FORMULATION AND EVALUATION OF ZOLPIDEM TARTRATE LAYERED TABLETS BY MELT GRANULATION TECHNIQUE FOR TREATMENT OF INSOMNIA

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INTRODUCTION

Oral drug delivery is the most preferred method of administering the drugs for the systemic effects. In addition, the oral medication is, generally, considered as the first choice for investigated new drugs in the discovery and development of pharmaceutical formulations because of patient compliance, convenience in administration and economic manufacturing process [1].

Oral drug delivery systems can be classified into immediate release and modified release systems. Immediate release dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. However, they have some disadvantages such as increased frequency of administration and fluctuations in drug plasma levels [2]. To overcome these disadvantages the modified release systems have been developed. Modified release dosage forms are designed to extend the release of the drug over a period of time or after the dosage form reaches the required site.

Oral modified release delivery systems are most commonly used for (1) delayed-release using an enteric coating, which are formulated to release the drug with a time lag not immediately after administration, (2) Extended-release (e.g. zero-order, first-order, and biphasic release) where the drug to be released over prolonged period of time. It can be achieved using sustained or controlled release dosage forms. (3) Programmed release such as pulsatile and triggered aims to release drugs on a predetermined pattern and (4) site-specific or timed release (e.g. for colonic delivery or gastric retention and chronotherapeutic drug delivery system) [3]. These systems release the drug to a specific site and/or time.

The present study aims to formulate and evaluate sustained release three-layered tablets of zolpidem tartrate, a BCS Class I drug with short half-life for treatment of insomnia, using a combination of hydrophobic and hydrophilic polymers [4]. The goal of the study is the development of matrix tablets using Lubritab and layered with the hydrophilic polymer to prolong the duration of action thereby reduces the frequency of administration and improves the patient compliance. Slow and extended-release is advisable for treatment of insomnia.

METHODS

Zolpidem tartrate, Lubritab are gift samples from Microlabs, Bengaluru, HPMC K100, HPMC K4M, AVICEL PH 102 purchased from Yarrow chem. Products.

Preformulation studies

Preformulation testing is the foremost primitive step in the rational development of dosage forms by investigation of physical and chemical properties of a drug alone and combination with excipients.

Preparation of blend of drug and excipients

All the ingredients were subjected to grinding to a required degree of fineness and passed through sieve no 60 then powder blend was subjected to precompression parameters.

Angle of repose

This is the maximum angle formed between the pile of powder and horizontal plane. The frictional forces which are equal to the coefficient friction (\(\mu\)) between the particles in loose powder can be measured.
by angle of repose. Hence, the rough and more irregular surfaces of particles form the greater angle of repose.

**Procedure**

About 100 g of the blend was weighed and poured through the funnel whose tip was fixed at the height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend was poured till the apex of the pile touches the tip of the funnel. Angle of repose is then calculated by the following formula.

$$\theta = \tan^{-1} \left( \frac{h}{r} \right)$$  \hspace{1cm} (1)

Where, $\theta$ = angle of repose, $r$ = radius of the pile, $h$ = height of the pile.

**Bulk density**

Bulk density is defined as a mass of a powder divided by the bulk volume.

Procedure

Parent bulk density ($b$) was determined by pouring the blend into a graduated cylinder. The bulk volume ($V^*$) and weight of the powder ($M$) were determined. The bulk density was calculated using the formula.

$$b = \frac{M}{V^*}$$  \hspace{1cm} (2)

**Compressibility index (C.I)**

The free flow of powder is measured by compressibility, an indication of the ease with which a material can be induced to flow is given by C.I which is calculated using the formula.

$$\text{C.I} (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$  \hspace{1cm} (3)

**Hausner's ratio**

Hausner’s ratio is an indirect index of the free flow of powder. It was calculated by the using the formula:

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$  \hspace{1cm} (5)

Where, *t*=tapped density, *d*=bulk density

**Preparation of tablets by direct compression (DC)**

In DC drug and polymer were mixed thoroughly in geometrical proportions, and then the remaining ingredients were added and compressed at maximum compression force with 6 mm flat round punch.

**Preparation of tablets by melt granulation (MG)**

In MG granules were prepared by melting Lubritab at a constant temperature of 55–60°C. Drug and diluents were gradually added to the molten mass with continuous stirring. The molten mixture was then allowed to cool and solidify at room temperature and pulverized in a mortar and passed through a sieve No. 16 for dry screening. Magnesium stearate and talc were added and compressed at maximum compression force with 6 mm flat round punch [5-8].

Tablets were prepared using the drug to polymer ratios from 1:1 to 1:6 by MG technique as given in Table 1. Preparations ZT7-ZT9 were given in Table 2 containing the drug to polymer ratio 1:0.5 and 1:1 are formulated. Formulations ZT8 and ZT9 were layered top and bottom using a hydrophilic polymer. Initially, the core tablet was slightly precompressed and was layered top and bottom with HPMC K4M [9-11]. Tablets were prepared with different diluents and channeling agents (HPMC K100 and lactose monohydrate at concentrations of 2.5%, 5%, and 10%) (Table 3). Tablets were

| Ingredients (mg) | Formulations |
|-----------------|--------------|
| Zolpidem tartrate | 6.25 6.25 6.25 6.25 6.25 6.25 |
| Lubritab | 3.125 6.25 12.5 18.75 25 31.25 37.5 |
| AVICEL PH 102 | 39.125 36 29.75 23.5 17.25 11 4.75 |
| Magnesium stearate | 0.5 0.5 0.5 0.5 0.5 0.5 |
| Talc | 1 1 1 1 1 1 |
| Total weight (mg) | 50 50 50 50 50 50 |

Table 2: Formulations for optimization of polymer concentration

| Ingredients (mg) | Formulations |
|-----------------|--------------|
| Zolpidem tartrate | 6.25 6.25 6.25 |
| Lubritab | 3.125 6.25 6.25 |
| AVICEL PH 102 | 39.125 36 36 |
| Magnesium stearate | 0.5 0.5 0.5 |
| Talc | 1 1 1 |
| HPMC K4M (upper CR layer) | - 12.5 25 |
| HPMC K4M (lower CR layer) | - 12.5 25 |
| Total weight (mg) | 50 75 100 |

Table 3: Formulations with channeling agents

| Ingredients (mg) | Formulations |
|-----------------|--------------|
| Zolpidem tartrate | 6.25 6.25 6.25 6.25 6.25 |
| Lubritab | 12.5 12.5 12.5 12.5 12.5 |
| HPMC K100 | 1.25 2.5 5 - - |
| Lactose | - - - 1.25 2.5 5 |
| HPMC K4M monohydrate | 28.5 27.25 24.75 28.5 27.25 24.75 |
| AVICEL PH 102 | 28.5 27.25 24.75 28.5 27.25 24.75 |
| Magnesium stearate | 0.5 0.5 0.5 0.5 0.5 0.5 |
| Talc | 1 1 1 1 1 |
| Total weight (mg) | 50 50 50 50 50 50 |

Table 4: Formulations layered with HPMC K4M

| Ingredients (mg) | Formulations |
|-----------------|--------------|
| Zolpidem tartrate | 6.25 6.25 6.25 6.25 |
| Lubritab | 12.5 12.5 12.5 12.5 |
| HPMC K100 | 5 - - - |
| Lactose monohydrate | - 1.25 2.5 5 |
| AVICEL PH 102 | 24.75 28.5 27.25 24.75 |
| Magnesium stearate | 0.5 0.5 0.5 0.5 |
| Talc | 1 1 1 1 |
| HPMC K4M (upper layer) | 12.5 12.5 12.5 12.5 |
| HPMC K4M (lower layer) | 12.5 12.5 12.5 12.5 |
| Total weight (mg) | 75 75 75 75 |

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prepared using the channeling agent at different concentrations (10% HPMC K100 and 2.5, and 5 and 10% lactose monohydrate) as given in Table 4 and subsequent formulations were prepared with different concentrations of channeling agents and HPMC K4M layers (15%, 20%, and 22.5% HPMC K100 and 5%, 10%, and 12.5% lactose monohydrate) as given in Table 5. To optimize dissolution media for complete drug release in 12 h the dissolution was performed in both 7.4 and 6.8 pH buffers.

Evaluation of sustained release matrix tablets
The prepared tablets were evaluated for various parameters such as weight variation, thickness, hardness, friability, drug content, content uniformity, and in vitro dissolution studies [12].

Weight variation
Twenty tablets were randomly selected, and average weight was determined. Then, individual tablets were weighed, and percent deviation from the average was calculated. Percentage deviation allowed for the tablets is given in Table 7.

Table 5: Formulations for optimization of channeling agents in layered tablets

| Ingredients (mg) | Formulations |
|-----------------|--------------|
|                 | ZT20 | ZT21 | ZT22 | ZT23 | ZT24 | ZT25 |
| Zolpidem tartrate | 6.25 | 6.25 | 6.25 | 6.25 | 6.25 | 6.25 |
| Lubritab | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| HPMC K100 | 7.5 | 10 | 11.25 | - | - | - |
| Lactose | - | 2.5 | 5 | 5 | 5 | 5 |
| monohydrate AVICEL PH 102 | 22.25 | 19.75 | 18.5 | 27.25 | 24.75 | 23.5 |
| Magnesium stearate | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Talc | 1 | 1 | 1 | 1 | 1 | 1 |
| HPMC | 12.5 | 12.5 | 12.5 | 25 | 25 | 25 |
| K4M (upper layer) | 12.5 | 12.5 | 12.5 | 25 | 25 | 25 |
| HPMC K4M (lower layer) | 75 | 75 | 75 | 100 | 100 | 100 |

Table 6: Precompression parameters of the powder blend of all formulations

| Formula tion | Angle of repose (θ)° | Bulk density (g/cm³)° | Tapped density (g/cm³)° | Hausner’s ratio° | C.I. (%)° |
|--------------|----------------------|-----------------------|------------------------|-----------------|----------|
| ZT1 | 25.26±0.03 | 0.642±0.014 | 0.735±0.004 | 1.14±0.019 | 12.5±1.520 |
| ZT2 | 25.12±0.98 | 0.646±0.006 | 0.735±0.009 | 1.13±0.003 | 12.09±0.233 |
| ZT3 | 25.78±0.82 | 0.617±0.004 | 0.722±0.003 | 1.17±0.013 | 14.53±0.926 |
| ZT4 | 26.89±0.90 | 0.634±0.005 | 0.729±0.008 | 1.13±0.022 | 11.99±1.739 |
| ZT5 | 27.21±0.72 | 0.645±0.005 | 0.742±0.005 | 1.15±0.001 | 13.16±0.019 |
| ZT6 | 25.62±0.53 | 0.652±0.012 | 0.740±0.003 | 1.13±0.021 | 11.89±0.562 |
| ZT7 | 27.89±0.92 | 0.692±0.024 | 0.757±0.002 | 1.13±0.019 | 11.62±0.332 |
| ZT8 | 26.47±0.92 | 0.641±0.004 | 0.727±0.002 | 1.13±0.004 | 11.88±0.332 |
| ZT9 | 26.97±0.86 | 0.630±0.005 | 0.710±0.006 | 1.12±0.020 | 11.24±0.491 |
| ZT10 | 27.78±0.78 | 0.642±0.007 | 0.712±0.009 | 1.12±0.007 | 11.82±0.070 |
| ZT11 | 26.58±0.94 | 0.654±0.011 | 0.728±0.003 | 1.13±0.009 | 12.16±1.202 |
| ZT12 | 26.62±0.90 | 0.658±0.003 | 0.749±0.002 | 1.13±0.002 | 12.20±0.127 |
| ZT13 | 27.26±0.69 | 0.692±0.002 | 0.788±0.006 | 1.12±0.002 | 11.29±0.324 |
| ZT14 | 27.26±0.69 | 0.669±0.002 | 0.788±0.006 | 1.12±0.002 | 11.29±0.324 |
| ZT15 | 27.76±0.76 | 0.610±0.013 | 0.692±0.005 | 1.13±0.004 | 11.84±0.141 |
| ZT16 | 26.32±0.69 | 0.660±0.010 | 0.750±0.011 | 1.13±0.001 | 11.93±0.084 |
| ZT17 | 27.79±0.72 | 0.650±0.002 | 0.738±0.009 | 1.13±0.010 | 11.90±0.813 |
| ZT18 | 26.26±0.11 | 0.644±0.006 | 0.732±0.013 | 1.17±0.011 | 12.06±0.841 |
| ZT19 | 26.26±0.69 | 0.668±0.010 | 0.758±0.016 | 1.13±0.004 | 11.87±0.816 |
| ZT20 | 27.54±0.81 | 0.646±0.005 | 0.728±0.003 | 1.12±0.004 | 11.94±0.334 |
| ZT21 | 25.21±0.68 | 0.615±0.005 | 0.694±0.006 | 1.12±0.018 | 11.44±1.435 |
| ZT22 | 26.78±0.03 | 0.670±0.002 | 0.755±0.003 | 1.12±0.011 | 12.51±1.332 |
| ZT23 | 27.78±0.78 | 0.642±0.012 | 0.740±0.003 | 1.13±0.009 | 11.19±0.562 |
| ZT24 | 27.65±0.53 | 0.659±0.024 | 0.727±0.002 | 1.13±0.002 | 11.32±0.327 |
| ZT25 | 26.12±0.03 | 0.641±0.004 | 0.752±0.002 | 1.12±0.002 | 11.58±0.332 |

Values are expressed as mean±SD, *n=3. SD: Standard deviation, C.I.: Compressibility index
In vitro dissolution studies

The in vitro drug release of zolpidem tartrate sustained-release tablets was determined using USP Dissolution Apparatus I (basket type) (Electrolab TDT-08L). For first 2 h, 900 ml of 0.01N HCl was used later for next 10 h, 7.4 pH buffer at a speed of 50 rpm, 5 ml aliquot withdrawn for every hour up to 12 h. Samples collected were analyzed by UV spectrophotometer (ELICO-164 double beam spectrophotometer) at a wavelength of 294.4 nm and 241.8 nm.

Drug-excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopy analysis

The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for the preparation of tablets was studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Kyoto, Japan) facility (model -8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6–8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer, and the IR spectrum was recorded from 4000/cm to 500/cm in a scan time of 0.045 steps/0.5 s.

Differential scanning calorimetry

The physical nature of the drug, polymer and optimized formulations were studied by differential scanning calorimeter (DSC). DSC analysis was performed using Shimadzu DSC-60 DSC. The instrument was calibrated with indium standard. 3-5 mg samples were weighed and placed in a closed, hermetic sample pans with pinhole. Thermograms were obtained by heating the sample at a constant rate 10°C/min.
A dry purge of nitrogen gas (50 ml/min) was used for all runs. Samples were heated from 0°C to 350.0°C. The melting point, heat of fusion, disappearance of the crystalline sharp peak of the drug and appearance of any new peak and peak shape were noted [13].

Model dependent methods
Regression coefficients (r²) were calculated for all the formulations. Release component "n" was calculated from Korsmeyer–Peppas equation. Based on n value the release mechanism was characterized [14,15].

Comparison of prepared optimized formulation with marketed formulation
The in vitro dissolution release of the optimized formulations was compared with the marketed STILNOCT 12.5 mg tablets. The STILNOCT 12.5 mg tablets were packed and marketed by Sanofi-Synthelabo Ltd, Mumbai, India. As the 6.25 mg twice a day tablets are not available in the market the comparison with optimized formulation was done by 12.5 mg per day tablet.

Performing accelerated stability studies for the optimized formulations
The optimized formulation was subjected to stability studies at 40°C±2°C/75%±2%RH (zone III) for a period of 3 months. Each tablet was individually wrapped in aluminum foil and packed in amber colored bottle and put at the above-specified condition in a heating humidity chamber for 3 months. For every month tablets were analyzed for the physicochemical evaluation and in vitro drug release studies.

RESULTS AND DISCUSSION
Preformulation studies
Values for the angle of repose were found in the range of 25.78±0.82–27.89±0.92 (LP limits 25–30) showing that the blend of powder was free-flowing. The value for Carr’s compressibility was in between 11.19±0.339 and 14.53±0.926 (LP limits 11–15) indicating that all batches of powder blends were having good compressibility. Hausner’s ratio was to be within the limits 1.126±0.011–1.150±0.001 (LP limits 1.12–1.18). The results showed that all the formulations showed good blend properties.

Evaluation of prepared tablets
Evaluation of prepared matrix tablets were conducted, and the values for wt variation are in the range of 49±0.12–51±0.82, 74±0.45–76±0.68, 100±0.52–102±0.46 (limits 10% deviation), hardness 7–8 (LP limits 4–9), friability 0.1±0.24–0.17±0.45 (limits 0.5–1%), thickness 2.60±0.24–2.89±0.24 (limits ±5% deviation), drug content 97.54±0.15–99.75±0.12, and content uniformity 97.4±0.43–98.97±0.79 (limits 85–115%). This indicates that the evaluation parameters for all the formulations are within the limits Table 7.

Appearance of tablets
To discriminate the control release upper and lower layers, they are colored with Erythrosine B is shown in Plate 1. The swelling of the top and bottom layers of the triple-layered tablets during the dissolution is shown in Plate 2.

In vitro dissolution studies
Sustained release matrix tablet was formulated using Lubritab as a hydrophobic polymer, AVICEL PH 102 as diluent, magnesium stearate and talc as lubricant and glidant. Initially, the formulations were prepared by MG and DC techniques. But from the results, it was observed that the formulation prepared by DC could not sustain the drug release on account of its eroding nature. Hence, MG was followed for the preparation of polymer granules, and this step improved the flow properties suitable for compression of the tablets as shown in (Fig. 1). As zolpidem tartrate has absorption throughout the GIT, the dissolution was performed in 7.4 and 6.8 pH for optimizing media. From the dissolution results, it was observed that there was no significant difference in the drug release from both media, so further work is continued with the 7.4pH media which covers most of the intestinal part (Fig. 2).

The effect of polymer in different ratios was investigated for optimizing the complete drug release in 12 h. The results showed that the formulation ZT1 exhibited initial burst release of drug and the drug release was 98.3% at 12th h whereas in the remaining formulations there is no initial burst release, but further retardation of drug release was observed. ZT2 showed 29.3% drug release in 2th h which is within the limits but could release only 56.1% at 12th h. Hence, there is a chance for optimizing ZT1 for further study as shown in (Fig. 3). As ZT1 exhibited initial burst release, it was layered with different concentrations of HPMC K4M to control the initial release. However, further retardation of drug release was observed so to enhance the drug release channeling agents can be included in it, but the problem with this is the initial drug release also increases. As the capacity of 6mm punch is up to 100 mg which is not suitable if the concentration of HPMC K4M is increased in formulations ZT9 and ZT9 to reduce the initial drug release. Hence, the formulation ZT1 was not optimized, and the further study was continued with ZT2 (Fig. 4).

The optimized formula contained the polymer (Lubritab) of 25%, diluent (AVICEL PH 102) of 50%, and glidant of 0.3%. The drug release was slow and extended over time depending on the concentration of polymer. Hence, along with polymer, different concentrations of HPMC K100 and lactose monohydrate as channeling agents were added for complete release of drug within 12 h. These formulations failed to produce the required initial release of 20% (Fig. 5).

Then three-layered tablets as shown in Plates 1 and 2 were prepared where the top and bottom layers are of highly viscous polymer HPMC 4KM at concentrations 33.3% and 50% to control the initial burst release. Moreover, the complete release of drug within 12 h was obtained by changing concentration of channeling agents (Fig. 6). Formulations ZT22 containing 22.5% of channeling agent layered with 33.3% HPMC K4M and ZT25 containing 12.5% of lactose monohydrate as channeling agent layered with 50% HPMC K4M showed effective control of initial release and attained 98% of drug release in 12 h were finally optimized (Fig. 7).

Powder XRD analysis
The powder XRD pattern of pure drug exhibited sharp, highly intense peaks indicating the crystalline nature of drug at 2θ diffraction angels of 17.2°, 19.4°, 21.3°, 23.4°, 30.6°, 44.1°, 65.3°, and 88.5° as shown in Fig. 9a. The peaks remained unaltered in the ZT22, but their relative intensity was decreased due to change in resolution of Y-axis as...
Differential scanning calorimetry

The principal peaks of zolpidem tartrate were observed at 1635.52, 1508.23, 1404.08, and 1342.36/cm indicating the presence of C=O, N-H, and C-N groups as shown in Fig. 8a. It was observed that there was no change in the characteristic peaks of the drug in the FTIR spectra of ZT22 as shown in Fig. 8c suggesting that there were no physical or chemical interactions and there is no functional alteration of the drug as reported in previous literature [6].

Drug-excipients compatibility studies

FTIR spectroscopy analysis

DSC of the drug showed a sharp characteristic endothermic peak at 193.48°C corresponding to the melting point of zolpidem tartrate; thus, it signifies the presence of a pure form of zolpidem tartrate as shown in Fig. 10a. The thermogram of Lubritab showed a sharp endothermic peak at 63.39°C corresponding to the melting point of Lubritab as shown in Fig. 10b. The thermogram of the drug in ZT22 does not show a profound shift in peaks as shown in Fig. 10c indicating compatibility which is similar to previous literature report.

The drug excipient compatibility studies revealed from FTIR, PXRD, and DSC infers that there is no change in the characteristics of the drug during the formulation development and compression.
Model dependent methods

Release kinetics for all the formulations were calculated using Microsoft Office Excel 2007 version. The release data were analyzed by fitting the drug release profiles of all the formulations into zero-order release model, first-order release model, Higuchi model, and Korsmeyer-Peppas model. Regression coefficients \( r^2 \) were calculated for all the formulations. The apparent dissolution rate constant or zero-order release constant \( K_0 \) was calculated for zero-order release model, first-order release constant \( K_1 \) was calculated for first-order release model, Higuchi dissolution constant \( K_H \) was calculated for Higuchi model, and release exponent \( n \) was calculated for Korsmeyer-Peppas model.

Regression coefficients were reported for all the formulations. ZT22 and ZT25 were considered as optimized formulations on account of their reproducible and promising drug release modulation. The optimized formulations by kinetics (based on the highest \( r^2 \) values) followed zero order. The release component "n" was calculated from the Korsmeyer–Peppas model.
Fig. 9: P-XRD spectra of (a) zolpidem tartrate (b) Lubritab (c) ZT22

Fig. 10: DSC thermograms of (a) zolpidem tartrate (b) Lubritab (c) ZT22
Performing accelerated stability studies for the optimized formulations
The stability of promising zolpidem tartrate matrix tablets ZT22 and ZT25 were determined by performing stability studies for 3 months at accelerated conditions of 40±2°C/75±2%RH. The optimized formulations were found to be stable, with insignificant change in the appearance, hardness, drug content, and in vitro drug release as given in Tables 9 and 10 as well as shown in Figs. 12 and 13.

CONCLUSIONS
Insomnia is characterized by difficulties with sleep onset and or sleep maintenance can be treated successfully using the optimized formulations ZT22 and ZT25 for prompt onset of action of drug over a prolonged period of time which may lead to improved efficacy, better patient compliance, reduction of frequency of administration, and avoidance of fluctuations associated with the conventional immediate release formulations.

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