 75% RH. During storage drug content, pH, drug release and other parameters were observed. Films were transparent and were no change in color. The results from the Table: 5-6 indicate that prepared films were stable.

## CONCLUSION:

From the present investigation, the obtained result concludes that the drug delivery systems of ZT were designed using different polymers and evaluated i*n vitro*. The oral thin films were prepared by the coating solvent casting method. The prepared films were evaluated for thickness, elongation (%), moisture studies, content uniformity, *in vitro* dissolution and pharmacokinetic parameters. The following are some of the important conclusions made from the present study; the data on the physical parameters generated are such as thickness, moisture content, moisture uptake and surface flatness are found to be favorable for the development of oral thin films. Oral thin films developed show acceptable physical properties and rapid desirable disintegration. The *in vitro* results reveal that the F7 formulation releases the drug immediately compared to other formulations. The formulation F7 was found to be stable, since no significant changes in drug release, content uniformity and other physical properties are observed. These present findings, suggest that the oral thin film containing ZT developed disintegrate within a minute and hence is potentially useful in managing the INSOMNIA and in patients suffering from dysphasia or aphasia and also in the case of geriatric patients who show unwillingness to take tablets.

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