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Development of gastroretentive drug delivery system of ziprasaidone hydrochloride

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ABSTRACT

Ziprasidone hydrochloride is a psychotropic agent. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of Ziprasidone hydrochloride is desirable. The aim of the present work is to develop a hydrodynamically balanced drug delivery system based on the platform of direct compression. The system shall be designed to release at least 65% of the drug over a period of 8 hours and not less than 80% release in 12 hours. Sodium bicarbonate was incorporated as a gas-generating agent along with independent variables of natural resin olibanum, hydroxy propyl methyl cellulose (HPMC) grade K4M and hydroxy propyl methyl cellulose (HPMC) grade K100M at 25%, 35%, 45% and 60%, to achieve sustained release effect. The drug-excipient compatibility was studied with the help of Infrared-red spectroscopy. Dissolution studies using the USP basket method were performed at 37 ± 0.5 °C in 0.1N HCl and 2% SLS. Fourier transformer infrared spectroscopy (FTIR) was performed for the physicochemical interaction between drug and carrier, hence its effect on dissolution. It was observed that formulation containing 60% hydroxy propyl methyl cellulose (HPMC) grade K4M (F4) shows optimum sustained drug release pattern with adequate floating. Thus this technique can be successfully used for improvement of dissolution of ziprasidone hydrochloride.

Keywords: Ziprasidone hydrochloride, Olibanum resin, HPMC K4M, HPMC K100M, Direct compression technique.

INTRODUCTION

It is evident from the recent scientific and patient literature, that there is an increased interest in novel dosage forms that are retained for a prolonged and predictable period of time. Poor absorption of many drugs in the lower GI tract makes it necessary for controlled release dosage forms to be maintained in the upper GIT, particularly in the stomach and upper small intestine.

One of the approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT). Dosage forms with prolonged gastric residence and controlled drug delivery are called gastro retentive drug delivery systems (GRDDS), these are also known as gastro retentive dosage form (GRDF or GRDS). GRDFs extend significantly the period of time over which the drugs may be released. The various pharmaceutical approaches for gastro retention are classified as follows: Mucoadhesive systems, Modified shape systems, Altered density systems. Mucoadhesives enhances the efficacy of drug delivery, through an intimate and prolonged contact between the drug delivery device and the site of absorption. The dosage forms are coated with bioadhesive

polymers, so that it adheres to gastric mucosa, thus results in increased gastric retention time of the dosage form. Although this concept gains increasing interest in alternative routes of administration, only few approaches for prolonged gastric residence have been reported. Modified shaped systems/ unfolding system consist of compressed dosage forms, packed into capsules that expand rapidly after dissolution of the capsule. Drugs are of different geometric shapes, such as ring, cloverleaf, tetrahedron, disc, sphere, pellet etc. The structures generally expand from 1.6cm to 5.0cm. These systems unfold to a large size that prevents the passage of the dosage form through the pyloric sphincter. Drawback in this is that, the expanded material may reside in the stomach for a long period of time. Altered density systems owing to the differences in densities between the dosage form and the gastric fluid, there is a resulting force on the dosage form which maintains it away from the pyloric opening. When the buoyant force exerted by the gastric fluid is more than the weight of the dosage form, it results in flotation. If the force is less than the weight of the dosage form, it results in submersion. Altered density systems are generally of two types: 1. High density or non-floating drug delivery systems, 2. Low density or floating drug delivery systems (FDDS). 1. High density or non-floating drug delivery systems are retained in the bottom of the stomach. They use their weight as a retention mechanism. When the density of the dosage form is more than that of gastric juice, it sinks to bottom of the stomach, below the pylorus. 2. Low density or floating drug delivery systems (FDDS)

The density of these systems is less than that of gastric fluid, and remains buoyant in the stomach. They are also known as hydrodynamically balanced systems (HBS). Floating requires fed state of the stomach, so as to increase the gastric emptying time. If the difference in buoyancy force when the dosage form is entirely submerged and the weight of the dosage form is positive, it results in floating of the dosage form. Major requirements for FDDS formulations are, they must form a cohesive gel barrier, specific gravity must be less than that of gastric contents, should release contents slowly, such that it serves as a reservoir. They are generally classified into two main categories, effervescent or gas generating systems, non-effervescent systems. [1-3]

Direct compression tablets are compressed directly from powder blend of the active ingredients and suitable excipients. No pretreatment of the powder blends by wet or dry granulation procedure is necessary. Direct compression vehicles or carriers must possess good flow and compressible characteristics. The advantage of direct compression was made possible by the commercial availability of direct compression tablet vehicles that possess both fluidity and compressibility. Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with a suitable diluent that acts as a carrier or vehicle for the drug. [4-7]

The aim of the present study was to develop floating tablets of Ziprasidone HCl by direct compression method. Ziprasidone HCl whose physicochemical properties and short life makes it suitable candidate for floating drug delivery system and to achieve efficacious blood levels over long periods of time.

MATERIALS AND METHODS

Materials

Ziprasidone HCl was obtained from Aurobindo Pharma Ltd. as a gift sample. HPMC K4M and HPMC K100M were obtained from Dow chemicals, Chennai. Olibanum resin was obtained from Kanta chemicals pvt. Ltd., Delhi. All other chemicals used were of analytical grade.

Method

Calibration curves of Ziprasidone HCl were determined in 0.1 N HCl at 318 nm, using a UV-Visible spectrophotometer (Shimadzu, Japan). The calibration curve in 0.1 N HCl was used for dissolution studies.

Preparation of floating blend

The floating blend was prepared by taking Hydroxy propyl methyl cellulose (HPMC) grade 100M, Microcrystalline cellulose (MCC), Sodium bicarbonate (NaHCO_3) and Citric acid in a polythene bag and mix it.

Preparation of ziprasidone hydrochloride floating tablets

Ziprasidone hydrochloride tablets were prepared according to the composition of optimized batches (Table 1,2,3) Ziprasidone HCl tablets (500 mg) were prepared by the direct compression method. Initially, all ingredients were sieved through sieve no. 80, weighed and mixed for 10 min. The drug was mixed with olibanum resin, Hydroxy propyl methyl cellulose (HPMC) K4M, Hydroxy propyl methyl cellulose (HPMC) K100M, Floating blend. Finally

Magnesium stearate and aerosol was added as a lubricant and glidant, mixed for additional 2–3 min. Tablets were compressed on a tableting machine fitted with a 9mm circular shaped standard concave punch.

S.No	Ingredients	Quantity (mg)
1	HPMC K100M	60
2	MCC 102	300
3	Sodium bicarbonate	60
4	Citric acid	5

S.No	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1.	Ziprasidone HCl	80	80	80	80	80	80
2.	HPMC K4M	125	175	225	300	-	-
3.	HPMC K100M	-	-	-	-	125	175
4.	Olibanum resin	-	-	-	-	-	-
5.	Floating blend	294	244	194	119	294	244
6.	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
7.	Aerosil	0.5	0.5	0.5	0.5	0.5	0.5

S.No	INGREDIENTS	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
1.	Ziprasidone HCl	80	80	80	80	80	80
2.	HPMC K4M	-	-	-	-	-	-
3.	HPMC K100M	225	300	-	-	-	-
4.	Olibanum resin	-	-	125	175	225	300
5.	Floating blend	194	119	294	244	194	119
6.	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
7.	Aerosil	0.5	0.5	0.5	0.5	0.5	0.5

Characterization of ziprasidone HCl floating tablets[7]

The prepared Ziprasidone HCl tablets were tested for physical characteristics, viz., weight variation (measured using weighing balance, Mettler Toledo Pvt. Ltd., Mumbai, India), thickness (measured using a vernier caliper), hardness (measured with a hardness tester, Monsanto, Dolphin Ltd., Mumbai, India) and friability (determined using a Roche friabilator, Mumbai, India).

Content uniformity

Twenty tablets were weighed and the power equivalent to 80mg of Ziprasidone HCl was taken in 100ml volumetric flask containing 80ml of methanol. The content were shaken well for 30 minutes and made up to the volume with saline buffer pH 7.4 solutions and determined the Ziprasidone HCl content by measuring the absorbance at 318nm.

In vitro buoyancy studies

The *in-vitro* buoyancy was determined by floating lag time and floating time. The tablets were placed in dissolution vessel containing 900 ml of 0.1 N HCl. The time required for the tablets to rise to the surface and a float was determined as floating lag time. The duration for which the tablet remains afloat on surface of solution is known as floating time.

In vitro dissolution studies

The release rate of Ziprasidone Hcl floating matrix tablet was determined using USP Dissolution testing apparatus (basket type). The dissolution test was performed using 900 ml of 0.1 N HCl and 2% SLS, at $37 \pm 0.5^\circ\text{C}$ and speed of 50 rpm. Aliquots of 10 ml samples were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating basket not less than 1 cm apart from the vessel wall at one hour interval and were replaced with fresh dissolution medium for 12 hours. Absorbance of these solutions was recorded at 318 nm using UV spectrophotometer.

Analysis of Dissolution data: release kinetics[8,9,10,11]

Drug content in dissolution sample was determined by release kinetics. The dissolution data obtained was fitted to zero order, first order, Higuchi, Hixson- Crowell model and Korsmeyer-peppas to understand the order and mechanism of drug release from the tablets.

$$Q_t = Q_0 + K_0t \text{ -----Zero order kinetic}$$

Where, C is the drug conc. at time t , C_0 is the initial drug conc. and K_0 is the zero-order rate constant expressed in units of concentration/time.

$$\text{Log}C = \text{Log}C_0 - Kt / 2.303 \text{ ----- First order kinetics}$$

Where, C_0 is the initial concentration of drug, K is the first order constant and t is the time in hours.

$$Q_t = Kt^{1/2} \text{ ----- Higuchi model}$$

Where, Q_t is the amount of the release drug in time t , K is the kinetic constant and t is time in hours.

$$W_0^{1/3} - W_t^{1/3} = K_s t \text{ ----- Hixson- Crowell model}$$

Where, W_0 is the initial drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form, t is time and K_s is the constant incorporating the surface- volumerelation.

$$M_t / M_\infty = Kt^n \text{ ----- Korsmeyer- peppas model}$$

Where, M_t represents amount of the released drug at time t , M_∞ is the overall amount of the drug (whole dose) released after 12 hrs, K is the diffusional characteristic of drug/ polymer system constant, n is a diffusional exponent that characterizes the mechanism of release of drug.

Accelerated stability studies[15]

Formulation F4 was identified as the most promising formulation. This formulation was scaled up to a batch size of 1000 tablets size of three batches. These 3 batches of tablets were filled in 90 cc HDPE containers, 30's count/container. The samples were incubated at 40°C/75% RH incubators after initial testing. Samples were withdrawn at 1M, 2M and 3M intervals and tested for drug content and in vitro dissolution profile testing.

Table 4: Formula for the preparation of ziprasidone HCl tablets		
Ingredients	Quantity for 1 tab(mg)	Quantity for 3000 tab(gm)
Ziprasidone HCl	80	240
HPMC K4M (60%)	300	900
Floating blend	119	357
Magnesium stearate	0.5	1.5
Aerosil	0.5	1.5

The Ziprasidone HCL (80mg) tablets were prepared and tablets of each batch were filled in 90 cc HDPE containers 30's count/container. The containers were capped, induction sealed, and subjected to initial analysis. Based on the results of the initial testing, the batches were loaded in to stability chambers of 40°C/75% RH and 25°C/65% RH. Samples were withdrawn as per the sampling plan and subjected to analysis. The 3 months compiled stability data is given in **Table 5**.

S.No	Stability Condition	Sampling time point		
1	25°C/65% RH			3 rd Month
2	40°C/75% RH	1 st Month	2 nd Month	

RESULTS AND DISCUSSION

Absorption of Ziprasidone HCl floating tablets

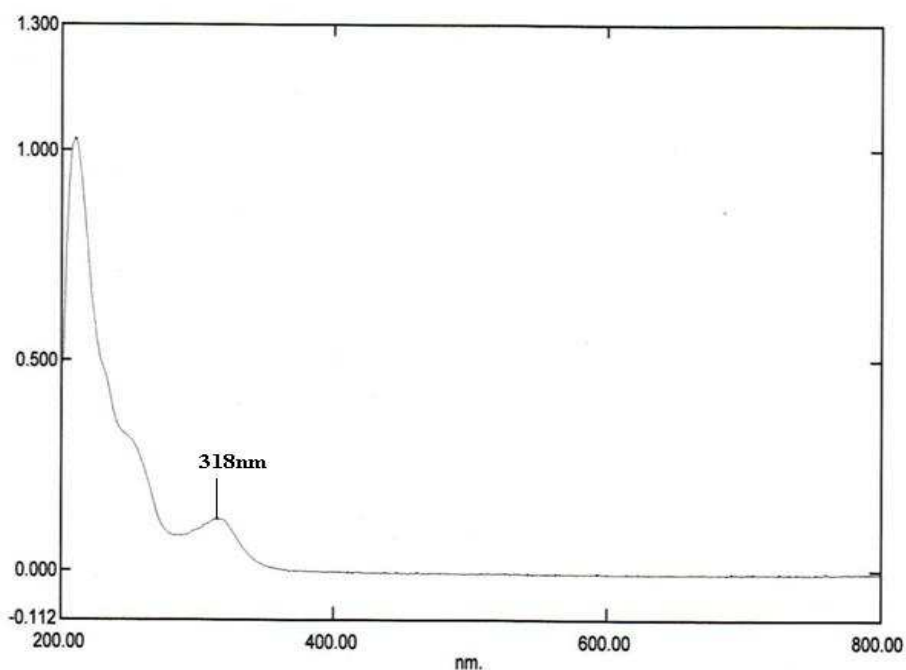


Fig no 1: UV absorption spectrum of Ziprasidone HCl in 0.1N HCl shows λ max at 318 nm

S.No	Concentration(μ g/ml)	Absorbance
1	10	0.1445
2	15	0.2113
3	20	0.2819
4	25	0.3530
5	30	0.4187

Physical characterization of the tablets

Tablet weight of all the formulations was found to be 500.0 ± 2.0 mg. Tablet thickness was found to be 4mm. The hardness of the formulation was 5.4 to 6.8 kg/cm², indicating satisfactory mechanical strength. Percentage mass loss in the friability test was 1% in all cases, which was an indication of good mechanical resistance of the tablet. Drug content of all tablets was found between 96.89 % to 100.10 % which is in limits of pharmacopoeia specifications (95% to 101%).

FTIR spectroscopy study

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. It can be concluded that there was no interference in the functional group as the principle peaks of the Ziprasidone HCl was found to be unaltered in the drug-polymer physical mixtures, indicating they were compatible.

In vitro buoyancy studies

The results of in vitro buoyancy studies showed quick floating of the tablet within 2 min after placing the tablet in dissolution medium (Fig 3). Floating lag time varied between 1.5 min to 3.8 min. Buoyancy mainly depended upon

the presence of sodium bicarbonate. Citric acid produces swelling of the tablet while sodium bicarbonate has the ability to generate gas in the presence of acid, which gets entrapped in the tablet. This leads to reduction in the density of the tablet, thereby producing floating.

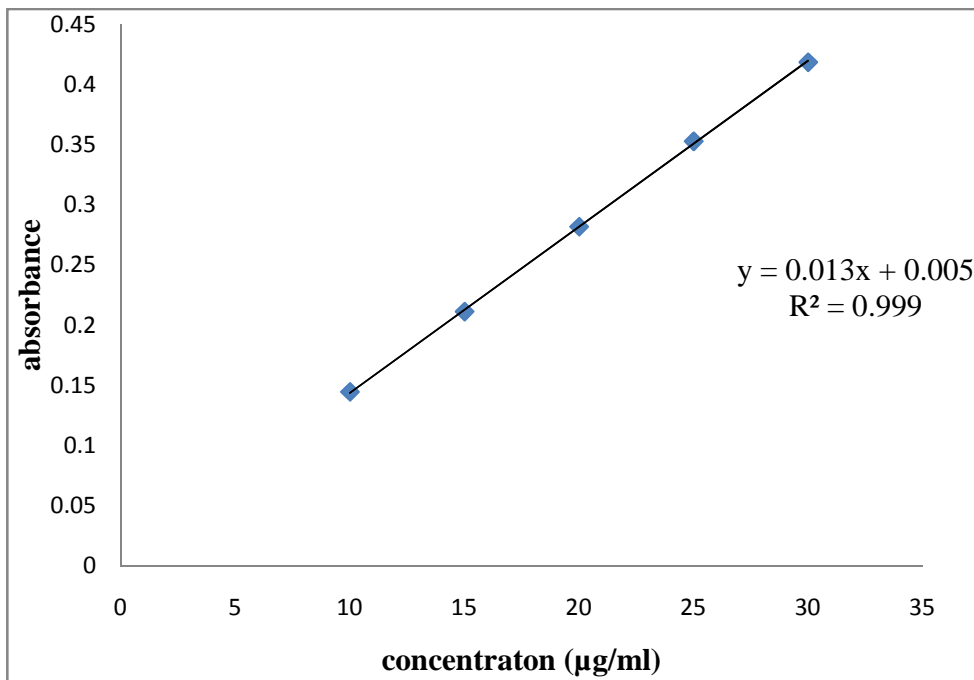


Fig no 2: calibration curve of Ziprasidone HCl in 0.1N HCl at 318 nm

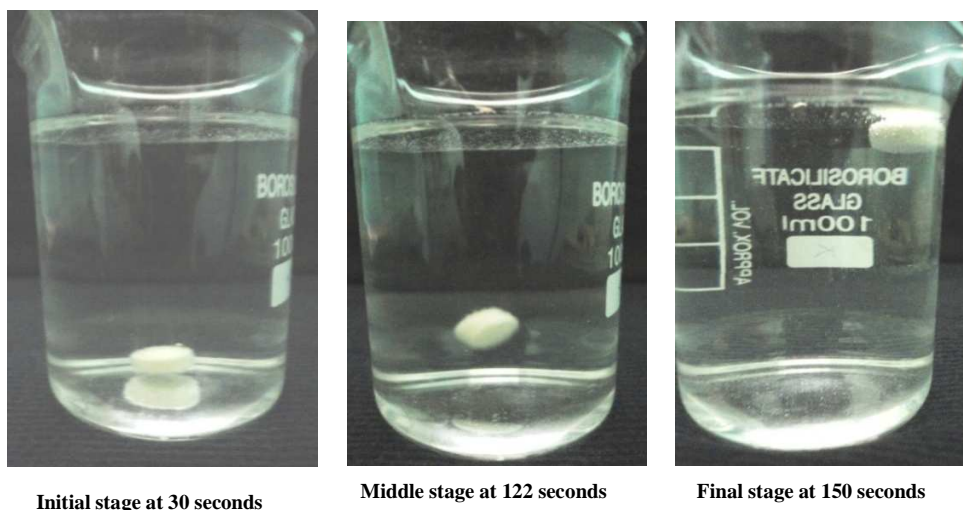


Fig no 3: *In-vitro* buoyancy studies of tablets of formulation

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

In-vitro drug release studies of all the formulation of Ziprasidone HCl tablets were carried out in 0.1 N HCl and 2% SLS. The study was performed for 8 hrs and cumulative drug release was calculated at different time interval. This showed that polymers hydrated more rapidly with high amount of SLS in the presence of 0.1 N HCl. Results were given in the Table 7 and 8 ,Figure 4.

Table 7: cumulative percentage drug release of the formulations F1 to F6

TIME (hrs)	Cumulative % drug release					
	HPMC K4M				HPMC K100M	
	F1 (25%)	F2 (35%)	F3 (45%)	F4 (60%)	F5 (25%)	F6 (35%)
0	0	0	0	0	0	0
0.5	57.56	35.68	25.8	10.08	23.25	12.23
1	78.34	40.89	35.57	23.89	43.62	19.07
2	87.56	57.8	60.98	32.47	65.33	29.81
4	90.07	95.1	80.46	61.22	78.62	51.45
8	100	100	93.89	86.64	90.62	76.69

Table 8: cumulative percentage drug release of the formulations F7 to F12

TIME (hrs)	Cumulative % drug release					
	HPMC K100M		Olibanum resin			
	F7 (45%)	F8 (60%)	F9 (25%)	F10 (35%)	F11 (45%)	F12 (60%)
0	0	0	0	0	0	0
0.5	3.2	2.13	66.67	49.48	32.34	18.68
1	8.16	5.41	76.67	69.48	52.34	35.68
2	16.23	12.55	86.84	78.56	68.51	60.67
4	35.04	20.78	98.56	97.61	88.76	87.54
8	64.29	40.97	100	100	97.25	92.29

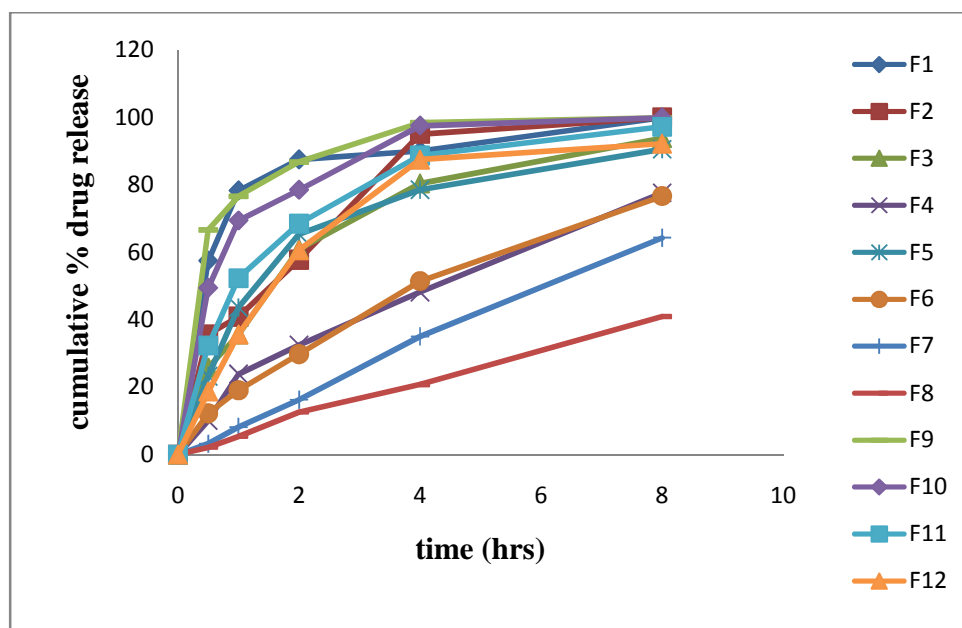


Fig no 4: comparison of dissolution profiles of formulations F1to F12

The drug release patterns from all the formulations are shown in **Tables 5 and 6**. The percent drug release after 8 hours is as shown in **Figure 4**. The formulations F1, F2, F5, F9 and F10 was found to release 50% of the drug in very short time and released 100% of the drug at the end of 8th hour, this was due to the less amount of polymer, the rapid drug release from the tablet, during the process of floating and hence no control over the drug release was achieved. From the drug release profile of F9 to F12, it was the formulation containing olibanum resin as a polymer which shows rapid drug release. This indicates that olibanum resin does not have control over the drug release. From the comparison of targeted release profile, it was observed that the formulation F4, which contain 60% of HPMC K100M shows acceptable range of drug release from the tablet and also floating more than 12 hours. It was observed that when the concentration of the polymer increases the drug release rate decreases.

Drug release kinetics

The results of kinetic models for Ziprasidone HCl release from floating matrix tablets are shown in **Table 9 and 10**. The coefficient of determination (R^2) was used as indicator of the best fitting for each of the models considered. To explore the mechanism of drug release, the results of in vitro data were fitted into the zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models. The results revealed that formulations F1, F2, F4, F8, F10 and F12 of floating matrix tablets were best fitted for the Hixson crowell model. Formulations F3 and F5 were best fitted for the Higuchi model. Formulations F6 and F9, F11 were best fitted for korsmeyer-peppas model. Formulation F7 is best fit for Zero order.

Code	Zero order	First order	Higuchi	Hixon crowell	Korsmeyer-peppas		Best fit model
					R^2	n	
F1	0.4604	-	0.7464	0.8884	0.8626	0.180	Hixon crowell
F2	0.7750	-	0.9455	0.9793	0.468	0.419	Hixon crowell
F3	0.8026	0.9895	0.9662	0.9474	0.9646	0.491	Higuchi
F4	0.9545	0.9906	0.9816	0.9896	0.9662	0.690	Hixon crowell
F5	0.7403	0.9522	0.9377	0.8925	0.9122	0.478	Higuchi
F6	0.9628	0.9960	0.9812	0.9955	0.9982	0.673	Peppas

R² – coefficient of determination, n- release exponent of korsmeyer – peppas

Code	Zero order	First order	Higuchi	Hixoncrowell	Korsmeyer-peppas		Best fit model
					R^2	n	
F7	0.9975	0.9913	0.9158	0.9971	0.9952	1.072	Zero
F8	0.9961	0.9961	0.9218	0.9973	0.9876	1.047	Hixoncrowell
F9	0.4370	-	0.7288	0.8813	0.9527	0.153	Peppas
F10	0.5639	-	0.8377	0.9359	0.9223	0.252	Hixoncrowell
F11	0.7121	0.9861	0.9315	0.9216	0.9411	0.394	Peppas
F12	0.7692	0.9155	0.9341	0.8747	0.9255	0.590	Hixoncrowell

R² – coefficient of determination, n- release exponent of korsmeyer – peppas

For matrix tablets, an “n” value near to 0.5 indicates diffusion control and an “n” value near to 1 indicates relaxation or erosion control. The intermediate value suggests that diffusion and erosion contributes to overall release mechanism. A value of “n” for all matrices studied here was ranged between 0.180 to 1.012 indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism. It was also observed that highest correlation was found for Peppas log time profile for formulations F7 ($R^2 > 0.99$), which indicates the drug release via diffusion mechanism from hydrophilic matrices. When the hydrophilic polymer tablets come in contact with the dissolution medium, they take up water and swell, forming a viscous gel barrier. In case of hydrophilic matrix tablets, the initial swelling may aid dissolution of the drug, and the dissolved drug diffuses out of the swollen gel barrier into the dissolution medium.

Matrix integrity:

It was found that the swollen mass of the tablets remains intact throughout the dissolution studies, revealing good matrix integrity.

Accelerated stability studies

Test	Specifications	Initial	40°C/75% RH			25°C/65% RH
			1M	2M	3M	
Assay (% w/w)	95 to 105	98.96	98.86	97.23	97.57	3M
Dissolution profile	Time Range (h) (%)					
	0 0	0	0	0	0	0
	1 10-30	24.89	24.62	23.99	24.20	24.35
	2 25-55	32.40	31.39	32.15	31.62	31.52
	4 50-85	51.10	50.99	50.56	51.58	50.98
8 85-100	86.10	85.09	84.99	85.65	84.38	

M- months, RH- relative humidity

This study indicates that the process for preparing tablets is reproducible and gives excellent results. The 3 months accelerated stability data indicates that the formulation is stable as far as the assay is concerned and the dissolution profile is within the acceptable limits of the Target Product Profile at the end of 3 months.

CONCLUSION

The hydro dynamically balanced dosage form of Ziprasidone HCl was targeted to be developed using direct compression technique. Ziprasidone HCl was formulated as a sustained release tablet. This was enrobed in a coating matrix containing HPMC of different viscosity grades mixed with a gas generating system. The purpose of fabricating the formulation in this manner was to ensure that the content uniformity of the potent drug was dependent on mixing of the drug with the polymeric layer. The product was designed as tablet of 500 mg sustained release tablet containing 80 mg drug. The effect of different viscosity grades of HPMC and olibanum resin in the tablet was evaluated at 0% to 60%. It was observed that formulation (F4) containing HPMC K4M 60% alone gave the acceptable release profile. The effect of three different levels of HPMC K4M in the tablet was evaluated at 25%, 35% and 45% and 60%. The results show that only formulation (F4) with 60% K4M were acceptable. Reproducibility of F4 was studied by scaling it up to 1000 tablet batch size and fabricating 3 consecutive batches. These batches were incubated at accelerated stability study for 3 months in HDPE container. The three month accelerated stability data indicates that is product has acceptable stability as far as assay and dissolution profile is concerned.

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