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Formulation and *in vitro* evaluation of Bilayer Tablets of Zolpidem tartrate for Biphasic Drug Release

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Abstract: The objective of this present study was to design bilayer tablet of Zolpidem Tartrate (ZT) for biphasic release and in vitro evaluation of the same. Bilayer tablets comprised two layers, i.e. immediate release and controlled release layer. The immediate release layer comprised croscarmellose sodium as a super disintegrant and the controlled release layer comprised HPMC K100M as the release retarding polymers. Direct compression method was used for formulation of the bilayer tablets. *In vitro* dissolution studies were carried out in a USP apparatus I, basket method. HPMC K100M extended the release of drug from the extended release layer for 6 hr. FTIR studies revealed that there was no interaction between the drug and polymers used in the study. The release of Zolpidem Tartrate was found to follow a pattern of Korsmeyer-Peppas, with Quasi-Fickian diffusion. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. There were no changes observed in physicochemical properties and drug release pattern of tablets. Biphasic drug release pattern was successfully achieved through the formulation of bilayer tablets in this study.
Keywords: Zolpidem Tartrate, bilayer tablet, biphasic release system.

INTRODUCTION:

In recent years, a growing interest has been developed in designing drug delivery systems that include an immediate release (IR) component to controlled release (CR) dosages. The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance [1].

Multi-layer tablet dosage forms were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredient(s) (API), to separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property), to modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery[2].

Generally, conventional extended release dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. Immediate release

drug delivery system (DDS) is intended to disintegrate rapidly, and exhibit instant drug release. It is associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract [3].

On the basis of these considerations, we have proposed a bilayer tablet, in which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is an controlled release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time.
The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer. The present study aims at formulating bilayer tablets of Zolpidem Tartrate with a IR layer using croscarmellose sodium and an CR layer using hydrophilic polymer HPMC K100M [4].

Zolpidem Tartrate, a non-benzodiazepine agent, is one of the most frequently prescribed hypnotic drugs. Zolpidem was proven as effective as benzodiazepine in the management of short-term insomnia [5]. Zolpidem is effective in reducing the time to sleep onset and increasing total sleep time. The hypnotic effects of Zolpidem have been reported primarily in the first 3 hours post-dose which can lead to sub therapeutic effects on sleep maintenance in the later portion of the night for some patients. In an effort to expand the coverage of sleep complaints and overcome the lack of efficacy in sleep maintenance, bilayer Zolpidem Tartrate tablet was prepared for biphasic release. The tablet was designed to mimic initial dosing while the controlled release of drug maintains a plasma concentration for a longer duration of time [6].

EXPERIMENTAL

MATERIALS:

Zolpidem Tartrate was obtained as gift sample from Microlabs Pvt. Ltd. (Bangalore, India) HPMC (Methocel K100M), microcrystalline cellulose (MCC) (Avicel PH 102) and Sodium Croscarmellose (CCS) (Ac-Di-Sol) were obtained as gift sample from Alembic Ltd., (Vadodara, India). The other ingredients were purchased from local markets and they all were of analytical grade. STILNOCT ® 12.5 mg was used as a marketed bilayer tablet (Sannofi – Synthelab) as a reference product.

FTIR SPECTROSCOPY:

The drug and optimised formulation were characterized by IR spectroscopy using a FTIR 8400S (Shimadzu, Japan). The spectra were taken by KBr discs method in the range of 4000–500 cm^{-1}.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDY

Differential scanning calorimetry (DSC) study of matrix tablets was performed using a
Toledo DSC (Mettler Star SW 9.20) to determine the drug excipients compatibility study.
The analysis was performed at a rate 5 °C min^{-1} from 50 to 300°C temperature range under nitrogen flow of 25 mL min^{-1}.

FORMULATION AND CHARACTERIZATION OF BILAYER TABLETS:

The bilayer tablets of Zolpidem Tartrate were prepared by the direct compression method. The drug and polymers for both IR and CR layer were passed through a # 60 sieve before their use in the formulation.

Dose Calculation [7, 8, 9]

For sustained drug release up to 6 hr, the immediate dose of drug was calculated from total dose of Zolpidem Tartrate extended release tablet, which is 12.5mg.

$$D\text{t} = \text{Dose}\ (1 + 0.693 \times t/t_{1/2})$$

Where, Dt = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, $t_{1/2}$ = Half-life of drug. Half-life of ZT ranges from 1.2 to 4.5 hr.

For example,

i. Zolpidem Tartrate: 12.5 = Dose [1+ (0.693 × 6)/4.5)], Dose = 6.496 mg Zolpidem Tartrate.
ii. Zolpidem Tartrate: 12.5 = Dose [1+ (0.693 × 6)/1.2)], Dose = 2.799 mg Zolpidem Tartrate.

According to dose calculation, IR dose of drug can be taken in between range of 2.799 mg to 6.496mg for the preparation of bilayer tablets; thus 50% dose i.e. 6.25 mg of Zolpidem Tartrate was taken in both IR and CR

layers to achieve 50–70% of drug release within 30 min. to meet USP dissolution criteria.

Formulation of the IR Layer [10, 11]
The IR ingredients (Table 1) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation and subjected for preformulation studies.

Formulation of the CR Layer
The ER ingredients were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation and subjected for preformulation studies.

Compression of Bilayer Tablet
In the present study bilayer tablet was prepared manually using single station punching machine. Accurately weighed amount of ER powder mix was fed manually into die cavity. CR layer was compressed at mild compression force. After that accurately weighed IR powder mix was manually fed into the die on CR layer and compressed using 8-mm flat punches (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat).

Table 1: Composition of Bilayer Biphasic Release Tablets of Zolpidem Tartrate.

Ingredients in mg	BF1	BF2	BF3	BF4	BF5	BF6	BF7	BF8	BF9
IMMEDIATE RELEASE COMPONENT									
Zolpidem Tartrate	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
CCS	20	30	40	40	40	40	40	30	30
MCC PH 101	30	30	30	30	30	30	30	30	20
Ludipress	36.75	26.75	16.75	21.75	21.75	21.75	21.75	31.75	16.75
HPMC K4M	5	5	5	-	-	-	-	-	-
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	70
EXTENDED RELEASE COMPONENT									
Zolpidem Tartrate	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
HPMC K100M	50	50	50	40	30	20	10	20	20
MCC PH 101	20	20	20	20	20	20	20	20	20
Ludipress	11.75	11.75	11.75	21.75	31.75	41.75	41.75	41.75	41.75
Tartaric acid	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

EVALUATION OF TABLETS: [12, 13, 14, 15]
The prepared tablets were evaluated for various official and non-official specifications. The thickness of the tablet is measured by Digital vernier calipers. Twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight. Tablets were evaluated for hardness using Monsanto hardness tester and friability using Roche friabilator.

Drug Content Uniformity:
Ten tablets were finely powdered and an amount equivalent to 100 mg of Zolpidem Tartrate was accurately weighed and transferred to a 100 ml volumetric flask, then 70 ml of buffer pH 2 (0.01N HCL) was added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for Zolpidem Tartrate content at 294 nm using a double beam UV/Visible spectrophotometer (Shimadzu 1800, Japan) and 0.01N HCL as blank.

***In-vitro* drug release study:**
The drug release studies were carried out using USP dissolution apparatus I (Electrolab Model TDT-08L, Mumbai) equipped with basket which was operated at the speed of 100 rpm. Five hundred milliliters of 0.01 N HCl (pH 2), as the dissolution medium, was placed in the glass vessel, assembled the apparatus, and equilibrated the dissolution medium to 37±0.5ºC[16]. The amount of drug released was measured at predetermined time intervals and assayed with UV/visible spectrophotometer (Shimadzu-1800, Japan) at a wavelength of 294 nm using a 1.0 cm quartz cell [17]. The study was performed in triplicate.

Dissolution profile [18, 19, 20, 21]
The similarity factor (f_2) given by SUPAC guidelines for modified release dosage forms was used as a basis for comparing dissolution profiles. Dissolution profiles are considered to be similar when f_2 is 50 to 100. This similarity factor was calculated by the following formula:

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum (R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where *Rt and Tt* are the mean percentage of dissolved drug from the reference and test formulations at time t respectively.

Kinetic analysis of dissolution data: [22, 23]
The rate and mechanism of release of Zolpidem Tartate from the prepared bilayer tablets were analysed by fitting the dissolution data into the zero-order equation:

$$Q = k_0 t \qquad (1)$$

Where Q is the amount of drug released at time t, and k_0 is the zero order release rate constant.
The first order equation:

$$\ln (100–Q) = \ln 100 – k_1 t \qquad (2)$$

where k_1 is the first order release rate constant.
The dissolution data was fitted to the Higuchi's equation:

$$Q = k_2 t_{1/2} \qquad (3)$$

Where k_2 is the diffusion rate constant.
The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems:

$$\log (Mt/M\infty) = \log k + n \log t \qquad (4)$$

Where Mt is the amount of drug released at time t, M_∞ is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent indicative of the mechanism of drug release.

RESULTS AND DISCUSSION:
Bilayer tablet is one of the approaches for biphasic release system. Attempts have been made for preparation of biphasic release with variable concentration of superdisintegrant in IR layer and rate retarding polymer in CR layer for adjusting release pattern according to marketed formulation and USP guidelines of Zolpidem Tartrate Extended release tablet. In the bilayer tablet one of the layers was formulated with superdisintegrant CCS for immediate drug release while another layer was formulated with the hydrophilic polymer HPMC K100M for extended drug release.

Figure 1 demonstrates the FTIR spectra of pure Zolpidem Tartrate (A) and Optimized formulation BF8 (B). The same characteristic peaks were observed for the drug-excipients mixture, indicating that no chemical reaction or interaction between the drug and excipients took place.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDY
Differential scanning calorimetry (DSC) studies of drug-polymer mixtures were performed using a Toledo DSC (Mettler Star SW 9.20) to determine the drug excipient compatibility study. The analysis was performed at a rate 50°C min^{-1} from 500 to 2000 °C

temperature range under nitrogen flow of 25 mL min^{-1}. Thermograms of pure Zolpidem Tartrate showed sharp endothermic peak at 186 °C. Similar peaks were obtained in the prepared drug-polymer mixtures (Figure 2). This clearly indicated the nil drug polymer interaction.

Micromeritic properties of powder blend for IR & CR layers:

The powder blends of both IR and CR layers of different formulations of bilayer tablets were evaluated for various physical properties (Table 2). The bulk densities for the powder blend of IR and CR layer of various formulations ranged between 0.32 to 0.39 g $mL^{-1}$and tapped density ranged between 0.40 to 0.49 g ml^{-1} as determined by the tap densitometer. This value of bulk density indicated good packing characteristics. The Carr's index (CI) for all the formulations was ranged from 9.61 to 18.61, indicating desirable flow properties. The value of Hausner's ratio was ranged from 1.10 to 1.23. The flow properties of powder blends were further analysed by determining the angle of repose for all formulations; it ranged between 24.47 to 32.38°. The values indicated satisfactory flow behaviour.

Physical properties of Bilayer Tablets:

All the batches of tablets were produced under similar conditions to avoid processing variables. The weight variation, hardness, friability, thickness and content uniformity of all formulations were found to be within acceptable limits as per official specifications. Weight of the optimized bilayer tablet formulation BF8 was 199.90±1.41 mg, hardness was 3.4±0.223 kg cm^{-2} and thickness was 3.68±0.02854mm. The percentage friability of all the formulations was ranged from 0.100 to 0.598% which is less than 1.0% of their weight. Values of the hardness test and percent friability indicated good handling properties of the prepared bilayer tablets. The drug content uniformity in the bilayer tablets was ranged from 98.15 to 101.62%.

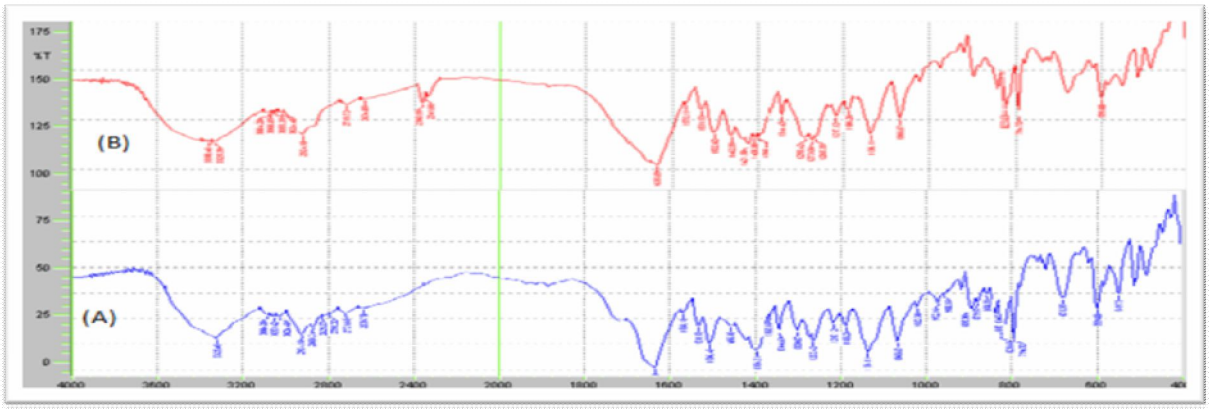

Figure 1: FTIR spectra of pure Zolpidem Tartrate (A) and Optimized formulation BF8 (B)

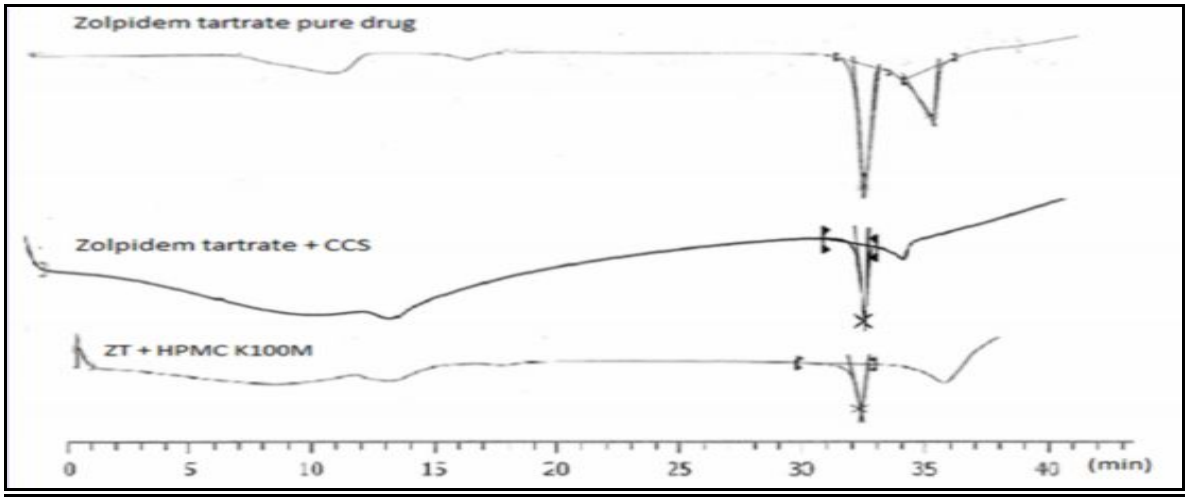

Figure 1: DSC curve of Pure Zolpidem Tartrate, mixture of ZT+CCS and mixture of ZT+ HPMC K100m.

Table 2: Micromeretic properties of powder blend for IR and CR layers of bilayer tablet.

Formulation code	Angle of Repose (θ)		Bulk Density (g/ml)		Tapped Density (g/ml)		Carr's Index. (%)		Hausner's ratio	
	IR	**CR**	**IR**	**CR**	**IR**	**CR**	**IR**	**CR**	**IR**	**CR**
BF1	32.38	27.80	0.36	0.384	0.43	0.434	16.48	11.53	1.21	1.13
BF2	27.52	27.34	0.35	0.377	0.40	0.434	16.08	13.20	1.19	1.15
BF3	26.39	27.78	0.39	0.392	0.49	0.454	18.41	13.72	1.23	1.15
BF4	27.67	28.04	0.34	0.377	0.41	0.425	15.43	11.32	1.22	1.12
BF5	28.62	26.68	0.39	0.384	0.48	0.425	16.10	9.61	1.17	1.10
BF6	29.22	29.74	0.38	0.377	0.47	0.425	18.61	11.32	1.23	1.12
BF7	26.57	27.51	0.34	0.392	0.42	0.444	16.51	11.76	1.22	1.13
BF8	25.44	27.83	0.38	0.363	0.47	0.416	16.30	12.72	1.18	1.14
BF9	24.47	27.35	0.32	0.394	0.41	0.434	14.35	11.53	1.21	1.13

Table 3: Physical Properties of All Formulations

Formula	Weight (mean ± SD, mg) (n = 20)	Hardness (mean ± SD, MPa) (n = 10)	Thickness (mean ± SD, mm) (n = 10)	Friability (%) (n = 10)	Drug content (mean ± SD) (n=10) (%)
BF1	200.75±1.44	4.2±0.273	3.81±0.0054	0.300	99.45±0.21
BF2	200.70±1.38	3.5±0.353	3.85±0.0167	0.399	98.15±0.28
BF3	200.60±1.35	4.5±0.353	3.87±0.0130	0.100	101.23±0.25
BF4	200.50±1.43	4.1±0.223	3.74±0.0114	0.597	100.57±0.15
BF5	199.80±1.43	4.3±0.273	3.74±0.0181	0.199	99.56±0.52
BF6	200.70±1.49	4.4±0.273	3.69±0.0181	0.200	101.62±0.47
BF7	198.55±1.39	4.9±0.223	3.69±0.0260	0.300	99.34±0.31
BF8	199.90±1.41	4.4±0.223	3.68±0.0258	0.400	100.25±0.23
BF9	171.50±1.31	4.1±0.223	3.54±0.0364	0.598	101.29±1.21
BF8 (after stability)	197.32±1.21	4.3±0.124	3.53±0.0263	0.412	99.68±0.27

***In Vitro* drug release study:**

In case of formulation BF1, retardation in the release of Zolpidem tartrate was observed from beginning of the dissolution (Figure 3). This may be due to small amount of CCS (20 mg) in IR layer and large amount of HPMC K100M in CR layer of the tablet. An increase in the amount of CCS in the IR layer as observed for formulations BF2 and BF3, did not show a prominent increase in the release rate as compared to formulation BF1 (Figure 3).

As the concentration of the rate retarding polymer from CR layer was decreased from 40 mg to 10 mg for formulations BF4 to BF7 respectively, the release pattern was found to be improved with initial burst release (Figure 4). Formulation BF6 containing 40 mg CCS and 20 mg HPMC K100M showed release pattern identical to the marketed product. Formulation BF7 containing 40 mg CCS and 10 mg HPMC K100M showed rapid initial release and was unable to retard the drug release. So it was concluded that to extend release up to 6 hrs, 20 mg HPMC K100M was necessary.

of Zolpidem Tartrate released can be attributed to the immediate release layer of the formulation. Further, release of Zolpidem Tartrate was extended up to 6 hr because of HPMC K 100M in CR layer. It was also found that formulations BF6 to BF9 obeyed the preferred amount to be dissolved at different time points as per USP (Table 4).

The immediate release layer of the bilayer tablet containing CCS swells rapidly upto 4-8 times its original volume on contact with water. So, it performs its disintegrating action by wicking through capillary action and fibrous structure respectively with minimum gelling and liberated Zolpidem Tartrate for immediate action. Disintegration of the immediate release layer did not have any effect on characteristics

Formulation BF8 containing 30 mg CCS in the IR layer and 20 mg HPMC K100M showed desired initial rapid release. From the release profile of formulation BF8 and BF9 (Figure 5), it was found that there was no significant effect of the ludipress in the release pattern for bilayer tablets.

Simple visual observation of the Figure 4 and Figure 5 showed an initial burst effect in formulations BF4 to BF9. From formulations BF6 to BF9, more than 50% of the Zolpidem Tartrate was released in the first 30 min of the dissolution study. This initial high amount

of extended release layer. As soon as the bilayer tablet comes in contact with the dissolution media, IR layer disintegrated with initial immediate release of drug within 30 min. with simultaneous imbibition of dissolution medium by the tablet with the formation of gel layer of polymer around the tablet. The controlled release of Zolpidem Tartrate was found to be a function of the polymer concentration. The effect of HPMC K100M on drug release was due to swelling nature of polymer which causes subsequent thicker gel formation with decrease in drug release. So it was concluded from different trials that biphasic release of the Zolpidem Tartrate from bilayer tablets was mainly due to proper proportion of CCS in IR layer and rate retarding polymer in the CR layer.

Table 4: In Vitro Dissolution Data at Different Time Points as per USP

Time (min)	Preferred Amount Dissolved (USP)	% Cumulative drug release									
		MF*	**BF1**	**BF2**	**BF3**	**BF4**	**BF5**	**BF6**	**BF7**	**BF8**	**BF9**
30	50–70%	59.68 ± 1.48	33.72 ± 4.36	38.20 ± 1.56	40.06 ± 1.43	34.37 ± 4.97	38.12 ± 2.18	60.72 ± 2.53	70.12 ± 2.72	58.99 ± 5.19	55.38 ± 3.37
90	70–85%	71.33 ± 1.55	54.12 ± 4.18	57.85 ± 3.01	59.74 ± 2.57	54.63 ± 1.67	64.12 ± 2.15	72.32 ± 1.73	84.35 ± 0.09	72.56 ± 0.32	72.16 ± 2.85
240	NLT 85%	93.87 ± 0.11	68.12 ± 1.41	70.90 ± 0.24	77.78 ± 0.90	74.73 ± 8.73	81.45 ± 1.24	93.18 ± 3.13	95.32 ± 0.68	93.68 ± 1.69	94.54 ± 3.30

*MF – Marketed formulation – STILNOCT
All values are represented as mean ± SD (n=3)

Table 5: Drug Release Kinetic Data Derived From Various Mathematical Models

Formulations code	Zero order		First order		Higuchi (Matrix)		Korsmeyer Peppas			Best Fit Model	f_2
	K_0	R^2	K_1	R^2	K_H	R^2	K_K	R^2	N		
BF1	34.50	0.945	1.870	0.990	-3.799	0.992	1.054	0.980	0.345	Higuchi	28.83
BF2	50.14	0.840	1.768	0.977	-8.262	0.947	1.217	0.985	0.281	Peppas	31.91
BF3	41.02	0.896	1.816	0.983	-6.693	0.973	1.188	0.980	0.293	First order	35.82
BF4	58.63	0.950	1.673	0.995	-19.16	0.990	1.549	0.961	0.156	First order	32.38
BF5	57.57	0.896	1.792	0.992	-11.73	0.977	1.432	0.993	0.225	Peppas	40.79
BF6	56.94	0.887	1.765	0.987	-11.40	0.966	1.417	0.980	0.230	First order	71.30
BF7	58.76	0.761	1.786	0.995	-8.841	0.895	1.349	0.972	0.272	First order	58.17
BF8	56.79	0.886	1.775	0.988	-11.37	0.969	1.414	0.990	0.232	Peppas	75.58
BF9	55.13	0.916	1.860	0.950	-10.38	0.983	1.400	0.988	0.237	Peppas	72.60
BF8 After stability	55.79	0.876	1.875	0.968	-10.37	0.959	1.314	0.989	0.252	Peppas	73.58
STILNOCT	57.69	0.917	1.806	0.973	-11.58	0.985	1.463	0.993	0.214	Peppas	-

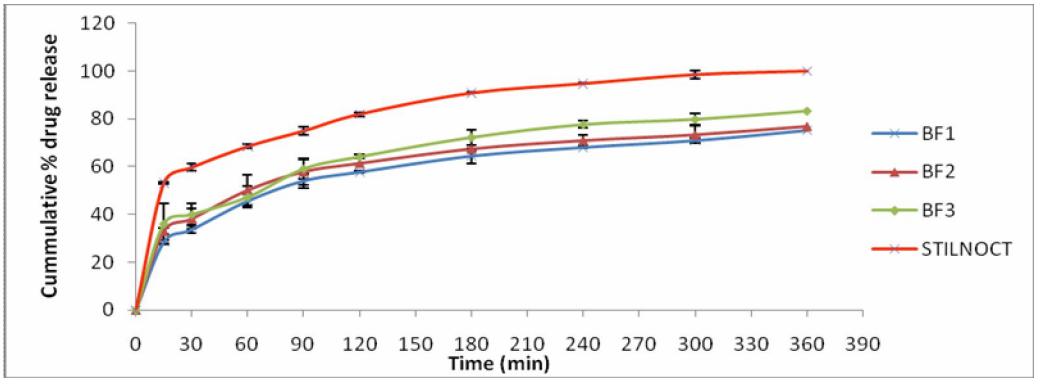

Figure 3: *In vitro* drug release profile of formulation (BF1 to BF3 and STILNOCT)

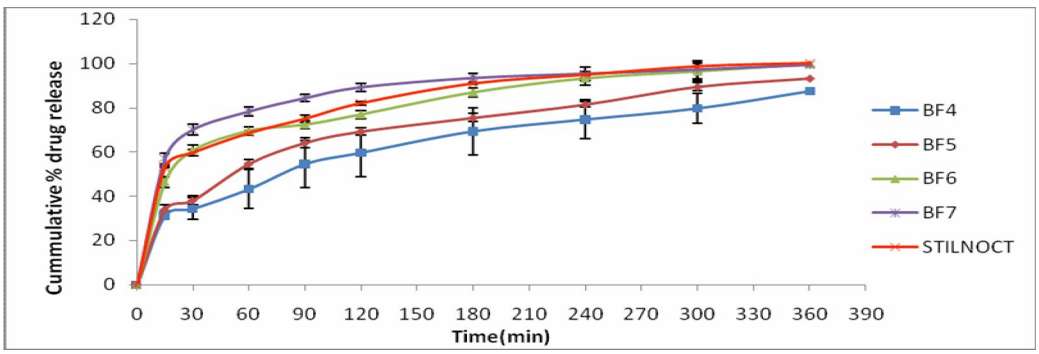

Figure 4: *In vitro* drug release profile of formulation (BF4 to BF7 and STILNOCT)

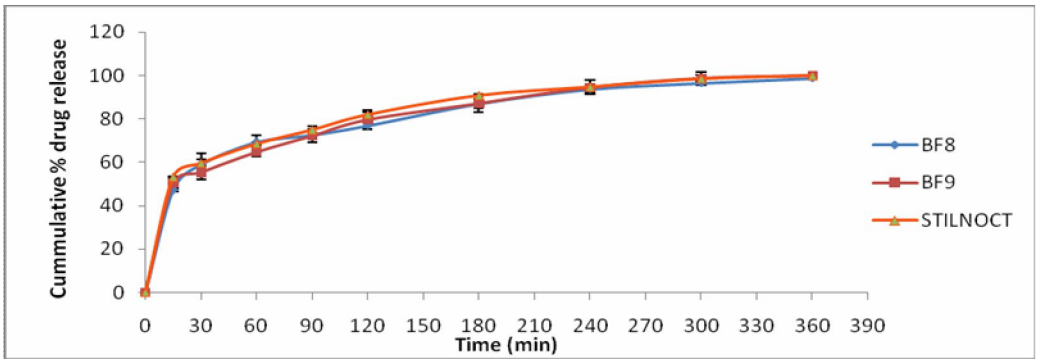

Figure 5: *In vitro* drug release profile of formulation (BF8, BF9 and STILNOCT

Similarity factor

Similarity factor (*f2*) for all formulations are shown in Table 4. Formulations BF1 to BF5 showed (*f2*) value less than 50 indicating dissimilar release profiles of formulations BF1 to BF5 with marketed product. Formulations BF6 to BF9 showed (*f2*) value more than 50 indicating similar release profiles of the formulations BF6 to BF9 and STILNOCT (Table 5) As value of (*f2*) was found to be 75.58 for BF8, it was chosen as optimized formulation.

Kinetic Analysis of Drug Release

In order to establish the mechanism of drug release and swelling kinetics, the experimental data were fitted to zero-order, first order, Higuchi and Korsmeyer–Peppas models. The results for the kinetics model fitting of the different formulations are shown in Table 5. The coefficients of regression were in a range between 0.761–0.950 (Zero order), 0.950–0.995 (First order), 0.895–0.992 (Higuchi) and 0.961–0.993 (Peppas).

Based on correlation coefficients (R^2), the best fit model were determined. Formulation BF1 followed Higuchi model; BF2, BF5, BF8 and BF9 followed Korsmeyer-Peppas while formulations BF3, BF4, BF6 and BF7 showed first order model.

The n value for BF8 was found to be 0.232, which meant that the mechanism of release for the BF8 was fickian diffusion and best fit model was Korsmeyer-Peppas. The n value for all formulations was in the range of 0.156 to 0.345 indicating Fickian diffusion. Overall, the release mechanisms from these bilayer systems can be explained as a result of diffusion of drug through porous matrix in which pores are created by superdisintegrant by disintegrating immediate release layer; thus more contribution of erosion to release mechanism.

Stability Studies

The accelerated stability studies were carried out on the optimized formulation i.e. BF8. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 3 months to assess their long term stability. After stability study tablets were subjected to various tests like hardness, thickness, friability, drug content and in-vitro drug release study. (Figure 5) The results indicated that, irrespective of the concentration of polymer, there were no any changes observed in tablets characteristics after stability study.

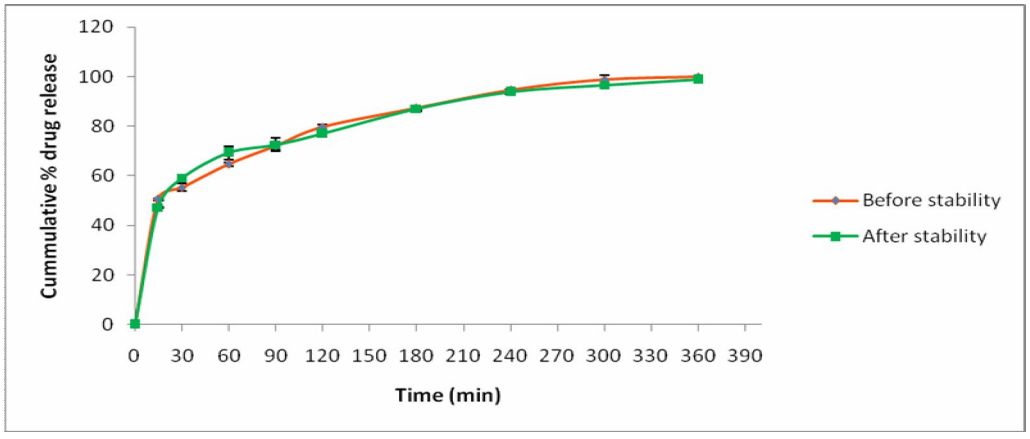

Figure 6: *In vitro* drug release profile of formulation BF8, before and after Stability study.

CONCLUSION:

It was found that biphasic release tablet formulation which is in agreement with marketed formulation and USP pharmacopoeial requirements can be prepared as bilayer tablets by using HPMC K100M in ER layer and CCS in IR layer. Optimized formulation BF8 releases more than 50% of the Zolpidem Tartrate within the first 30 min, and remaining drug release can be extended upto 6 hr. The formulated optimized bilayer tablet of Zolpidem Tartrate may able to solve the sleep complaints and prolong the total sleep duration.

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