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Research Article

FORMULATION AND EVALUATION OF BILAYER SUSTAINED RELEASE TABLET OF ZOLPIDEM TARTRATE

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ABSTRACT

The purpose of the present study was to develop a bilayer tablet of zolpidem tartrate (ZT) using sodium starch glycolate (SSG) as superdisintegrant in the immediate release (IR) layer and hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC K4M), metalose 90 SH 4000, carbapol 974 PNF in sustained release (SR) layer. Both the IR and SR granules of ZT were evaluated for bulk density, tapped density, angle of repose, Carr's index, Hausner ratio and loss on drying. All the values were found to be satisfactoy. The prepared bilayer tablets were evaluated for weight variation, hardness, friability, drug content, *in vitro* drug release, FT-IR studies, similarity factor and stability studies. *In vitro* dissolution studies were carried out in a USP dissolution apparatus I using 500mL of 0.01N HCl as dissolution medium. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 4 h. The data obtained were fitted to Zero order, First order, Higuchi's model and Korsmeyer-Peppas equations. The release exponent (n) values for all the formulations were less than 0.45 indicating Fickian diffusion was the drug release mechanism. FT-IR studies indicated that there are no drug-excipient interactions. The similarity factor (f2) was calculated by comparing dissolution data of all the formulations with that of marketed bilayer tablet of ZT (Ambien CR). The f2 value was highest (70) for the formulation SF8 and was selected as promising formulation among all the developed formulations. The stability study was performed on the formulation SF8 at 25°C/60% RH, 30°C/75% RH and 40°C/75% RH (accelerated condition) for 3 months. The results indicated that there were no significant changes in aforesaid tablet properties.

Key words: bilayer tablets, zolpidem tartrate, sustained release, higuchi's equation, similarity factor

INTRODUCTION

About 25% of the adults experience insomnia at some time of their life and at least 1 in 10 of the general population have its chronic form (Mendelson *et al*., 2004, Sateia *et al*., 2004). It is associated with impaired concentration and daytime functioning, reduced health-related quality of life and an increased risk of depression (Walsh *et al*., 2004). The treatment options currently available for insomnia are benzodiazepines receptor agonists, nonbenzodiazepine hypnotics and off-label use of sedating antidepressants (National Institutes of Health, 2005). The problem associated with benzodiazepines receptor agonists are residual daytime sleepiness, anterograde amnesia and, importantly, withdrawal symptoms on discontinuation of therapy (Zhdanova *et al*., 2004). Off-label antidepressants such as trazodone or the tricyclic doxepin are also commonly used in insomnia treatment. However, this agent carries a risk of hypotension, dizziness, and daytime sedation, and doxepin in particular is associated with cardiotoxic effects (Ebert *et al*., 2006). The non-benzodiazepine hypnotics generally represent an improvement over benzodiazepines as a result of improved binding selectivity towards α1-containing receptors and enhanced pharmacokinetic properties such as bioavailability, plasma half-life, elimination rate, and blood-brain barrier penetration influence the onset and duration of hypnotic effects.

Zolpidem tartrate belongs to the α-1 $GABA_A$ receptors selective imidazopyradine group of compounds with intermediate potency

at α2 and α3 receptors and negligible activity at α5 receptors (Puia, 2001, Sanna *et al*., 2002). The oral bioavailability of ZT is 70% due to its first pass metabolism in liver. In addition, it has short biological half-life of 2.5 hr (Drover, 2004, Krystal, 2009). Above properties make ZT a suitable candidate for the development into a SR formulation.

The main objective in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action and to reduce the dose required or providing uniform drug concentration in systemic circulation for prolonged period of time (Rahman *et al*., 2006).

The multilayered tablet concept has been long utilized to develop SR formulation. Such a tablet is generally having a fast releasing layer and may contain bi- or triple layer to sustain the drug release (Abraham *et al*., 1997). Bilayer tablet is suitable for sequential release of two drugs in combination (Ramesh *et al*., 2010, Reddy *et al*., 2010), separate two incompatible substances and also for SR tablet in which one layer is IR as initial dose and second layer is maintenance dose (Swamy *et al*., 2011, Kumar *et al*., 2010). In the latter case the bilayer tablet allows a portion of the drug to be released immediately, with a slower release of the remaining content for steady plasma concentrations.

The purpose of the present study was to develop bilayer tablet of ZT with the goal to provide greater flexibility in treating both sleep onset and sleep maintenance difficulties in patients and letting individuals to awaken in the morning without feeling residual side effects whch is common with original zolpidem by maintaining constant plasma concentrations of ZT during the middle portion of the night (3-6h after dosing) (Moen *et al*., 2006). The polymer such as HPMC K5M, carbopol 974P and Metalose 90 SH 4000 were used in SR layer as release retardant. Superdisintegrant used was SSG in IR layer.

MATERIAL AND METHODS

Zolpidem tartrate, gifted by Aurobindu Pharma Ltd, Hyderabad, India, was used as active pharmaceutical ingredient. Lactose monohydrate (Pharmatose 200M) and sodium starch glycolate (SSG, Primojel) were obtained from DMV-Fonterra exipients GmbH & Co. KG, Klever Strasse Goch, Germany. Microcrystalline cellulose (MCC, Avicel PH101) was supplied by FMC BioPolymer, Bangalore, India. Hydroxypropyl methylcellulose (HPMC K4M, HPMC E5 LV premium), Carbapol 974P NF, opadry pink and opadry blue were purchased from Colorcon Asia Pvt Ltd, Goa, India. Metalose 90 SH 4000 was obtained from Shin Etsu Chemical Co., Ltd, Chiyoda-ku, Tokyo, Japan. Other chemicals are off analytical grade.

Drug-excipient interaction study

Drug-excipient interaction study was carried out by FT-IR technique (FTIR-1700, Shimadzu, Kyoto, Japan) in order to determine the interaction of ZT with the excipients used in the formulation. The pure drug, IR layer, and SR layer were scanned in KBr discs in the range of 4000–500cm^{-1}.

Solubility study of the drug in different media

Solubility study was carried out in different medium over the pH range 1- 8.0 in order to acertain variable solubility of ZT. An excess quantity of ZT was taken in each of the medium (10mL) and was shaken in water bath shaker for 24h at 37°C (Mutalik *et al*., 2007). The solution was then passed through a Whatmann (No-1) filter paper. The filtrate was suitably diluted and the amount of drug dissolved was determined spectrophotometrically at 294nm.

Preparation of bilayer tablet

The SR bilayer tablets of ZT were prepared by wet granulation technique and the IR dose and maintenance dose or sustained dose was maintained at 6.436mg. The composition for IR and SR layer is shown in table I.

Formulation of the immediate release layer

The IR granules of ZT were prepared as follows. At first, the drug with lactose monohydrate, MCC, and SSG were passed through # 40 and mixed well in a double cone blender (Rinek, KALWEKA, HD-410AC) for 10min at 25rpm. Binder solution was prepared

Table I. Other processing steps were similar to that of IR granules. Composition of immediate release and extended release layer of tablet of zolpidem tartarate

Ingredients	F-IR1 (mg)	F-IR2 (mg)	F-IR3 (mg)	ER1 (mg)	ER2 (mg)	ER3 (mg)	ER4 (mg)	ER5 (mg)	ER6 (mg)	ER7 (mg)	ER8 (mg)	ER9 (mg)
Zolpidem tartarate	6.436	6.436	6.436	6.43	6.43	6.43	6.43	6.43	6.43	6.43	6.43	6.43
Lactose monohydrate	22.00	22.00	22.00	90.86	85.86	90.86	85.86	80.86	90.86	85.86	80.86	75.86
Microcrystalline cellulose	99.01	98.36	96.41	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Sodium starch glycolate	2.60	2.60	5.20	-	-	-	-	-	-	-	-	-
HPMC E5 LV	0.65	1.30	0.65	-	-	-	-	-	-	-	-	-
Hydroxy propyle methyl cellulose (HPMC) K4 M	-	-	-	10.00	15.00	-	-	-	-	-	-	-
Metalose 90 SH -4000	-	-	-	-	-	-	-	-	10.00	15.00	20.00	25.00
Carbapol 974 p NF	-	-	-	-	-	10.00	15.00	20.00	-	-	-	-
Orthophosphoric acid 85%	-	-	-	1.40	1.40	1.40	1.40	1.40	1.40	1.40	1.40	1.40
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Opadry blue	0.2	0.2	0.2	-	-	-	-	-	-	-	-	-
Opadry pink	-	-	-	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

The weight of immediate release layer (F-IR class) was 130 mg and the total weight of bilayer tablet was 260mg.

by dissolving HPMC E5 LV in water. The binder solution was then added to drug-diluents mixture and granulated in rapid mixer granulator (HSMG 1, Gansons Ltd., Thane, India). The granules were kept for drying in rapid dryer (TG 200, Retsch, UK) for 10min. After drying, the dried granules were passed through # 40 and loss on drying was checked. For lubrication, magnesium stearate was passed through # 60 and mixed with dried granules for 5min.

Formulation of sustained release layer

Zolpidem tartrate along with other ingredients such as lactose monohydrate, MCC and HPMC K4M or Metalose 90 SH 4000 or Carbapol 974P were passed through # 40 and mixed well in double cone blender. The formulae for SR layer were given in table I. Other processing steps were similar to that of IR granules.

Compression of bilayer tablet

The accurate quantity of granules for IR were subjected to compression by using 16-station single rotary machine (Cadmach-CMD4) with B tooling having standard concave punch of 8.0mm diameter. These IR tablets were evaluated for various parameters such as hardness, friability, weight variation, content uniformity and *in-vitro* dissolution.

The bilayer tablet of ZT was prepared by directly compressing the IR layer on to the SR granules. Then, it was compressed by using 8mm flat face beveled edge punch with embosing y-on one side and 49 on other side. The prepared tablets were subjected to various evaluation tests.

Characterization of pure drug, immediate and extended release granules

Pure drug and granules, prior to compression, were evaluated for bulk density, tapped density, angle of repose, Carr's index, Hausner ratio, loss on drying and particle size distribution. Tapped density was carried out by using a digital tapped density apparatus (Electrolab-ETP-1020). Tapping was continued until the difference between successive volumes is less than 2%. Loss on drying was calculated by putting 1gm of granules on the pan of drying apparatus (Sartorius-MA 100, Germany) and the temperature was increased to 105^{o}C (Martin *et al.*, 2002).

Physical tests for the immediate release and bilayer tablets

Immediate release and bilayer tablets were subjected to standard physical tests (Goto *et al.,* 2004, Wu *et al.,* 2009). Thickness was measured for five tablets by using Vernier calipers and the average was expressed in mm. Mass variation was determined by weighing 20 tablets individually, the average mass was calculated and the percent variation of each tablet from the average value was determined. Hardness was determined by, randomly taking 10 tablets from each batch, using Monsanto hardness tester (Electrolab Pvt. Ltd., India) and the average diametric compression pressure (Kg/cm^2) to crush the tablets was determined. Friability was measured by weighing 20 tablets after dedusting and placing them in a Roche Friabilator (Electro lab, EF-2, mumbai, India), which was run at 25rpm for 4min. After dedusting, the tablets were weighed and the percent of friability was determined. For content uniformity, 20 tablets were randomly taken and powdered. The powder weight equivalent to 10mg of ZT was accurately weighed and transferred into a 100mL volumetric flask. Initially, 10 ml of 0.01N HCL was added and shaken for 10min. Then, the volume was made up to 100mL with same solution. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 294nm (Revision Bulletin Official, 2011).

In-vitro dissolution studies

Dissolution test for prepared and marketed bilayer tablets of ZT was performed by USP dissolution testing apparatus 1 (Electrolab TDT-08L, Mumbai), using 500mL of 0.01N HCl at 37±0.5°C as dissolution medium (Revision Bulletin Official, 2011). The rotational speed of basket was kept at 100 rpm. Ten milliliter of aliquotes were withdrawn at 5, 10, 15, 30, 90, 120 and 240min and replaced with fresh dissolution media maintained at same temperature. The samples were passed through membrane filter (pore size, 0.45µm) and assayed immediately for ZT content by UV spectrophotometer at 294nm (UV-1800, Shimadzu, Japan). Dissolution test was also conducted for IR tablets by maintaining same conditions and was carried out for 30min. This test was performed on 6 tablets and mean ± SD calculated.

Drug release kinetics

The kinetics of release of ZT from the prepared bilayer tablets were analysed by fitting *in-vitro* release data into Zero order, First order, Higuchi equation and Korsmeyer-Peppas equation (Patra *et al*., 2007)

Zero order release equation : $\mathbf{Q_t = K_0\, t}$; First order release equation: $\mathbf{Q_t = Q_0\, e^{-K_1 t}}$; Higuchi's square root of time equation**:** $\mathbf{Q_t = K_H\, t^{1/2}}$**;** Korsmeyer-Peppas equation: $\mathbf{Q_t/Q_\infty = K_m\, t^n}$;

Where, Q_t = amount of drug release at time t, Q_∞ = amount of drug release after infinite time, Q_t/Q_∞ = fraction of drug release at time t, K_0 = Zero order release rate constant, K_1 = First order release rate constant, K_H = Higuchi release rate constant, K_m = constant depend on the structure and geometry of dosage form, n=release exponent which characterizes the mechanism of drug release, i.e. for cylindrical systems: n=0.45 for purely Fickian diffusion, between 0.45 and 0.89 for anomalous (non-Fickian transport) controlled by both diffusion and swelling, n=0.89 for zero-order release (swelling controlled drug release) systems, and values > 0.89 indicate super case-II transport (Siepmann *et al*., 2008)

Statistical analysis

The similarity factor (*f2*) given by scale-up and post-approval changes (SUPAC) guidelines for modified release dosage forms was used as a basis for comparing dissolution profiles. This similarity factor is calculated by the following formula;

$$f_2 = 50 \times \log\{[1 + (1/n)\, \Sigma\, (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where *n* is the number of experimental points in the *in vitro* dissolution assay and R_t and T_t are the mean percentage of dissolved drug from the reference and test formulations. The similarity factor fits the result between 0 and 100. Two dissolution profiles are considered similar when the f_2 value is greater than or equal to 50 (Albertini *et al*., 2009).

In the view of potential utility, the dissolution profile of optimized formulation (SF8) is compared with marketed bilayer tablet of ZT (AMBIEN CR).

Table II. Physical Characteristics of pure drug, immediate and sustained release granules for all the formulation

Sl.no	Angle of repose(θ)	Loss on drying(%)	Bulk density (g/mL)	Tapped density (g/mL)	Hausner ratio	Carrs index	Flow
Pure Drug	10.34±0.02	0.41±0.05	0.31±0.06	0.43±0.03	1.5±0.02	27.16±0.56	Poor
IF1	23.12±0.02	1.86±0.98	0.58±0.01	0.64±0.02	1.11±0.04	10.00±20.7	Excellent
IF2	23.61±0.05	1.89±0.85	0.58±0.01	0.64±0.05	1.10±0.02	9.690±0.18	Excellent
IF3	22.20±0.03	1.82±0.89	0.56±0.01	0.64±0.04	1.14±0.01	12.84±0.18	Good
ER1	25.64±0.76	1.21±0.98	0.35±0.01	0.42±0.02	1.20±0.04	16.60±0.70	Fair
ER2	25.56±0.67	1.10±0.85	0.36±0.01	0.43±0.05	1.19±0.02	16.20±0.18	Fair
ER3	25.43±0.75	1.13±0.95	0.35±0.01	0.41±0.06	1.17±0.03	14.63±0.68	Good
ER4	26.42±0.39	1.10±0.95	0.38±0.01	0.45±0.04	1.20±0.02	15.50±0.71	Fair
ER5	26.03±0.59	1.11±0.85	0.35±0.01	0.42±0.05	1.18±0.02	15.43±0.65	Fair
ER6	25.98±0.42	1.21±0.98	0.35±0.01	0.41±0.03	1.17±0.04	14.80±0.52	Good
ER7	25.43±0.75	1.15±0.96	0.35±0.01	0.42±0.06	1.20±0.02	16.70±0.18	Fair
ER8	26.03±0.59	1.11±0.86	0.35±0.01	0.42±0.05	1.18±0.02	15.43±0.65	Fair
ER9	25.64±0.95	1.20±0.98	0.37±0.02	0.44±0.03	1.19±0.03	16.07±0.10	Fair

Table III. Comparison of physical parameters of all the of immediate release and bilayer tablet formulation

Formula Code	Weight (mean ± SD, mg)	Thickness (mean ± SD, mm)	Diameter (mean ± SD, mm)	Hardness (mean ± SD,kg/cm	Friability (%) (n=20)	Disintegration time (sec)	Drug Content (%) (n=10)
IF1	130±3	3.32±0.03	---	1.1±0.3	0.43±0.35	36±0.01	99.88±0.61
IF2	13±2	3.26±0.4	---	0.9±0.5	0.68±0.08	40±0.02	99.28±0.31
IF3	130±4	3.24±0.3	---	1.2±0.2	0.72±0.15	35±0.06	98.12±0.08
SF1	259±0.61	4.54±0.12	10.5±0.04	9.8±0.23	0.68±0.03	---	101.63±0.21
SF2	260±0.48	4.56±0.24	10.8±0.04	9.6±0.25	0.66±0.45	---	98.34±0.07
SF3	261±0.21	4.53±0.07	10.7±0.04	9.4±0.38	0.74±0.25	---	99.28±0.31
SF4	260±0.05	4.52±0.14	10.2±0.06	9.7±0.12	0.76±0.15	---	98.12±0.08
SF5	259±0.14	4.54±0.08	10.6±0.02	9.6±0.35	0.69±0.45	---	97.29±0.47
SF6	260±0.16	4.43±0.24	10.2±0.04	9.5±0.14	0.70±0.16	---	98.14±0.02
SF7	262±0.08	4.46±0.17	10.8±0.07	9.5±0.12	0.69±0.23	---	97.29±0.25
SF8	259±0.29	4.52±0.04	10.5±0.04	9.6±0.18	0.69±0.25	---	99.43±0.18
SF9	260±0.67	4.48±0.21	10.9±0.04	9.4±0.26	0.76±0.18	---	98.03±0.13

Stability studies

The optimized formulation (SF8) was subjected to stability study for 3 months at 25°C/60% RH, 30°C/75% RH, and at accelerated condition (40°C/75% RH) in a stability chamber (JRIC 11, Osworld, Mumbai). At the end of three months, tablets were withdrawn and evaluated for various parameters like thickness, diameter, weight variation, hardness, content uniformity and dissolution.

RESULT AND DISCUSSIONS

Drug-excipient interaction study

FT-IR spectra of pure ZT, IR layer and SR layer were presented in figure 1. The characteristic peaks of zolpidem tartrate were due to amide and alkene groups. There was no such significant change in the postion of major peaks in IR and SR layers indicating that no chemical reaction or interaction between the drug and excipients took place.

Solubility studies of zolpidem tartrate

The solubility of zolpidem tartrate in different medium such as 0.01 N HCL, 0.1 N HCL, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, water and pH 7.2 phosphate buffer were measured and found that highest (48.72 mg/ml) and lowest solubility (1.60mg/mL) of the drug was in pH 4.5 acetate and buffer pH 6.8 phosphate buffer, respectively. It was also confirmed that ZT showed pH dependent solubility. According to the biopharmaceutical classification system, a drug substance is considered as highly soluble when the highest does is soluble in 250mL or less of aqueous media over a pH range of 1-8. Highest dose of ZT is equivalent to 12.5mg and this is soluble in the entire pH range, hence it belongs to high soluble category.

Physical Characteristics of pure drug, immediate and sustained release granules for all the formulation

In the present investigation pure drug, IR and SR granules of ZT, prepared by wet granulation method, were evaluated for various physical characteristics and the values were presented in table II. The flow was poor for drug ZT, which necessitate the drug to be granulated. The bulk density for the granules of all the formulations ranged between 0.35±0.01 and 0.58±0.01, which indicate good packing. Resistance to particle movement can be judged from the angle of repose, which gives qualitative and quantitative assessment of internal cohesive and frictional force. Values for angle of repose were found in the range of 26% to 30% and Carr's index for all the formulation was found to be below 15%, indicating desirable flow properties (Staniforth, 2002). This was further supported by Hausner ratio values which were in the range of 1.04% to 1.17%. The loss on drying ranged between 1.1±0.85 to 1.89±0.85%. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture.

Physical parameters of immediate release tablet

All the IR tablets, prepared by wet granulation method, were subjected to various physical parameters and the data were shown in table III. All the formulations exhibited white colour, odourless, circular in shape with smooth surface. Weight variation of IR tablets was within 0.702%. Thickness and friability of all formulations were within acceptable limits. Hardness of all the three batches of tablets was in between 0.9±0.5 to 1.2±0.2kg/cm^2. Disintegration time is very important for IR tablets and is desired to be less than 60sec. Disintegration time of prepared IR tablets was in the range of 35 to 40sec.

Physical parameters of bilayer tablet

All the batches of bilayer tablets were prepared under similar conditions to avoid processing variability and the data were presented in table III. Weight of bilayer tablet was 260±3 mg, thickness was 4.40±0.5 mm, diameter was 10.57±0.4 mm, hardness was 9.56±0.22 kg/ cm^2 and friability was 0.7±0.23 %. Values of hardness test and percentage of friability indicate good handling properties of all the prepared bilayer tablets. The drug content uniformity in the bilayer tablets was 98.62±0.19 %.

***In vitro* dissolution studies**

In vitro dissolution studies of the prepared IR tablets was carried out in order to know better drug release profile among the IR formulations. The drug release at the end of 5 minutes were found to be 49%, 45%, 62% and at the end of 30 minutes were found to be 82%, 75% and 91% for IF1, IF2 and IF3, respectively. This result attributed to concentration level of SSG, as the concentration of SSG increased the drug release also increased. In addition, the drug release was less in case of formulation IF2 which was due to HPMC E5 LV content. More the polymer amount less was the drug release. From the above formulation IF3 was selected as optimized IR layer.

From the *in vitro* release study, it was observed that an initial burst release of approximately 60% of the active ingredient within 30 minutes in all the bilayer tablet formulation (SF1-SF9) followed by a slower rate of release of the remainining ZT as shown in figure 2. The initial high amount of ZT release can be attributed to the drug release from IR layer and also due to presence of drug on the surface of tablets.

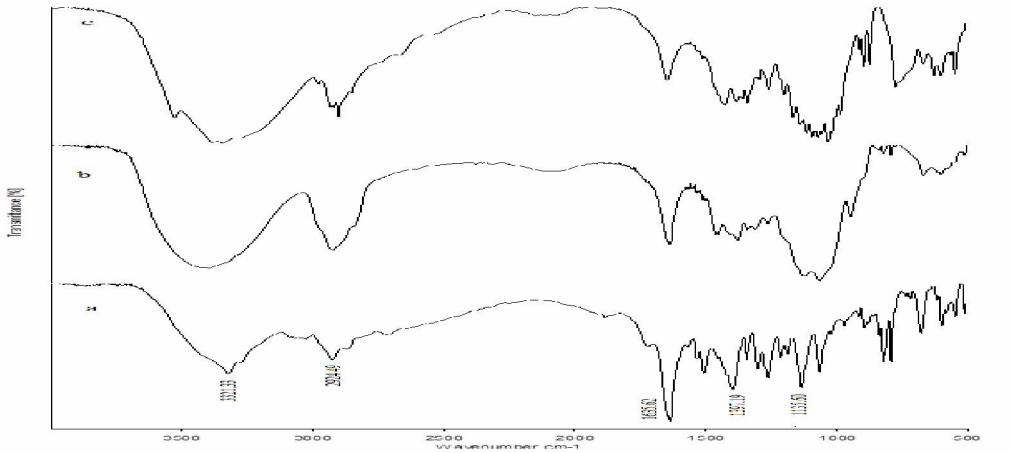

Figure 1. FT-IR spectra of (a) pure drug, (b) immediate release layer, and (c) sustained release layer.

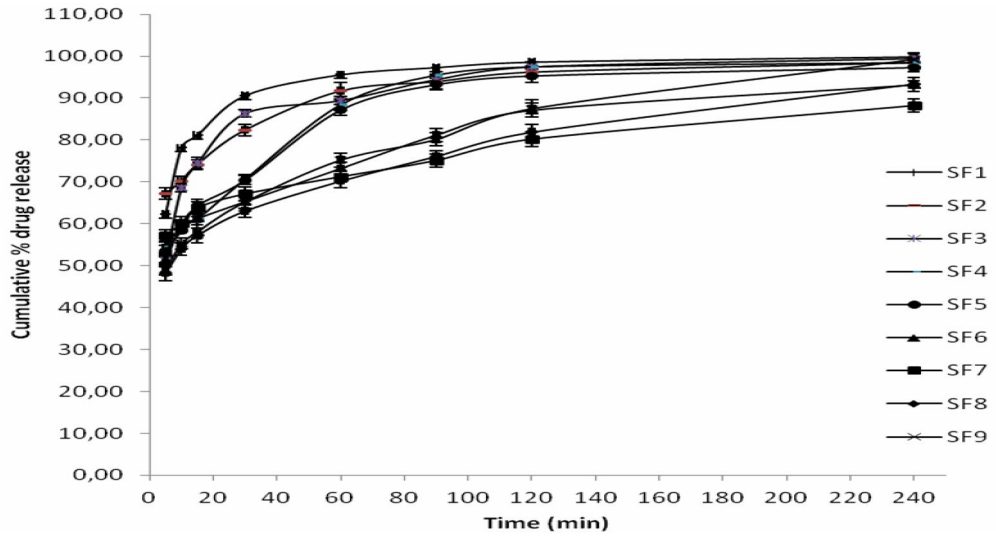

Figure 2. Dissolution profile of all formulations (mean ± SD, n = 6)

The highest and lowest amount of drug release was shown by the formulation SF1 (99.91±0.17%) and SF7 (88.17±1.58%), respectively.

Hydroxypropyl methylcellulose has been extensively used as rate controlling polymer in extended release dosage forms (Patra *et al.*, 2007, Ye *et al.*, 2007, Al-Saidan *et al.*, 2004). The rapid formation of a viscous gel layer upon hydration and the viscosity of HPMC regulate its performance in extended release matrix system (Rekhi *et al.*, 1999). In the formulation SF1 and SF2, the controlled realse polymer was HPMC K4M used at 10 and 20mg/tablet. Initially rapid *in vitro* release (burst release) of approximately 91% and 82% of the active ingredient within 30min followed by a slower rate of release of the remaining 9% and 18% of ZT in the formulation SF1 and SF2, respectively. This could be due to the increased path length for the drug to diffuse from the matrix. Same trend of decrease in initial burst effect and cumulative percentage of drug release was observed in the formulations (SF3-SF5) containing Carbopol 974P and the formulations (SF6-SF9) containing Metolose 90 SH 4000 as release retardant. In case of formulation containing carbopol,

Table IV. Drug release kinetics for different formulation of Zolpidem tartarate

Formulation Code	Drug rlease kinetics, correlation coefficient 'r²'				Release exponentional in Korsmeyer & Peppas (n)
	Zero order	First order	Higuchi	Korsmeyer and Peppas	
SF1	0.554	0.504	0.756	0.899	0.126
SF2	0.676	0.647	0.864	0.968	0.112
SF3	0.6	0.534	0.788	0.904	0.136
SF4	0.674	0.646	0.858	0.95	0.18
SF5	0.682	0.646	0.867	0.963	0.175
SF6	0.839	0.786	0.959	0.982	0.153
SF7	0.909	0.87	0.988	0.977	0.108
SF8	0.885	0.819	0.985	0.994	0.181
SF9	0.897	0.833	0.989	0.993	0.167

the result was attributed to more rapid hydration of carbopol 974 P in 0.01 N HCl at lower concentration than at higher concentration. In addition carbopol 974P which has pKa of 6.0, remains unionized in the acidic environment of dissolution medium (Seta *et al.*, 1988). It was found that bilayer tablet with controlled release polymer Metalose 90SH 4000 most effectively retarded the release of drug than that of other polymers (HPMC K4M, Carbopol 974 P NF) used.

Drug release kinetics

In vitro drug release data of all the bilayer tablet of ZT was fitted to different kinetic models like Zero order, First order, Higuchi and Korsmeyer-Peppas model to ascertain mechanism of drug release and the values obtained are presented in table IV. It was evident that the formulations SF6-SF9 adequatly fit to Higuchi model (r^2 values from 0.959 to 0.989), indicating that diffusion is the release mechanism of drug from the tablets. For further conformation, release exponent (n) were calculated from Korsmeyer-Peppas equation and the obtained 'n' values were less than 0.45 for all the formulation, which signifies Fickian type of diffusion of drug from the formulations.

Statistical analysis

Similarity factor was used for the comparison of release profile of different formulation. Here all the formulations were compared with that of marketed product (Ambien CR). The f2 value of all the formulations, from SF4 to SF9, was above 50 which indicates that those formulations are having similar dissolution profile with the marketed product and it is highest (*f*2=70) for formulation SF8. In the view of above f2 values, SF8 was selected as best formulation and was taken for stability study.

Stability studies

The physical parameters and *in vitro* dissolution profile for optimized formulation SF8 before and after 3 months of stability study were measured and found that there was no significant change in thickness, diameter, weight variation, hardness, content uniformity and *in vitro* dissolution profile of optimized formulation.

Comparative dissolution profile of Innovator (Ambien CR) and optimized formulation (SF8)

Among all the formulations, F8 containing 2.60mg of SSG in IR layer and 20mg of matalose 90 SH 4000 as controlled release polymer was showing similar to the innovator product in respect of all tablets properties. The percentage of drug release from both the prepared formulation F8 and AMBIEN CR was found to be between 49 to 99%. The formulation F8 shows better percentage of drug release between 97 to 99%. From the above fact, it was concluded that ZT extended release bilayer tablets can be prepared successfully as it satisfies all the criteria as a

bilayered tablet and would be alternative to the currently available conventional tablets.

CONCLUSIONS

The present research was carried out to develop a bilayer tablet of ZT (IR and SR layer each containing 6.43mg) using SSG for IR and HPMC K4M, Metalose 90 SH 4000, Carbapol 974 PNF for the sustaining layer. Bilayer tablet showed biphasic release pattern where IR layer released more than 75% of ZT as burst effect followed by a controlled release from the matrix layer for up to 4 h, intended for overnight action. Among all the hydrophillic polymers, Metalose 90 SH 4000 showed better control over ZT and the formulation SF8 was found out to be promising formulation because of its highest similarity factor of 70 in comparison to marketed bilayer tablet of ZT (Ambien CR). Results of the current study clearly indicate, bilayer tablet of ZT was a stable dosage form and a promising potential of the bilayer system as an alternative to the market dosage form.

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