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Research Article

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

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ABSTRACT

Objective: The main objective of this study was to formulate and evaluate the sustained release matrix tablets of zolpidem tartrate, using hydrogenated vegetable oil as a polymer.

Methods: Various formulations were prepared by melt granulation method using concentrations Lubritab, HPMC K100, and lactose monohydrate. The optimized formulations were prepared as three-layered tablets using HPMC K4M.

Results: All formulations blend were evaluated for various precompression parameters were found to be good. The drug and excipients compatibility study was performed, and the study revealed that there was no interaction between drug and excipients. The compressed tablets were evaluated for various physicochemical parameters. The initial release from the matrix tablet was higher which was reduced by the preparation of three-layered tablet using HPMC K4M. The initial release was controlled to 10–12%, but the complete release was not there in 12 h. To get the complete release of the drug pore forming agent such as lactose and HPMC K100 was included in the matrix. ZT22 and ZT25 were considered as optimized formulations, and the drug release at 12th h is 98.85% and 98.3% respectively. The optimized formulation was subjected to stability studies for 3 months as per ICH guidelines for climate zone III and was found to be stable.

Conclusion: Difficulties with sleep onset and or sleep maintenance can be treated successfully using the optimized formulations ZT22 and ZT25 for the prompt onset of action of the drug over a prolonged period of time which may lead to improved efficacy, better patient compliance.

Keywords: Matrix tablets, Sustained release formulations, Layered tablets, Melt granulation technique.

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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 (μ) 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.

$$\theta = Tan^{-1}(h/r) \quad (1)$$

Where, θ=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.

$$*b = M/V* \quad (2)$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula.

$$*t = M/V_t \quad (3)$$

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.

$$C.I\ (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (4)$$

Hausner's ratio

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

$$\text{Hausner ratio} = *t/*d \quad (5)$$

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

Table 1: Formulations with different concentrations of polymer

Ingredients (mg)	Formulations						
	ZT1	ZT2	ZT3	ZT4	ZT5	ZT6	ZT7
Zolpidem tartrate	6.25	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	0.5
Talc	1	1	1	1	1	1	1
Total weight (mg)	50	50	50	50	50	50	50

Table 2: Formulations for optimization of polymer concentration

Ingredients (mg)	Formulations		
	ZT7	ZT8	ZT9
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					
	ZT10	ZT11	ZT12	ZT13	ZT14	ZT15
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	1.25	2.5	5	-	-	-
Lactose monohydrate	-	-	-	1.25	2.5	5
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	1
Total weight (mg)	50	50	50	50	50	50

Table 4: Formulations layered with HPMC K4M

Ingredients (mg)	Formulations			
	ZT16	ZT17	ZT18	ZT19
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

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 are 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 monohydrate	-	-	-	2.5	5	6.25
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 K4M (upper layer)	12.5	12.5	12.5	25	25	25
HPMC K4M (lower layer)	12.5	12.5	12.5	25	25	25
Total weight (mg)	75	75	75	100	100	100

Thickness

Physical dimensions of the tablets such as size and thickness are essential for acceptance and tablet-tablet uniformity. The diameter of tablets depends on the size of die and punches. The thickness of tablet-related to the hardness and is measured by screw gauge. Tablet thickness should be controlled within the range of ±5% variation of standard value. The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets using screw gauge. The average thickness and standard deviation were reported.

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load is the force required to break a tablet into pieces by compression. It is measured using a tablet hardness tester (Monsanto hardness tester). Five tablets from each formulation batch were tested randomly, and the average reading noted.

Friability

Friability of the tablets is determined using Roche Friabilator (Electrolab, India). It consists of a plastic chamber which revolves at a speed of 25 rpm for 4 min and dropping the tablets at a distance of 6 inches for each revolution. A preweighed sample of tablets were placed in the friabilator and subjected for 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F%) is given by the formula

$$F\% = (1 - W_0/W) \times 100 \quad (6)$$

Where, W_0 is weight of the tablets before the test and W is the wt of the tablets after test.

Drug content

Twenty tablets were randomly selected and were powdered in a glass mortar. Powder equivalent to 12.5 mg was weighed and dissolved in 100 ml of 0.01 N HCl, filtered and analyzed by UV spectrophotometer at 294.4 nm.

Content uniformity

The content uniformity test is used to ensure that each tablet contains the amount of drug substance intended with little variation among

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

Formula tion	Angle of repose (θ)*	Bulk density (g/cm^3)*	Tapped density (g/cm^3)*	Hausner's ratio*	C.I (%)*
ZT1	25.26±1.03	0.642±0.014	0.735±0.004	1.144±0.019	12.58±1.520
ZT2	25.12±0.98	0.646±0.006	0.735±0.009	1.137±0.003	12.09±0.233
ZT3	25.78±0.82	0.617±0.004	0.722±0.003	1.170±0.013	14.53±0.926
ZT4	26.89±0.80	0.634±0.005	0.720±0.008	1.136±0.022	11.99±1.739
ZT5	27.21±0.72	0.645±0.005	0.742±0.005	1.150±0.001	13.24±0.169
ZT6	25.62±0.53	0.652±0.012	0.740±0.003	1.134±0.021	11.89±0.562
ZT7	27.89±0.92	0.669±0.024	0.757±0.002	1.131±0.019	11.62±0.327
ZT8	26.47±0.92	0.641±0.004	0.727±0.002	1.134±0.004	11.88±0.332
ZT9	26.97±0.86	0.630±0.005	0.710±0.006	1.126±0.019	11.24±1.491
ZT10	27.78±0.78	0.642±0.007	0.712±0.009	1.128±0.007	11.82±0.070
ZT11	26.58±0.94	0.654±0.011	0.728±0.003	1.130±0.009	12.16±1.202
ZT12	26.62±0.90	0.658±0.003	0.749±0.002	1.138±0.002	12.20±0.127
ZT13	27.26±0.69	0.669±0.002	0.788±0.006	1.127±0.002	11.29±0.324
ZT13	27.26±0.69	0.669±0.002	0.788±0.006	1.127±0.002	11.29±0.324
ZT14	27.76±0.76	0.610±0.013	0.692±0.005	1.134±0.009	11.84±0.141
ZT15	26.32±0.69	0.660±0.010	0.750±0.011	1.135±0.001	11.93±0.084
ZT16	27.79±0.72	0.650±0.002	0.738±0.009	1.135±0.010	11.90±0.813
ZT17	26.26±1.01	0.644±0.006	0.732±0.013	1.137±0.011	12.06±0.841
ZT18	26.34±0.82	0.661±0.008	0.746±0.012	1.128±0.010	11.39±0.782
ZT19	26.26±0.69	0.668±0.010	0.758±0.016	1.134±0.006	11.87±0.816
ZT20	27.54±0.81	0.646±0.005	0.728±0.003	1.126±0.004	11.19±0.339
ZT21	25.21±0.68	0.615±0.005	0.694±0.006	1.129±0.018	11.44±1.435
ZT22	26.78±1.03	0.670±0.002	0.755±0.003	1.126±0.011	11.25±1.332
ZT23	27.78±0.78	0.642±0.012	0.740±0.003	1.130±0.009	11.19±0.562
ZT24	27.65±0.53	0.659±0.024	0.727±0.002	1.138±0.002	11.32±0.327
ZT25	26.12±1.03	0.641±0.004	0.752±0.002	1.127±0.002	11.58±0.332

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

Table 7: Evaluation of the prepared zolpidem tartrate layered tablets

Formulation	Weight variation[a] (mg)	Hardness[b] (Kg/cm²)	Friability[c] (%)	Thickness[d] (mm)	Drug content[e]	Content uniformity[f]
ZT1	51±0.82	7–8	0.1±0.15	2.63±0.12	98.07±0.02	98.43±0.12
ZT2	51±0.78	7–8	0.105±0.34	2.61±0.54	98.43±0.007	97.36±0.57
ZT3	49±0.12	7–8	0.12±0.15	2.61±0.31	97.71±0.008	98.17±0.84
ZT4	50±0.53	7–8	0.109±0.34	2.62±0.31	99.08±0.28	97.84±0.16
ZT5	51±0.26	7–8	0.107±0.24	2.61±0.84	98.15±0.31	96.75±0.13
ZT6	52±0.45	7–8	0.152±0.35	2.63±0.16	98.54±0.15	98.39±0.73
ZT7	48±0.26	7–8	0.105±0.12	2.60±0.24	98.53±0.001	98.36±0.01
ZT8	50±0.92	7–8	0.114±0.13	2.61±0.35	98.75±0.91	98.97±0.79
ZT9	51±0.76	7–8	0.1±0.24	2.63±0.24	98.67±0.32	98.79±0.12
ZT10	51±0.42	7–8	0.15±0.16	2.62±0.36	98.43±0.07	97.19±0.97
ZT11	52±0.19	7–8	0.102±0.26	2.65±0.52	97.56±0.008	98.64±0.04
ZT12	51±0.35	7–8	0.101±0.12	2.61±0.11	99.18±0.28	97.94±0.76
ZT13	75±0.64	7–8	0.17±0.45	2.78±0.3	98.16±0.86	97.94±0.37
ZT14	76±0.53	7–8	0.125±0.21	2.79±0.52	98.54±0.65	97.37±0.46
ZT15	75±0.72	7–8	0.13±0.14	2.77±0.42	99.63±0.001	97.64±0.43
ZT16	74±0.45	7–8	0.105±0.21	2.74±0.21	98.75±0.21	98.34±0.76
ZT17	75±0.92	7–8	0.1±0.12	2.78±0.12	98.07±0.02	97.78±0.76
ZT18	76±0.68	7–8	0.105±0.13	2.76±0.32	98.43±0.007	98.49±0.07
ZT19	75±0.37	7–8	0.1±0.24	2.79±0.11	97.71±0.008	97.34±0.43
ZT20	100±0.52	7–8	0.101±0.15	2.88±0.23	99.08±0.58	98.49±0.48
ZT21	101±0.82	7–8	0.127±0.24	2.89±0.21	98.1±0.41	97.61±0.61
ZT22	102±0.46	7–8	0.152±0.81	2.89±0.24	97.54±0.15	98.64±0.51
ZT23	51±0.53	7–8	0.105±0.64	2.61±0.35	98.13±0.001	98.73±0.11
ZT24	75±0.46	7–8	0.11±0.24	2.76±0.11	98.65±0.56	98.84±0.26
ZT25	101±0.56	7–8	0.121±0.35	2.89±0.21	99.75±0.12	97.35±0.34
STILNOCT	101±0.18	7–8	0.101±0.26	2.13±0.23	99.43±0.68	98.56±0.81
ZT25	101±0.56	7-8	0.121±0.35	2.89±0.21	99.75±0.12	97.35±0.34
STILNOCT	101±0.18	7-8	0.101±0.26	2.13±0.23	99.43±0.68	98.56±0.81

Values are expressed as mean±SD for a: n=20, b and d: n=5, c, e and f: n=10. SD: standard deviation

Table 8: Model dependent kinetic study for all formulation

Formulations	Zero-order	First-order	Higuchi	Peppas	
	R2	R2	R2	R2	n
ZT1	0.773	0.908	0.948	0.976	0.315
ZT2	0.791	0.881	0.959	0.967	0.369
ZT3	0.752	0.829	0.939	0.951	0.349
ZT4	0.772	0.837	0.947	0.945	0.379
ZT5	0.787	0.841	0.951	0.934	0.409
ZT6	0.745	0.787	0.931	0.925	0.373
ZT7	0.737	0.968	0.939	0.904	0.342
ZT8	0.793	0.952	0.956	0.974	0.329
ZT9	0.893	0.967	0.991	0.992	0.418
ZT10	0.843	0.968	0.979	0.989	0.801
ZT11	0.808	0.965	0.964	0.992	0.807
ZT12	0.766	0.933	0.94	0.988	0.819
ZT13	0.829	0.824	0.973	0.981	0.764
ZT14	0.815	0.908	0.972	0.994	0.919
ZT15	0.799	0.904	0.97	0.996	0.889
ZT16	0.973	0.99	0.974	0.986	0.767
ZT17	0.915	0.979	0.996	0.993	0.456
ZT18	0.941	0.919	0.993	0.988	0.494
ZT19	0.905	0.85	0.99	0.976	0.418
ZT20	0.982	0.981	0.968	0.989	0.801
ZT21	0.982	0.945	0.968	0.992	0.807
ZT22	0.981	0.8	0.967	0.988	0.819
ZT23	0.976	0.972	0.968	0.981	0.764
ZT24	0.994	0.932	0.943	0.994	0.919
ZT25	0.994	0.825	0.946	0.996	0.889

tablets within a batch. Determine the amount of drug in each of 10 tablets using the analytical method as mentioned above.

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 12 min. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

Powder X-Ray diffraction (XRD) analysis

The crystallinity of the drug, polymer and optimized mixtures were studied by powder XRD. The powder XRD analysis was performed using Shimadzu XRD-7000, XRD using Copper K α (λ=1.5406 A°) radiation. The data were recorded over a scanning 2θ range of 5°–50°at a step 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 (r^2) 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 (I.P limits 25–30) showing that the blend of powder was free-flowing. The value for Carr's index was in between 11.19±0.339 and 14.53±0.926 (I.P 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 (I.P 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 (I.P limits 4–8), 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 97.34±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).

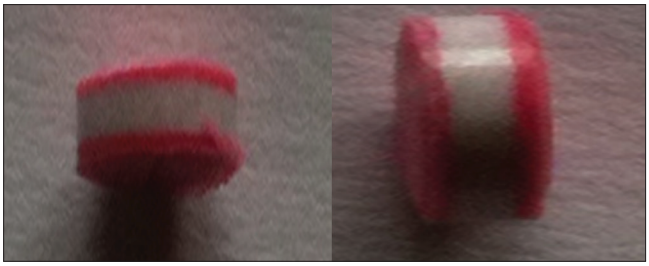

Plate 1: Vertical view of tri-layered tablets containing hydrophobic matrix core layered with hydrophilic polymer

Plate 2: Swelling of top and bottom HPMC K4M layers

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 2nd 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 ZT8 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

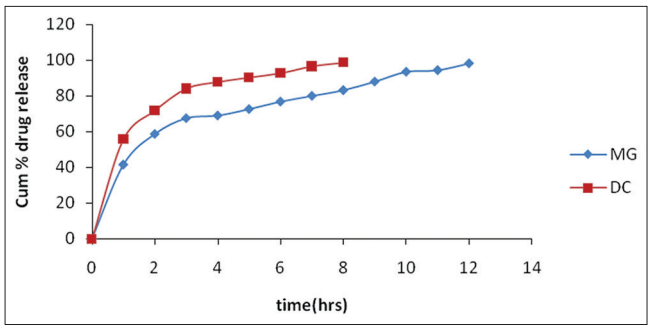

Fig. 1: Dissolution profile of formulation for optimization of tableting method

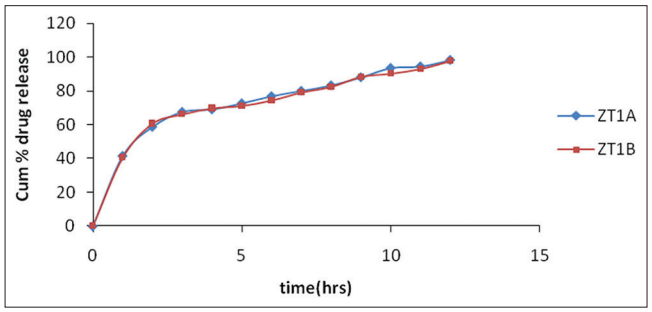

Fig. 2: Dissolution profile of ZT1A and ZT1B for media optimization

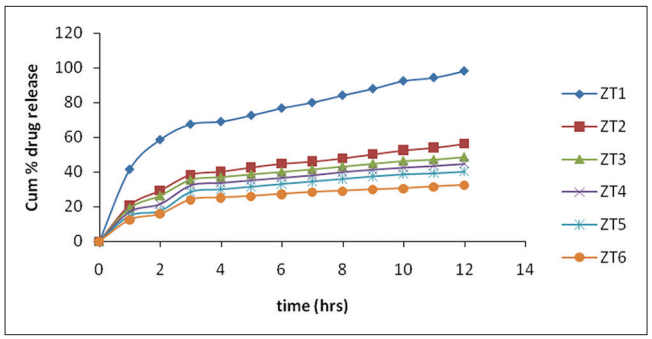

Fig. 3: Dissolution profiles of formulations with different concentrations of polymer

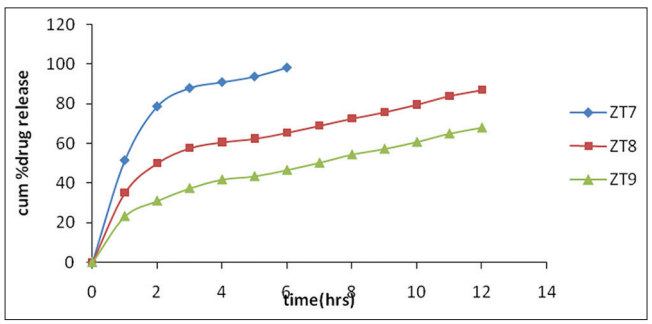

Fig. 4: Dissolution profiles of formulations for optimization of polymer concentration

shown in Fig. 9c and the results are found to be similar to the previous literature report.

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,

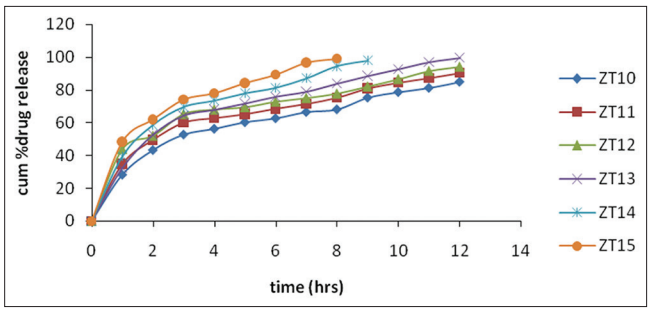

Fig. 5: Dissolution profiles of formulations with channeling agents

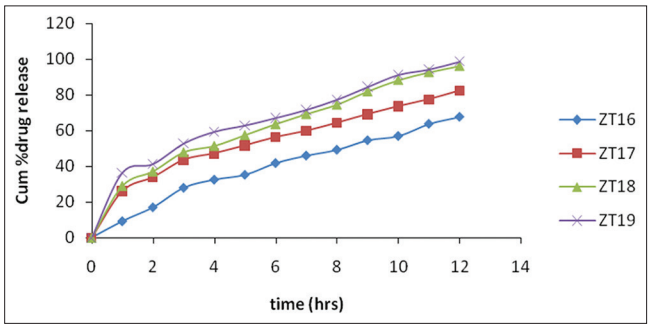

Fig. 6: Dissolution profiles of formulations layered with HPMC K4M

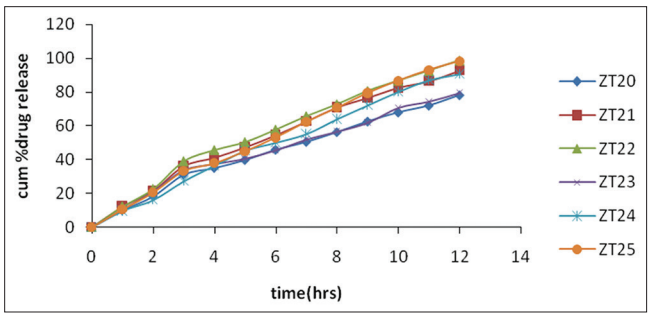

Fig. 7: Dissolution profiles of formulations for optimization of channeling agents in layered tablets

CH_3, 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°Ccorresponding 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.

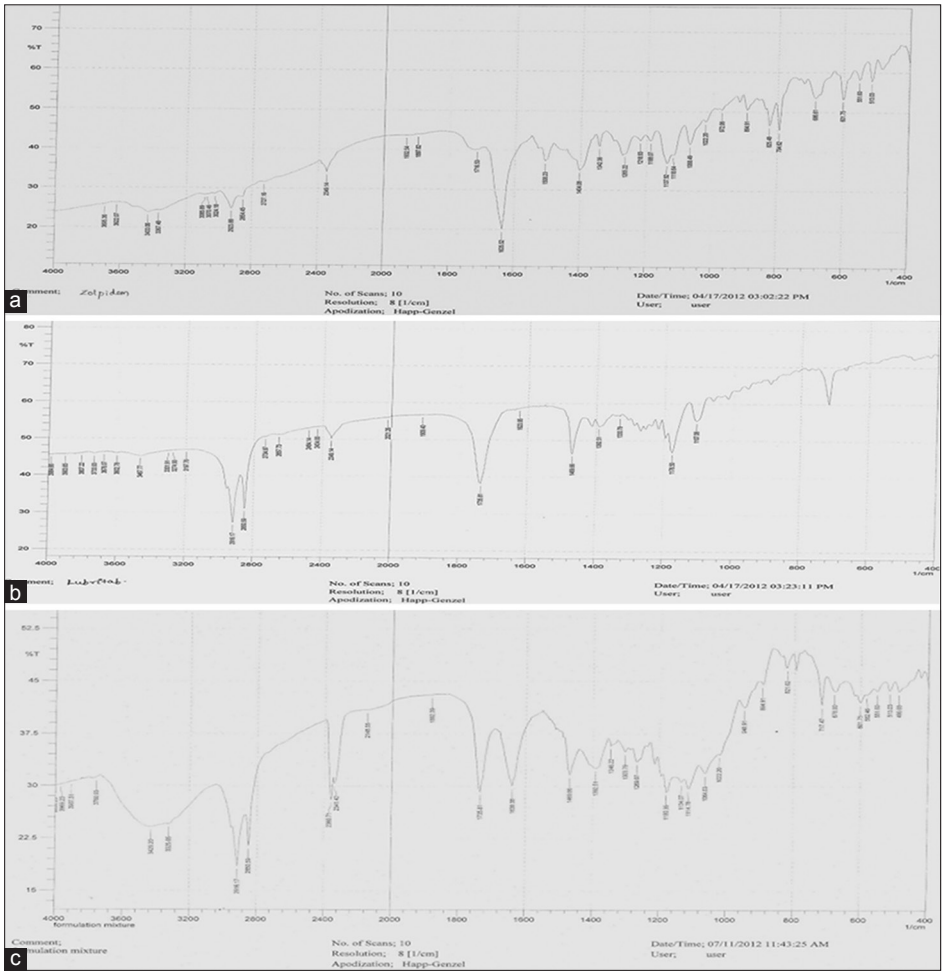

Fig. 8: Fourier transformer infrared spectra of (a) zolpidem tartrate (b) Lubritab (c) ZT22

Table 9: Physicochemical properties of ZT22 during accelerated stability studies

Parameters	Time in months			
	0 (initial)	1st month	2nd month	3rd month
Appearance	White to off-white	White to off-white	White to off-white	White to off-white
Hardness (kg/cm^2)	7.6±0.32	7.4±0.13	7.2±0.51	7.1±0.65
Drug content (%)	97.71±0.008	97.11±0.001	96.24±0.068	96.10±0.001

Values are expressed as mean±SD, n=3. SD: Standard deviation

Table 10: Physicochemical properties ofZT25 during accelerated stability studies

Parameters	Time in months			
	0 (Initial)	1st month	2nd month	3rd month
Appearance	White to off-white	White to off-white	White to off-white	White to off-white
Hardness (kg/cm^2)	7.6±0.22	7.54±0.52	7.42±0.43	7.3±0.12
Drug content (%)	97.54±15	96.12±0.55	95.91±0.26	95.82±0.53

Values are expressed as mean±SD, n=3. SD: Standard deviation

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–

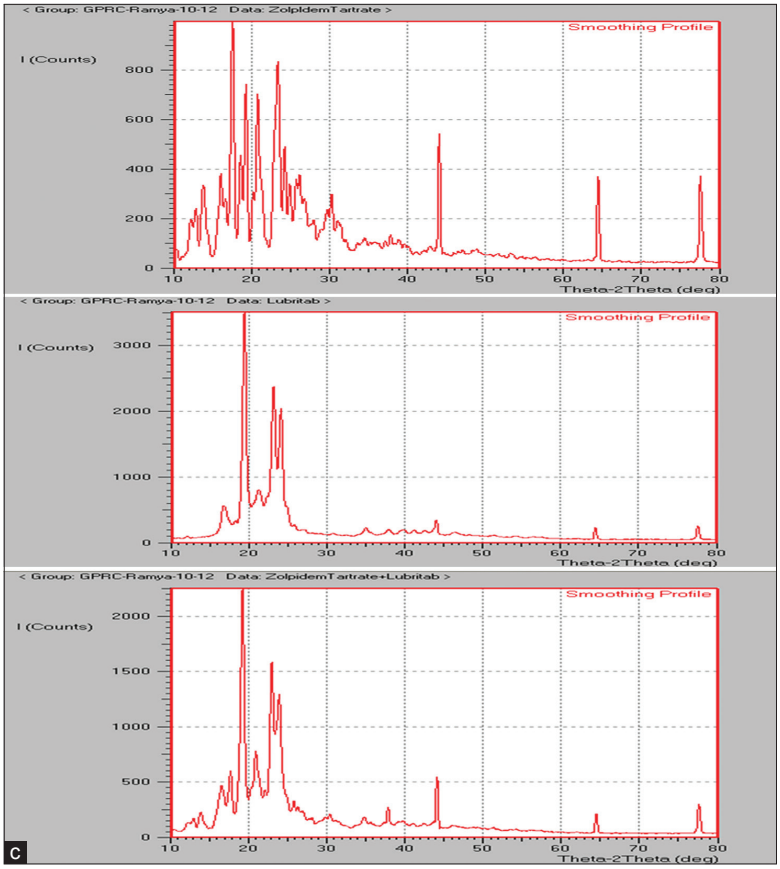

Fig. 9: P-XRD spectra of (a) zolpidem tartrate (b) Lubritab (c) ZT22

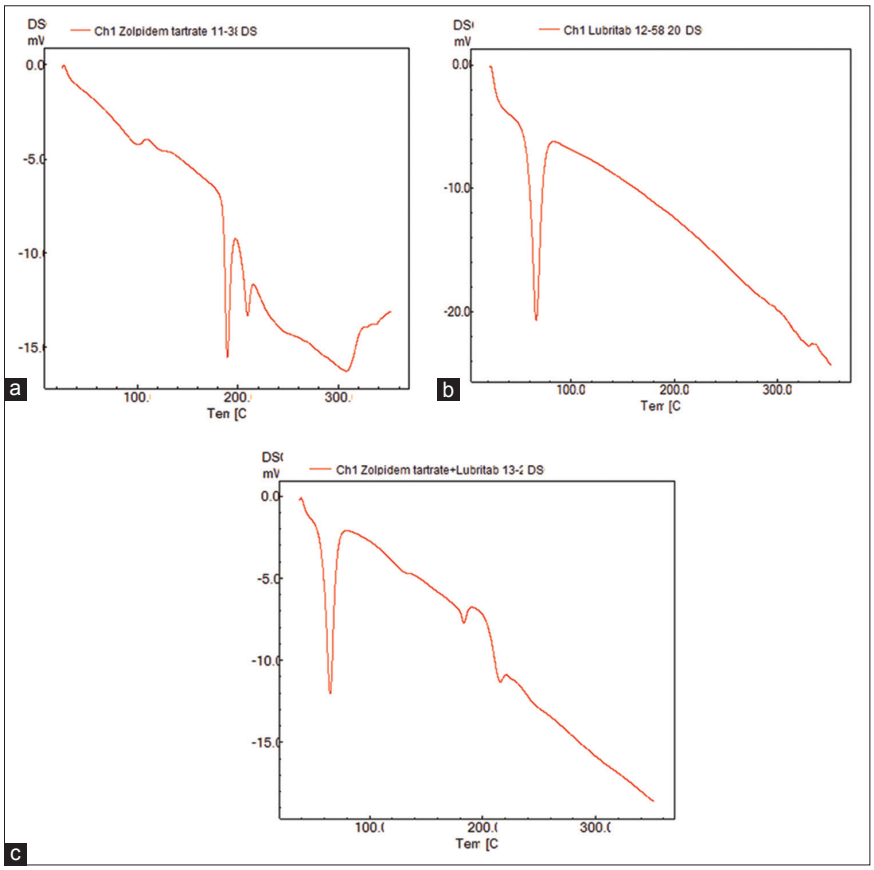

Fig. 10: DSC thermograms of (a) zolpidem tartrate (b) Lubritab (c) ZT22

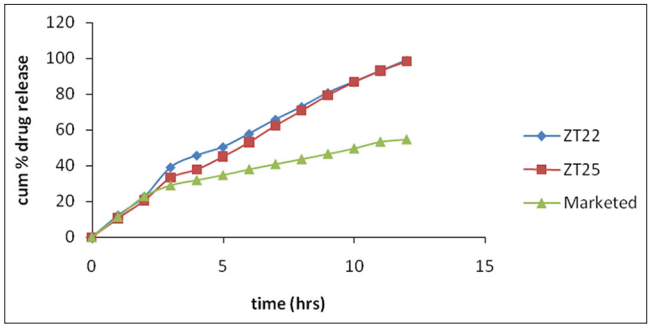

Fig. 11: Comparison of *in vitro* drug release of optimized formulations with marketed formulation

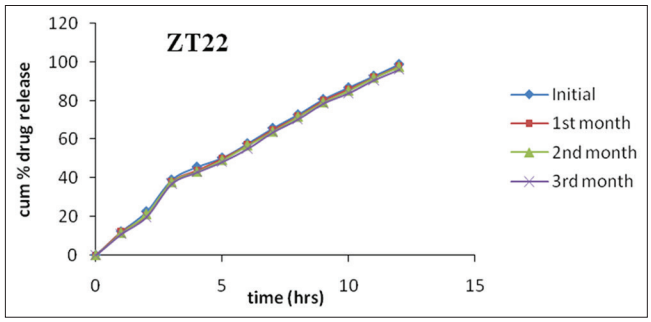

Fig. 12: Dissolution profile of optimized formulation ZT22

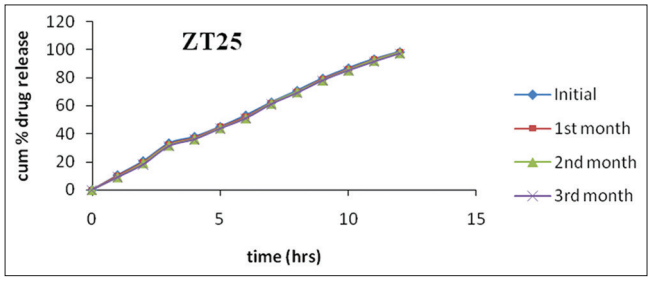

Fig. 13: Dissolution profile of optimized formulation ZT25

Peppas kinetics equation which revealed that the formulations followed anomalous transport mechanism in drug release Table 8.

Comparison of *in vitro* drug release of optimized formulations with marketed formulation

The *in vitro* drug release of the marketed formulation at 12th h was found to be 6.25 mg which is similar to the optimized formulations at the same time point (Fig. 11).

The optimized formulations were compared with the marketed formulation (STILNOCT 12.5 mg). As the 6.25 mg twice a day tablets are not available the comparison is done using 12.5 mg per day tablet. The *in vitro* drug release of the marketed formulation at 12th h was found to be 6.25 mg which is similar to the optimized formulations at the same time point.

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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