Research Article

A NOVEL APPROACH TO SUSTAINED ZOLPIDEM TARTRATE RELEASE: COMPRESSED MINI-TABLETS

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ABSTRACT

Compressed mini-tablets systems are presented as a biphasic delivery system. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a prolonged release. Fast releasing component comprising superdisintegrant croscarmellose sodium, while mini-tablet was formulated using different concentration of HPMC K100M to obtain different drug release rates. The *In-Vitro* performance of these systems showed the desired biphasic behavior. The drug contained in the fast releasing phase (powder enrobing the mini-tablets) dissolved within the first 15 min, whereas the drug contained in the mini-tablets was released at different rates, depending upon composition of mini tablets. Based on the release kinetic parameters calculated, it can be concluded that mini-tablets containing HPMC K100M were particularly suitable approaching to release over 8 hr time periods.

Keywords: Biphasic release system, Mini-tablets, Croscarmellose Sodium, HPMC K100, Zolpidem Tartrate.

INTRODUCTION

Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time and in slow/quick release system provides release vice versa. Biphasic release system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) antihypertensive, antihistaminic, and anti-allergic agents.[1]

Generally, conventional controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. While immediate release tablets gives fast release to provide rapid onset of action, but fails to provide longer duration of action.

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[2].

On the basis of these considerations, we have proposed a new oral delivery device, in the form of a double-component tablet, in which the one portion is formulated to obtain a prompt release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second portion is a prolonged-release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time[3].

This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release period of the drug, provided that the excipients powder that fills the void spaces between the mini-tablets incorporate a part of the total drug dose. This system can produce a rapid rise in the plasmatic concentrations for some drugs (such as analgesic, anti-inflammatory, antihypertensive and antihistaminic agents) that are requested to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations[4].

The pharmacokinetic advantage relies on the fact that drug release from fast releasing component 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 granules[5].

Zolpidem is a prescription medication used for the short-term treatment of insomnia, as well as some brain disorders. It is a short-acting nonbenzodiazepine hypnotic that potentiates gamma-amino butyric acid (GABA), an inhibitory neurotransmitter, by binding to gamma-amino butyric acid ($GABA_A$) receptors at the same location as benzodiazepines. It works quickly (usually within 15 minutes) and has a short half-life (2–3 hours).[6]

While Zolpidem is a rapidly acting hypnotic, it is also a rapidly eliminated hypnotic agent. As a result, Zolpidem typically starts acting within 15-30 minutes, or less, after ingestion of the tablet and its action can typically last for approximately 4-6 hours. However, this duration of action can be considered too short in some circumstances. Lengthening the duration of action would thus be desirable.[7]

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.

The compressed mini-tablet is a biphasic release dosage form. The outer layer immediately releases drug while the mini-tablets are controlled-release. The tablet was designed to mimic initial dosing while the extended-release of drug maintains a plasma concentration for a longer duration of time than the immediate-release product.[8]

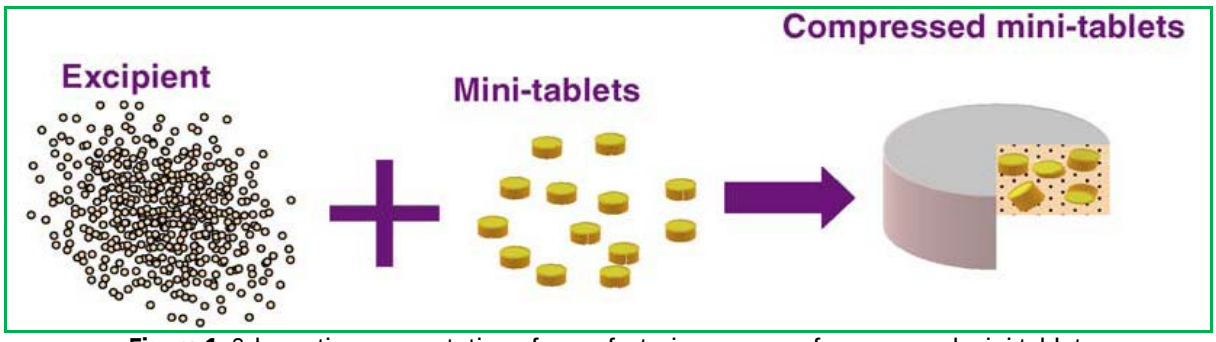

Figure 1: Schematic representation of manufacturing process of compressed mini tablet.

Table 1: Composition of fast releasing component

Ingredients (IR)	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
Immediate release component									
Zolpidem Tartrate	5.23	6.87	6.87	5.23	5.23	5.23	5.23	6.25	6.25
Croscarmellose sodium	75	75	100	100	50	30	30	30	25
MCC PH 102	83.77	82.13	80	80	80	80	80	80	80
Ludiflash	74	74	63.13	64.77	64.77	84.77	84.77	83.75	83.75
HPMC E50	10	10	-	-	-	-	-	-	-
Magnesium stearate	2	2	-	-	-	-	-	-	-
Total weight	250	250	250	250	200	200	200	200	200
Extended release component									
Zolpidem Tartrate	7.27	5.63	5.63	7.27	7.27	7.27	7.27	7.8	7.8
HPMC K100M	30	30	25	20	20	20	20	20	20
MCC PH 102	40	40	30	40	-	40	-	-	-
Lactose	30.73	32.37	27.37	20.73	67.73	20.73	67.73	61.75	61.75
Tartaric acid	10	10	10	10	10	10	10	10	10
Magnesium stearate	2	2	2	2	2	2	2	2	2
Croscarmellose Na	-	-	20	20	20	20	20	20	20
Total weight	120	120	120	120	120	120	120	120	120

MATERIALS AND METHODS

Materials

Zolpidem Tartrate, a sparingly soluble drug (Gifted by Microlab Pvt Ltd.) was incorporated in both components of the biphasic delivery system. For the preparation of the prolonged release component (mini-tablets), Hydroxypropyl Methylcellulose (HPMC, Methocel® K100M,) was considered, whereas for the fast release component, Microcrystalline Cellulose (Avicel PH 102) and Sodium Croscarmellose (Ac-Di-Sol) were used.

Preparation of the biphasic delivery system

The qualitative and quantitative composition of the different formulations of the biphasic delivery system can be seen in Table 1.

Dose Calculation[9, 10.]

For sustained drug release up to 12h, the total dose of drug required was calculated based on the conventional dose. The total dose was calculated using the following equation (1).

$$Dt = \text{Dose}\ (1 + 0.693 \times t/t1/2) \quad (1)$$

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. For Zolpidem Tartrate: 12.5 = Dose [1+ (0.693 × 6)/4)], *D*ose = 6.13 mg Diclofenac sodium.

Prolonged-release component (mini-tablets)

The mini-tablets contained HPMC as controlling agents. All materials were sieved and the fractions below 63µm were considered to minimize the lag time observed during drug release when coarse fractions were used and to prevent changes on properties of the tablets due to changes on the size of particles Mini-tablets, weighing 40.0±1.0 mg, were prepared by direct compression with flat tip punches and dies with 4mm diameter.

Fast release component

Microcrystalline cellulose (Avicel PH 102) was used because of its good compaction and disintegration properties. Sodium croscarmellose was used as a super disintegrant to obtain an immediate release of the drug.

Preparation of compressed mini tablet

For the preparation of the biphasic delivery system we had used 250mg of fast releasing component for single tablet. Compressed mini-tablet was prepared using 9.45mm punch. (Rimek mini press-1, Karnavati Engineering Ltd, Mehsana, Gujarat). The die of the tabletting machine was progressively filled by hand with the half amounts of the fast release component and then 3 mini-tablets were placed inside the die cavity. Then half of the remaining fast releasing component was placed over mini tablet (Table 1) prior to compression.

Physical characterization of the compressed mini-tablets system [4,11,12,13].

Compressed mini-tablets were characterized for weight variation, thickness, hardness, friability and dissolution.

Weight variation test

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight.

Hardness test:

The hardness of the tablet was determined using Monsanto Hardness Tester.

Friability test

Six tablets from each batch were examined for friability using Roche Friabilator (Electro lab EF-2, USP) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated.

%Friability = (Loss in weight/Initial weight) x 100 (2)

Dissolution profile[14, 15, 16]

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 between 50 to 100. This similarity factor is calculated by the following formula:

$$f_2 = 50 \times \log \{[1+ (1/n) \sum_{t=1}^{n} (Rt - Tt)^2]^{-0.5} \times 100\}$$

where n is the number of experimental points in the *in vitro* dissolution assay and Rt and Tt are the mean percentage of dissolved drug from the reference and test formulations.

Kinetic analysis of dissolution data[17,18,19]

The rate and mechanism of release of Zolpidem Tartrate from the prepared compressed mini-tablets were analyzed by fitting the dissolution data into the zero-order equation:

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

where Q is the amount of drug released at time t, and k_0 is the release rate constant, fitted to the first order equation:

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

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

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

Where k_2 is the diffusion rate constant.

The dissolution data was also fitted to the well known equation (Korsmeyer equation), which is often used to describe the drug release behaviour from polymeric systems:

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

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.

***In vitro* dissolution testing**

Dissolution study was conducted for all the formulation using USP type-I, basket apparatus (Elect lab, Mumbai, India.). The dissolution test was performed using 900 ml 0.01N HCl as the dissolution medium at 100 rpm and 37°C±0.5°C. Five millilitres of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium.[20] The samples were analyzed spectrophotometrically at 294 nm. The cumulative fraction of the drug released was calculated from the total amount of Zolpidem Tartrate and plotted as a function of time.[21]

Figure 2: Fracture equatorial showing surfaces of the compressed mini-tablets system.

RESULTS AND DISCUSSION

Physical properties of the compressed mini-tablets Systems: Compressed mini-tablets were prepared for biphasic drug delivery successfully. For the preparation of compressed mini-tablets different fraction of dose in the both the fast release component and extended release component was tried to get release pattern that matches the guideline for Zolpidem Tartrate extended release tablet as per USP monograph. Different viscosity grade polymer and different amount of polymer in both the component was tried to get better control on release rate.

Table 2 and 3 lists the physical properties (weight variation, thickness, hardness and friability) of the mini-tablet alone and compressed mini-tablets systems. One of the major characteristics of the mini-tablets is that they should not fuse into a non-disintegrating matrix during compaction.

Table 2: Results of physical test of mini-tablets

Formula	Weight (mean ± SD, mg) (n = 20)*	Tensile Strength (mean ± SD, MPa) (n = 10)*	Thickness (mean ± SD, mm) (n = 40)*	Friability (%) (n = 20)
MF1	39.90±0.64	4.7±0.44	3.24±0.048	0.83
MF2	39.75±0.63	4.8±0.27	3.20±0.035	0.41
MF3	39.70±0.57	4.9±0.22	3.18±0.008	0.82
MF4	39.85±0.58	4.7±0.44	3.17±0.013	0.41
MF5	39.80±0.61	4.8±0.27	3.19±0.008	0.82
MF6	39.85±0.67	4.5±0.35	3.17±0.008	0.83
MF7	39.84±0.68	4.5±0.50	3.19±0.015	0.83
MF8	39.85±0.67	4.2±0.27	3.20±0.015	0.82
MF9	39.85±0.58	4.7±0.27	3.18±0.010	0.83

*All results presented in mean (±S.D)

Table 3: Results of physical test of compressed mini-tablet

Formula	Weight (mean ± SD, mg) (n = 20)*	Tensile Strength (mean ± SD, MPa) (n = 10)*	Thickness (mean ± SD, mm) (n = 40)*	Friability (%) (n = 20)
MF1	370.15±0.87	3.1±0.22	6.76±0.032	0.315
MF2	370.10±0.91	3.5±0.50	6.74±0.029	0.495
MF3	370.05±0.94	3.6±0.22	6.78±0.023	0.495
MF4	370.20±0.89	3.1±0.22	6.74±0.040	0.539
MF5	320.10±0.55	3.3±0.44	6.40±0.018	0.520
MF6	320.05±0.68	3.4±0.41	6.43±0.027	0.520
MF7	320.15±0.67	3.2±0.27	6.53±0.046	0.416
MF8	319.90±0.71	3.6±0.41	6.48±0.027	0.521
MF9	320.10±0.55	3.9±0.22	6.39±0.016	0.624

*All results presented in mean (±S.D)

Table 4: Fitting of the kinetics model (release rate constants, K_0, K_H, K_K, and exponent n, together with the determination coefficients, R^2) for compressed mini-tablets system.

Formulation	Zero order Equation		First order Equation		Higuchi Equation		K-P Equation		
	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2	N
MF1	40.56	0.908	1.831	0.994	-6.036	0.978	1.169	0.982	0.305
MF2	41.60	0.856	1.891	0.965	-3.688	0.952	1.059	0.993	0.376
MF3	56.79	0.838	1.711	0.981	-12.65	0.946	1.424	0.995	0.221
MF4	56.76	0.822	1.958	0.966	-8.732	0.936	1.345	0.990	0.271
MF5	52.42	0.795	1.91	0.991	-5.989	0.911	1.243	0.969	0.314
MF6	54.66	0.899	1.854	0.975	-9.37	0.978	1.375	0.995	0.249
MF7	57.35	0.887	1.793	0.983	-10.40	0.970	1.418	0.990	0.231
MF8	57.17	0.868	1.860	0.947	-10.58	0.958	1.395	0.983	0.244
MF9	55.92	0.913	1.877	0.938	-10.69	0.983	1.410	0.989	0.238

It was observed that red colored mini-tablets were able to withstand the compression force after the crushing test. Visual inspection of the fracture surfaces of the biphasic system revealed that the appearance of the mini-tablets in the compact system was similar to the original mini-tablets. Thus, these subunits tended to keep their integrity when compacted and remained as coherent individual units after the process of tabletting (Fig. 2). These units did not fragment into smaller units after the compaction process. This lack of fragmentation might be caused by the unique stress conditions of the mini-tablets during uniaxial compression in the die, i.e., the mini-tablets are stressed from several directions simultaneously, making the fracturing of these subunits relatively difficult.

Dissolution testing of the compressed mini-tablets system: Figs. 3 to 5 show the Zolpidem Tartrate release profiles from compressed mini-tablets systems. For the compressed mini-tablets systems under investigation, the release profiles are characterized by a burst release of Zolpidem Tartrate, followed by a slow release phase, typical of a biphasic delivery system. For all formulations, the large tablets were rapidly disintegrated into both powder (releasing the immediate dose of the drug) and individual mini-tablets, which sustained the release of the drug. In fact, the dissolution profile of the fast release component occurs within a few minutes, due to the prompt disintegration of the system in contact with the dissolution media. The mini-tablets, upon dispersion in the dissolution media, controlled the Zolpidem tartrate release at a slow rate for almost 6-7 h.

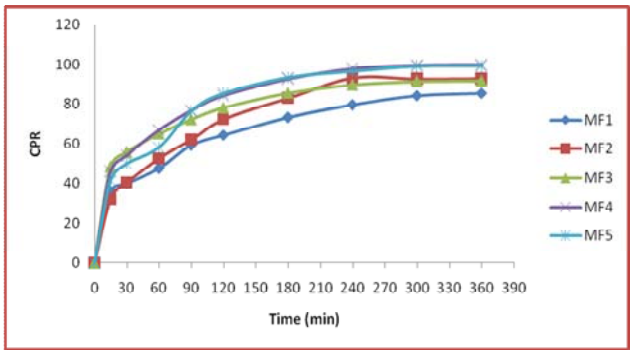

Figure.3. In vitro Zolpidem Tartrate release profiles of MF1 to MF5

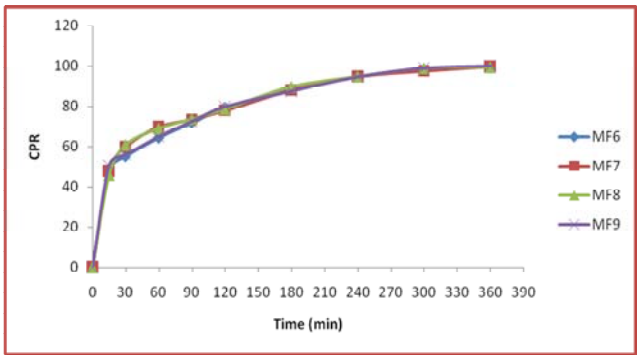

Figure 4: In vitro Zolpidem Tartrate release profiles of MF6 to MF9

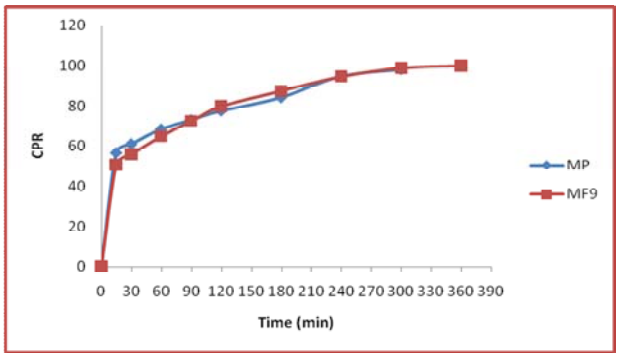

Figure 5: In vitro Zolpidem Tartrate release profiles of MF9 and marketed product (MP)

Comparison of drug release profile

Similarity factor was used for the comparison of release profile of different formulation. Here formulation coded MF9 was compared with that of marketed product, which have biphasic release characteristics. It was found that release pattern of prepared formulation was similar to that of marketed product (f_2>73).

Drug release from compressed mini-tablets system

The results for the fitting of the kinetics model for Zolpidem Tartrate release from compressed mini tablets are shown in Tables 4, (release rate constants, K_0, K_H, K_K, the determination coefficients, R^2, and the release exponent, n). The correlation coefficient (R^2) was used as indicator of the best fitting, for each of the models considered. From the R^2 it was found that compressed mini tablet (MF9) follows first order release kinetics.

CONCLUSION

A biphasic oral delivery system was developed by compressing mini-tablets into a tablet dosage form. The compressed mini-tablets showed slight deformation and no fragmentation. This technology may be achieved by fast/slow delivery system. This is characterized by an initial rapid release phase, corresponding to the drug release contained in the powder layer filled between mini-tablets, followed by a period of slow release, corresponding to the drug release of mini-tablets. The two different release phases can be easily adjusted in a wide range of values of both delivery rate and ratio of the dose fractions, on the basis of the pharmacokinetics and therapeutic needs, to perform the desired in vivo profile. Key variables of this study included the external powder/mini-tablets ratio and type of matrix mini-tablets. The results show that the release profile is strongly dependent on composition of subunits, making up the drug sustained dose. After the disintegration of this system, the HPMC mini-tablets were able to release a second fraction of the dose in a prolonged time (6 h) at a constant rate and with an identical dissolution profile to the non-compressed mini-tablets, suggesting their physical integrity after compression.

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