Int J Pharma Res Health Sci. 2017; 5 (5): 1404-10
DOI:10.21276/ijprhs.2017.05.16
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CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Original Article

Formulation and Evaluation of Floating Drug Delivery System of Zolpidem Tartrate Tablets

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ARTICLE INFO

Received: 15 Oct 2017
Accepted: 25 Oct 2017

ABSTRACT

The present investigation concerns the formulation and evaluation of floating tablets of zolpidem tartrate which after oral administration are designed to prolong the gastric residence time and increase drug bioavailability. A floating drug delivery system (FDDS) was developed using gas-forming agents like sodium bicarbonate and citric acid and polymers Hydroxyl propyl methyl cellulose (HPMCK4M) and xanthan gum. The prepared tablets were evaluated in terms of their precompression and post compression parameters, buoyancy lag time, total floating time and in-vitro drug release. The formulations were optimized for the grades of HPMCk4M and xanthan gum and its concentrations and combinations. The results of the in-vitro drug release studies showed that the optimized formulation (F12) could sustain drug release i.e.95.6% for12hrs and buoyancy lag time and total floating time were found to be 59sec and >24 hrs respectively. The mechanism of drug release for optimized formulation F12 was found to be Non-Fickian diffusion transport with Zero order of release. Optimized formulation (F12) showed no significant change in physical appearance, drug content, total buoyancy time and in-vitro dissolution study after storage at 400 C/75% RH for three months. Zolpidem tartrate floating tablets prepared by employing xanthan gum at concentration 57.5%w/w with 10% w/w sodium bicarbonate and 5% citric acid (F12) was the best formulation with desired in-vitro floating time and drug dissolution.

Key words: Floating drug delivery system, Gastric residence time, in-vitro dissolution study,lag time

1. INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable[1,2].In recent years, peroral dosage forms for gastric retention have attracted more attention for their theoretical advantage in gaining control over time and

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the site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine. Various approaches have been used to prepare dosage forms for gastric retention[3] .These systems mainly consist of swelling and expanding systems,[4,5] floating capsules,[6-8] floating pellets,[9] and floating granules[10] Gastric retention of the drugs provides such advantages as better delivery of the drugs with narrow absorption windows in the small intestinal region and longer residence time in the stomach, which could be advantageous for local action in the upper part of small intestine. The current investigation aims at development of floating matrix tablets of different release patterns for zolpidem tartrate using a gas generating agent. zolpidem tartrate is a member of the group of drugs known as benzodiazepines, which are a class of calcium channel blockers, used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. Formulation of floating tablets containing zolpidem tartrate as a drug candidate, which would remain in stomach and or upper part of GIT for prolonged period of time thereby maximizing the drug release at the desired site within the stipulated time and the oral bioavailability has been reported to be 70%. Thus, it seems that an increase in gastric retention time may increase the extent of absorption and bioavailability of the drug. Hence, the aim of this research is to prepare the zolpidem tartrate in order to increase the gastric residence time (GRT) and evaluation for better sustained effect and to study the effect of drug release profile for formulation with zolpidem tartrate and polymer ratio.

2. MATERIALS AND METHODS

Zolpidem tartrate was obtained gift sample from Hetero labs Ltd,Hyderabad, India. HPMC K4M, Sodium CMC,carbopol and Xanthan gum were obtained as gift samples from Central drug house Pvt. Ltd, New delhi. Sodium bicarbonate, citric acid, magnesium Stearate, talc and Lactose were obtained S.D. Fine Chemicals, Mumbai, India .All others chemicals were used as analytical grades.

Drug-excipients compatability studies:

Fourier transform infrared (FTIR) spectroscopy[11]

Infrared spectrophotometry is an analytical technique utilized to check the chemical interaction between the drug and other excipients used in the formulation. One milligram of the sample was powdered and intimately mixed with 100mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400cm^{-1} in an FTIR spectrophotometer (Bruker). The IR spectrum of the drug was compared with that of the physical mixture to check for any possible drug-excipients interaction.

Formulation of floating tablets: [12]

All ingredients were collected and weighed accurately. Sift zolpidem tartrate with polymers through sieve no. 60 and then rinse the remaining excipients. Pre-blend all ingredients (except lubricant- magnesium stearate) in mortar for 15 minutes. Then add magnesium stearate and blend again for 5-6 minutes. Lubricated powder was compressed under 8 mm punch of Rimek tableting machine, Mini press - I 12 station D tooling**.**

Table 1: Composition of different formulations

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Zolpidem tartrate	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M	90	95	100	105	110	115	---	---	---	---	---	---
Xanthum gum	---	--	---	---	---	----	90	95	100	105	110	115
NaHCO3	15	20	25	30	30	30	15	20	25	30	30	30
Citric acid	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	69	59	49	39	34	29	69	59	49	39	34	29
Carbopal	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg.stearate	2	2	2	2	2	2	2	2	2	2	2	2
total(wt)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Precompression parameters[13]

The following tests were performed for polymers as well as for drug substance.

Bulk density:

The powder sample under test was screened through sieve #18 and the sample equivalent to 10g was accurately weighed and filled in a 50ml graduated cylinder and the powder was leveled and the unsettled volume (V_0) was noted. The bulk density was calculated in g/cm^3 by the formula,

$$\text{Bulk density } (\rho_0) = \frac{M}{V_0}$$ Where,

M = mass of powder taken

V_0= apparent unstirred volume

Tapped density:

The powder sample under test was screened through sieve #18 and the weight of sample equivalent to 10g was filled in 50ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times Volume was considered as tapped volume (V_f). The tapped density was calculated in g/cm^3 by the formula,

$$\text{Tapped density } (\rho_t) = \frac{M}{V_f}$$ Where,

M = weight of sample powder taken

V_f = tapped volume

Percentage compressibility or Carr's index:

Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula,

Carr's index (%)

$$= \frac{tapped\ density - poured\ density}{tapped\ density} x\ 100$$

Table 2: Carr's index as an indication of powder flow

Carr's index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable*
23-35	Poor
33-38	Very poor
> 40	Extremely poor

*May be improved by glidant

Hausner's ratio:

Hausner's ratio was calculated using the formula,

$$Hausner's\ ratio = \frac{tapped\ density}{poured\ density}$$

Table 3: Values of Hausner's ratio

Values	Comments
Less than 1.25	Good flow
Greater than 1.5	Poor flow
Between 1.25-1.5	Glidant normally improves the flow

Angle of repose:

Angle of repose of the granules was determined by the height cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula,

$$tan^{-} = \frac{2h}{D}$$

Where, h and D are height and diameter of the pile respectively

Table 4: Angle of repose as an indication of powder flow properties

Angle of repose (degrees)	Type of flow
< 20	Excellent
20-30	Good
30-34	Passable
> 40	Very poor

Post compression parameters[14]

All the prepared matrix tablets were evaluated for the following official and unofficial parameters.

Hardness

The hardness of ten tablets was measured using Monsanto hardness tester. The mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

Friability:

The friability of the tablets was determined using electrolabfriabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25rpm for 4min. After 4min the tablets were weighed again. The friability was then calculated using the formula,

$$Friability\ (\%) = \frac{initial\ weight - final\ weight}{initial\ weight} x\ 100$$

Weight variation test:

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in table 9 and none deviate by more than twice the percentage shown.

Table 5: Weight variation for uncoated tablets

Average weight of tablets (mg)	Maxim percentage difference allowed
130 or less	10.0
130-324	7.5
More than 324	5.0

Drug content:

Ten tablets were weighed and average weight was calculated. All the 10 tablets were crushed in mortar. The powder equivalent to 100mg of zolpidem tartrate was dissolved in 100ml of 0.1N HCl and shaken for 20min. Solution was filtered and 5ml of the filtrate was diluted to 100ml using 0.1N HCl. Absorbance of resultant solution was measured at 280nm using 0.1N HCl as a blank. The amount of drug present in one tablet was calculated.

***In-vitro* floating study[15]**

The time taken by the tablet to emerge onto the surface of the medium after adding to the dissolution medium is called Buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerges on surface of medium called Total floating time (TFT) Both BLT & TFT were determined by placing the tablet in 900ml of simulated gastric fluid without pepsin, at pH 1.2, temperature 37±0.5ºC, basket rotation at 50rpm.

***In-vitro* Dissolution study[16]**

Dissolution of the tablets of each batch was carried out using USP type-I apparatus using basket. The dissolution medium consisted of 900ml of 0.1N HCl (pH 1.2) for 12h, maintained at 37 $\pm$ 0.5°C. One tablet was placed in basket of each dissolution vessel and the basket rotation speed was set at 50rpm. 5ml of the sample was withdrawn every hour for 8h and for every 1h to 12h the same volume of the fresh medium was replaced every time. The samples were analyzed for drug content at a wavelength of 280 nm using double beam UV-Visible spectrophotometer. The content of the drug was calculated using the equation generated from the standard curve. The percentage cumulative drug released was calculated.

***In-vitro* drug release kinetics study**

The dosage forms that do not disaggregate and release the drug slowly (assuming that the area does not change and no

equilibrium conditions are obtained) could be represented by zero order kinetics equation. It suggested that the quantity of drug released from the matrix tablets is often analyzed as a function of the square root of time, which is typical for systems where drug release is governed by pure diffusion. However, the use of this relationship in swellable systems is not justified completely as such systems can be erodible. Therefore, analysis of drug release from swellable matrices must be performed with a flexible model that can identify the contribution to overall kinetics; an equation proposed by Ritger and Peppas[17]. The suitability of several equations, which are reported in the literature to define drug release mechanisms, was tested with respect to the release data. To analyze the mechanism of drug release from the matrix tablets, the data obtained from the drug release studies was analyzed according to the following equations

1. Zero order model:[18]

$$[Q = K_0 t]$$

2. Higuchi model:[19]

$$[Q = K_H t^{½}]$$

3. Korsmeyer-Peppa's model:[20]

$$F = (M_t/M) = K_m t^n$$

4.First order model:

$$Q=Q_O\ e^{-kt}$$

5. Hixson- crowell model:

$$Q_O^{1/3}-Q^{1/3}=kt$$

In all mathematical equations, Q is the amount of drug released at time t, M_t is the drug released at time t, M is the total amount of drug in the dosage form, F is the fraction of the drug released at time t, K_0 is the zero order release rate constant, K_H is the Higuchi square root of time release rate constant, K_m is constant which depends on the geometry of the dosage form and n is the diffusion exponent indicating the mechanism of drug release. The value n = <0.45 indicates Fickian diffusion, the value of n between 0.45 and 0.89 indicates non-fickian diffusion and the value n = 0.89 indicates case-II transport.

Stability studies:[21, 22, 23]

A study of stability of pharmaceutical product is essential. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Stability studies are important to prevent economic repercussions may lead to considerable financial loss. From the point of view of safety to patient it is important that the patient receives a uniform dose of the drug throughout the shelf life of the product. The formulation stored at elevated temperatures such as 40^0C ± / 2^0C / 75% ±/ 5% RH for 3 months. The samples were withdrawn at end of 3 months checked for BLT, drug content

3. RESULTS AND DISCUSSIONS

Drug-excipients compatability studies:

FTIR studies indicated that the drug is compatible with the polymers.So,there is no interaction between drug and polymers. The results are mentioned in Fig. 01-04.

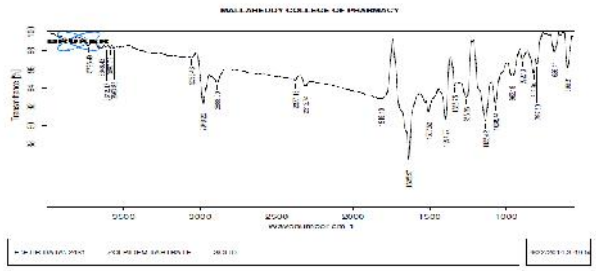

Fig 1: The FTIR spectra of zolpidem tartrate

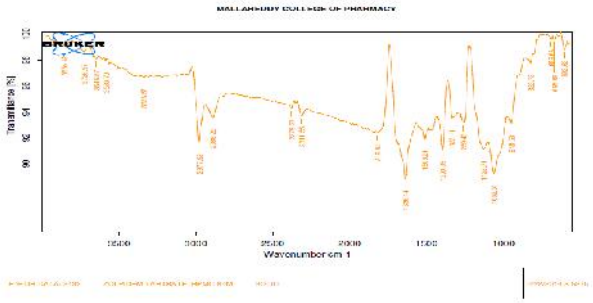

Fig 2: the FTIR spectra of zolpidem tartrates with HPMC K4M

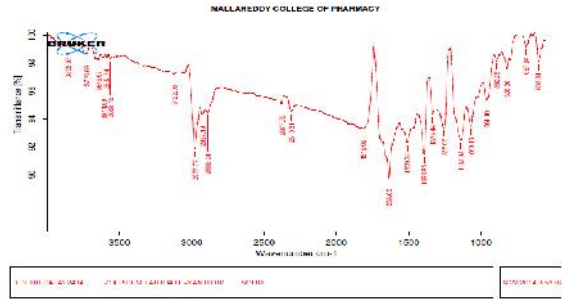

Fig 3: The FTIR Spectra of zolpidem tartrates with xanthan gum

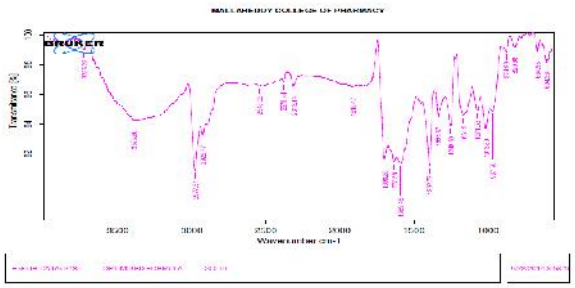

Fig 4: The FTIR Spectra of optimized formulation (F12)

Precompression parameters:

The powder such as like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were determined and the results were reported as shown in Table no 6.

Table: 6: Precompression parameters for the powder blend F1-F12

FORMULATION CODE	ANGLE OF REPOSE (Θ^0)	BULK DENSITY (gm/cc)	TAPPED DENSITY (gm/cc)	CARR'S INDEX (%)	HAUSNER RATIO (H_R)
F1	27.5±0.02	0.57±0.02	0.67±0.02	20.8±0.03	1.26±0.04
F2	25.1±0.03	0.52±0.04	0.68±0.01	16.1±0.03	1.29±0.04

F3	27.5±0.04	0.57±0.03	0.67±0.01	21.6±0.02	1.30±0.02
F4	26.1±0.01	0.58±0.01	0.73±0.01	21.1±0.02	1.32±0.01
F5	28.0±0.01	0.57±0.01	0.69±0.01	17.6±0.05	1.24±0.04
F6	29.7±0.02	0.55±0.02	0.73±0.02	24.7±0.04	1.22±0.05
F7	27.5±0.03	0.57±0.02	0.67±0.02	20.8±0.03	1.26±0.04
F8	25.1±0.04	0.52±0.04	0.68±0.02	16.1±0.03	1.29 ±0.04
F9	27.5±0.01	0.57±0.03	0.67±0.01	21.6±0.02	1.30±0.02
F10	24.6+0.60	0.58±0.08	0.73±0.02	21.1±0.05	1.22±0.09
F11	25.6+0.08	0.57±0.04	0.69±0.07	25.8±0.04	1.27±0.05
F12	26.8+0.04	0.55±0.09	0.73±0.04	17.6±0.08	1.25 ±0.03

*The values represent mean ± SD, n = 3.

The tablets were prepared by direct compression method. Thus the powder was evaluated for bulk density, tapped density, carr's index, Hausner's ratio and angle of repose.The bulk density and tapped density were tabulated and was found to be 0.52±0.04to 0.57±0.04 and 0.67±0.01to 0.73±0.04 respectively.Carr's index or compressibility index and hausner's ratio was found to be in between 16.1 ±0.03 to 25.8±0.04and 1.22±0.05to 1.30±0.02.The angle of repose for different formulations was less than 30^0, which indicates good flow properties of the powder. The values were found to be in between 24.6+0.60 to 29.7±0.02. All these results indicate that the powder possessed satisfactory flow properties.

Post compression parameters:

The properties of tablets such as thickness, hardness, friability, weight variation, buoyancy lag time total floating time and drug content for the formulations F1-F12 were determined and the results were reported as shown in Table no 7.

Table: 7: **Post compression parameters (F1-F12)**

Formulation (code)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Weight variation (mg)	Buoyancy lag time (sec)	Total floating time (Hrs)
F1	4.0±0.02	4.5±0.01	0.78±0.02	99.45±0.02	197±0.0230		>12hrs
F2	4.2±0.01	4.8±0.01	0.92±0.04	99.94±0.03	202±0.0270		>14hrs
F3	4.3±0.02	4.5±0.03	0.98±0.05	99.63±0.02	199±0.0350		>17hrs
F4	4.0±0.01	4.4±0.02	0.82±0.02	99.56±0.02	200±0.0131		>13hrs
F5	4.3±0.02	5.2±0.01	0.94±0.04	97.98±0.03	201±0.0216		>12 hrs
F6	4.2±0.01	4.8±0.02	0.86±0.03	98.85±0.02	197±0.0315		>12 hrs
F7	4.2±0.02	4.5±0.02	0.94±0.04	97.81±0.03	203±0.0169		>12 hrs
F8	4.3±0.01	4.4±0.02	0.93±0.05	99.83±0.03	201±0.0255		>18hrs
F9	4.3±0.02	4.4±0.01	0.97±0.05	99.55±0.02	199±0.0349		>17hrs
F10	4.5+0.01	4.8+0.01	0.85+0.02	98.22+0.04	199+0.0543		>12 hrs
F11	4.1±0.02	4.5±0.01	0.82±0.02	97.98±0.03	202±0.0248		>16hrs
F12	4.3±0.01	5.2±0.03	0.94±0.04	98.85±0.02	199±0.0359		>24hrs

*The values represent mean ± SD, n = 3.

The tablets of different formulations were evaluated for thickness, hardness, friability, weight variation test, drug content and *in-vitro* release studies. The thickness of the tablets was found to be in the range of 4.0±0.02mm to 4.5±0.01. According to the weight variation test in U.S.P., the percentage deviation of the tablets weighing in the range of 130-324mg is ±7.5%. The weight of all tablets were found to be within the above limit and hence all formulations passed the weight variation test as per the official requirements. Good uniformity in drug content was found amongst all formulations(F1-F12) and the drug content was more than 97%.The hardness of the tablets was found to be in the range of 4.5±0.01to 5.2±0.03kg/cm^2 **.**Tablet hardness is not an absolute indicator of strength. Another measure of tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered accepted. In the present study, the friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The buoyancy lag time for all formulations (F1-F12) were found to be in the range of 15 sec to 70 sec and total floating time for all the formulations(F1-F12) were found to be 12hrs to 24hrs. [24, 25, 26, 27]

***In-vitro* drug release studies:**

Primarily formulations were formulated by varying the concentration of two polymers and they are treated as trial formulations as they show burst release and relatively less sustainity, but all the formulations showed good floating lag time and buoyancy log time. In F1 - F6 formulation only HPMC k4M is used as a polymer which also showed burst release F1-81.1%,F2-77.1%,F3-74.2%,F4-73.1%,F5-84.1%,F6-87.6% but had good matrix integrity when compared to F7 - F12 formulations. In F7-F12 formulations only xanthan gum is used as polymer which showed burst release because of rapid swelling.F7-76.9%,F8-84.15%,F9-78.6%,F10-84.6%,F11-83.6%,F12-95.16%.By increasing the concentration of HPMC K4M in F1- F6 the burst release is controlled mostly when compared to previous formulations. For decreasing the burst release and improving the polymer ratio and improving sustained when xanthan gum concentration is increased slowly and finally optimized at F12 formulations amount of drug release (95.6%).

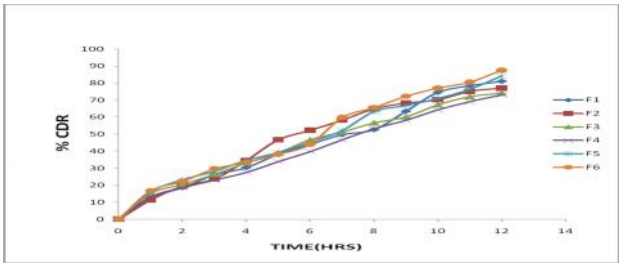

Fig 5: Comparative *In-vitro* Drug release for formulatons F1-F6 by using HPMC K4M

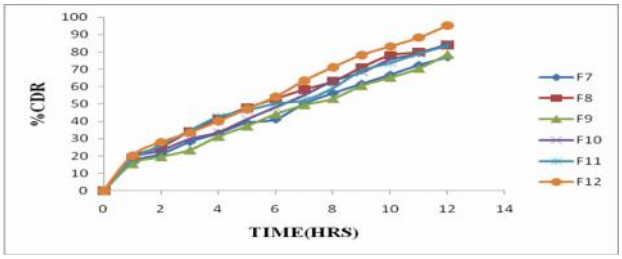

Fig 6: Comparative *In-vitro* Drug release for formulatons F7-F12 by using Xanthan Gum

On increase of the polymer HPMC K4M results the drug release decreases due to its formation of the thick micro gel formation. All batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. The tablets with high viscosity grade HPMC

K4M had less floating lag time but after adding xanthan gum in increased concentration lag time increased by a short duration but maintained good sustained. With reference to buoyancy studies it can be concluded that F12 formulation showed good floating lag time and total floating time. Thus a formulation F12 containing combination of sodium bicarbonate and citric acid with and xanthan gum was found to achieve optimum *in-vitro* buoyancy and floatability > 24hrs.

Stability studies:

The optimized formulation F12 stored at elevated temperature such as 40^0C ± / 2^0C / 75% ±/ 5% RH for 3 months. The results of stability studies revealed no physical appearance, hardness, drug content, buoyancy lag time, floating time and *in-vitro* drug release were determined. The results were shown in table 8.

Table 8: Stability studies of F12 at 40^0C ± / 2^0C / 75% ±/ 5% RH

Formulation F12	0 Month	1st month	2nd month	3rd month
Hardness(Kg/cm^2)	3.86 ± 0.08	3.86 ± 0.08	3.85 ± 0.02	3.85 ± 0.05
Drug content (%)	98.71	98.68	98.68	98.67
Buoyancy lag time	43 sec	43 sec	50 sec	55 sec
In vitro floating time	>12 h	>12 h	>12 h	>12 h
*in-vitro*drug release	95.6%	95.2%	94.6%	93.8%

The results of kinetic treatment applied to dissolution profiles of tablets of each batch were determined. The mechanism of drug release for optimized formulation F12 was found to be Non-Fickian diffusion transport with Zero order of release.The results are shown in table 9.

FORMULATION (CODE)	ZERO (r^2)	HIGUCHI (r^2)	PEEPAS (r^2)	PEEPAS n	FIRST (r^2)	HIXSON CROWEL(r^2)
F1	0.990	0.930	0.991	0.725	0.934	0.963
F2	0.961	0.940	0.983	0.877	0.947	0.961
F3	0.984	0.969	0.982	0.659	0.988	0.994
F4	0.993	0.945	0.977	0.689	0.978	0.989
F5	0.920	0.852	0.925	0.648	0.943	0.944
F6	0.982	0.937	0.953	0.727	0.959	0.976
F7	0.974	0.940	0.979	0.611	0.986	0.993
F8	0.980	0.973	0.989	0.606	0.978	0.986
F9	0.986	0.958	0.952	0.648	0.9822	0.990
F10	0.985	0.956	0.962	0.655	0.9696	0.985
F11	0.980	0.968	0.988	0.591	0.978	0.990
F12	0.983	0.966	0.980	0.621	0.952	0.982

Table: 9: ***In-vitro* drug release kinetics study of Formulation (F1-F12)**

4. CONCLUSION

FDDSs are promising dosage forms for zolpidem tartrate which could be a better alternative to the conventional oral dosage forms in order to improve bioavailability by increasing the gastric retention time of the drug and to minimize the side effects of the drug such as gastric bleeding and to prevent the development of drug resistance. Xanthan gum is suitable as compared to HPMC K4M polymer for the development of zolpidem tartrate floating tablets based on the results obtained. Zolpidem tartrate floating tablets prepared by employing Xanthan gum at concentration 57.5%w/w with 10% w/w sodium bicarbonate and 5% citric acid (F12) was the best formulation with desired *in-vitro* floating time and drug dissolution. Thus all the major objectives of this investigation were fulfilled.

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Conflict of Interest: None

Source of Funding: Nil