

Original Article

Formulation and evaluation of controlled floating tablet of Alprazolam

Anupam K. Sachan, Swati Singh*

Dayanand Dinanath College, Institute of Pharmacy, Ramaipur, Kanpur, India.

*Corresponding Author: Tel.: +91 9005614409, E-mail address: 00swatisingh@gmail.com

ARTICLE INFO

Received 8 July 2016

Revised 24 July 2016

Accepted 28 July 2016

Keywords:

- Floating tablets
- Alprazolam
- HPMC
- In-vitro buoyancy
- Release kinetics

ABSTRACT

The objective of this work was to formulate and evaluate a floating drug delivery of alprazolam. Gastroretentive floating tablets of alprazolam were prepared by direct compression method employing three different polymers (HPMC K100M, HPMC K15M and HPMC K4M), which prolonged the drug release from the dosage forms. Tablets were prepared by the direct compression technique, using polymers such as different grades of HPMC. The buoyant layer, prepared with hydroxypropyl methylcellulose HPMC, citric acid, and sodium bicarbonate, provides buoyancy to increase the retention of the oral dosage form in the stomach. Tablets were evaluated for their physical characteristics, viz., hardness, thickness, friability, and mass variation, drug content and floating properties. The prepared tablets were characterized and found to exhibit satisfactory physico-chemical characteristics. The properties of the tablets in terms of floating lag time, floating time and in-vitro release were evaluated. The optimized formulation (F9) exhibited 99.01% drug release in 24 hrs, while the buoyancy lag time was 2.66 min. In-vitro drug release kinetics was found to follow the Korsmeyer and Peppas equation.

1. INTRODUCTION

All the drug delivery systems aim at providing adequate drug concentration at site of action and maintain the desired drug concentration. A good knowledge about the physiological and biological parameter of the drug is the key parameter for developing the drug delivery system. Major difficulties of the oral drug delivery are physiological due to the failure to maintain and localize the drug delivery system within the desired region of GIT. These difficulties are due to variation in gastric emptying, leading to non-uniform absorption profile, shorter residence time of the dosage form in the stomach and insufficient drug release [1]. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste and improves solubility of the drug [2]. Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs that are preferentially absorbed from upper GIT [3]. To formulate a successful gastroretentive drug delivery system, several techniques are currently used such as floating drug delivery system, low density systems, raft systems incorporating alginate

gel, bioadhesive or mucoadhesive systems, high density systems, superporous hydrogel and magnetic system. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration [4].

Alprazolam (ALP) {8-chloro-1-methyl-6-phenyl-4H-s-triazolo(4,3-a)(1,4)benzo diazepine} belongs to the class of benzodiazepine with anxiolytic, muscle relaxant, anticonvulsant properties which is generally used as a hypnotic and as a tranquilizer. It is most frequently prescribed in the therapy of anxiety as being relatively safe with mild side effects. It has no appreciable solubility in water at physiological pH. It is rapidly and completely absorbed after oral administration, with peak levels in plasma occurring within 1–2 h after oral administration. The predominant metabolites in human plasma are α' -hydroxy alprazolam, 4-hydroxyalprazolam and α' -benzophenone.

The pharmacological activity of α' -hydroxyalprazolam and 4-hydroxyalprazolam is about 60% and 20% less than that of alprazolam, respectively, and the benzophenone is essentially inactive. Alprazolam was found to be highly photolabile and special care should be taken to avoid light exposure during its storage and handling [5]. The recommended initial adult dose for anxiety is 0.25–0.5 milligrams (mg) taken three times daily. This dosage may be increased every three to four days to a maximum total of 4 mg daily [6]. However, the three times a day dosing regimen often tends to poor patient compliance. Studies have shown that patient compliance increases as the dosing regimen goes from three times a day to twice or once a day. Therefore, a dosage form that reduces the alprazolam daily dosing regimen, while maintaining a stable plasma level of alprazolam i.e. a sustained release form, would be advantageous.

2. MATERIALS AND METHODS

Alprazolam was received as a gift sample from Alembic Limited, Vadodara, India. HPMC (K4M, K15M and K100M) were purchased from Sigma Aldrich, India. Microcrystalline Cellulose Powder PH 101 was obtained from Sigachi Chemicals, India. Magnesium stearate, hydrochloric acid, sodium bicarbonate and citric acid anhydrous (hereafter referred to as citric acid) were purchased from S.D. Fine-Chem Ltd., Ahmedabad, India. Purified talc was purchased from E. Merck (India) Ltd., Mumbai. All other ingredients were of laboratory grade.

Preparation of standard curve of Alprazolam: 100 mg of alprazolam was taken in a 100 ml volumetric flask and hydrochloric acid buffer pH – 1.2 was added into it. Then volume was made up to the mark by same solution. Different concentrations of alprazolam ranging from 2.0 to 10.0 $\mu\text{g/ml}$ were obtained. Then the absorbance of the solutions was recorded at 260 nm. The absorbance vs. concentration curve was plotted (Fig. 1)

Preparation of Alprazolam floating tablets: Floating tablets containing alprazolam were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and citric acid. Sodium bicarbonate was incorporated as an effervescent substance to aid buoyancy to the dosage form. Citric acid was used as acid source. Magnesium stearate (2% w/w) was employed as a lubricant. All the powders were accurately weighed and passed through a 40

mesh sieve. Then, except magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The blend was compressed into tablets having average weight of 250 mg using a ten station tablet punching tableting machine fitted with a 9 mm concave punches [7]. The compositions of all formulations are given in Table 1.

Pre-compression evaluation: Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner ratio were calculated. While the flow properties of the powder blend were accessed from the angle of repose.

Evaluation of floating tablets: The prepared tablets were evaluated for their physical parameters like hardness, thickness, weight variation and friability.

Weight variation: To study weight variation, twenty tablets of each formulation were selected from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this, percentage weight difference was calculated and then checked for USP specifications.

Tablet dimensions: Thickness and diameter of tablets was determined using Vernier calliper. Ten tablets were selected randomly for this test and the average value was reported.

Hardness and friability: Hardness of ten tablets of each formulation was determined using Monsanto hardness tester. Friability of twenty tablets was determined using the Roche friabilator. This test subjects a number of tablets to the combined effect of shock and abrasion by utilizing a plastic chamber which revolves at speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche friabilator, which was then operated for 100 revolutions for 4 min. The tablets were then dusted and reweighed [8].

In-vitro buoyancy studies: The *in-vitro* buoyancy test was determined by floating lag time. The tablets were placed in a 100-ml beaker containing 0.1 N HCl (pH 1.2). The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the time for which the tablet constantly floats on the surface of the medium (duration of floating), was measured [9].

Table 1. Composition of floating tablets of alprazolam

Formulation code	Alprazolam (mg)	HPMC K100M (mg)	HPMC K15M (mg)	HPMC K4M (mg)	NaHCO ₃ (mg)	Citric Acid (mg)	MCC (mg)	Magnesium Stearate (mg)	Talc (mg)
F1	1	70	-	-	40	25	105	4	5
F2	1	80	-	-	40	25	95	4	5
F3	1	90	-	-	40	25	85	4	5
F4	1	-	70	-	40	25	105	4	5
F5	1	-	80	-	40	25	95	4	5
F6	1	-	90	-	40	25	85	4	5
F7	1	-	-	70	40	25	105	4	5
F8	1	-	-	80	40	25	95	4	5
F9	1	-	-	90	40	25	85	4	5

Swelling study: The floating tablets were weighed individually and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at $37 \text{ }^\circ\text{C} \pm 1 \text{ }^\circ\text{C}$. At selected intervals, the tablets were withdrawn from beaker, and the excess surface liquid was removed carefully using the tissue paper. The swelling index was calculated using equation: $(W_t - W_0 / W_0) \times 100$. Where W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t.

Content uniformity test: Twenty tablets were finely powdered; quantities of the powder equivalent to 5 mg of alprazolam were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with 0.1N HCl (pH 1.2 buffer) solution and mixed thoroughly. The solution was made up to volume 100ml and filtered. Dilute 1 ml of the resulting solution to 10 ml with 0.1N HCl. The absorbance of the resulting solution was measured at 260 nm using a Shimadzu UV-visible spectrophotometer.

In-vitro dissolution studies: The *in-vitro* dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 50 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at $37 \text{ }^\circ\text{C} \pm 0.5 \text{ }^\circ\text{C}$. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 24 hrs and the same volume was replaced with pre-warmed fresh dissolution media. The samples were filtered through a whatman filter paper and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 260 nm using a UV spectrophotometer [10].

3. RESULTS AND DISCUSSION

Pre-compression parameters

The results of pre-compression evaluation parameters are shown in Table 2. The powder mixtures of all the formulations were tested by various studies including angle of repose (ranging from 22.29° to 29.88°), bulk density (ranging from 0.32 to 0.48 gm/ml), tapped density (ranging from 0.40 to 0.59 gm/ml), Hausner's ratio (ranging from 1.20 to 1.33) and Carr's index (ranging from 13.46 to 25%). Angle of repose of all the formulations was found to be less than 30° , which indicates a good flow property of the powders. Carr's index greater than 25% indicates of poor flowability and below 15% of good flowability. A Hausner ratio greater than 1.25 is an indication of poor flowability. All the results showed moderate flow property.

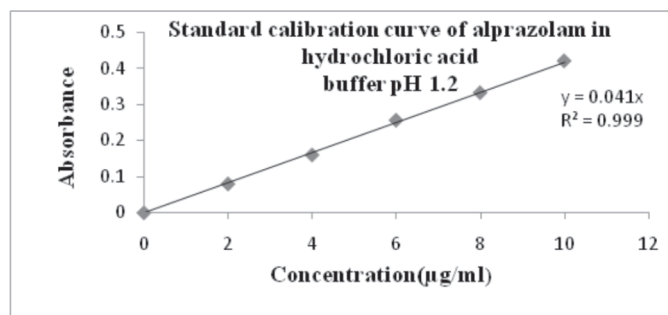


Fig. 1. Standard Curve of Alprazolam in Hydrochloric acid buffer pH 1.2

Physical parameters of the prepared tablets

Table 3 shows post compressional parameters of the prepared tablets. The hardness of the tablets was found to be $4.20 \pm 0.33 - 5.00 \pm 0.17 \text{ kg/cm}^2$ and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be $3.41 \pm 0.03 - 3.59 \pm 0.06$. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits.

Buoyancy lag time studies

All tablet formulations exhibited satisfactory floatation ability and remained buoyant for 10-24 h in the dissolution medium (Table 4). The buoyancy lag time of tablets depends on the amount of sodium bicarbonate and citric acid involved in CO_2 formation and the concentration of polymers used. All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (methocel), thus decreasing the density of the tablet below 1 and tablet becomes buoyant [11]. The optimized concentration of sodium bicarbonate was found to be 16% of total tablet weight and it was maintained constant in all the floating tablets prepared. From the buoyancy studies (as indicated in Table 4), it was evident that all the formulations showed similar buoyancy times (over 20 h).

Table 2: Pre-compression properties of prepared blends

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose ($^\circ$)	Compressibility index	Hausner's ratio
F1	0.36	0.48	24.47	25	1.33
F2	0.39	0.48	27.66	18.75	1.23
F3	0.41	0.52	22.53	21.05	1.26
F4	0.38	0.47	29.88	19.14	1.20
F5	0.40	0.49	27.10	18.36	1.22
F6	0.32	0.40	22.29	20	1.22
F7	0.33	0.40	26.45	17.73	1.21
F8	0.45	0.52	27.20	13.46	1.15
F9	0.48	0.59	25.12	18.60	1.22

Table 3. Post-compression evaluation parameters of designed formulations (F1–F9) ($n = 3$)

Formulation code	Thickness (mm)	Hardness (kg/cm ²)	Weight variation	Friability (%)	Drug Content (%)
F1	3.41±0.03	4.20±0.33	249±0.09	0.561	97.19±2.08
F2	3.45±0.02	4.81±0.25	252±0.10	0.450	97.01±1.01
F3	3.50±0.05	4.30±0.24	251±0.16	0.575	98.14±3.85
F4	3.52±0.01	4.60±0.66	254±0.12	0.489	95.45±2.18
F5	3.53±0.04	4.50±0.12	252±0.19	0.621	95.01±2.56
F6	3.55±0.03	4.80±0.31	250±0.16	0.415	94.99±2.17
F7	3.51±0.04	4.70±0.12	253±0.14	0.465	96.19±3.04
F8	3.59±0.06	4.90±0.44	251±0.18	0.698	94.14±2.19
F9	3.65±0.04	5.00±0.17	250±0.05	0.319	99.0±2.01

Table 4. Floating lag time, total floating time and swelling index of designed formulations (F1–F9)

Formulation code	Floating lag time (min)	Total floating time (min)	Swelling index (%)
F1	2.10	> 16 hrs.	80 ± 3.2
F2	2.09	> 20 hrs.	92 ± 0.12
F3	2.48	> 24 hrs.	112 ± 0.41
F4	2.14	> 20 hrs.	121 ± 5.2
F5	2.60	> 24hrs.	97 ± 2.1
F6	2.14	> 24 hrs.	93 ± 6.9
F7	2.48	> 20 hrs.	138 ± 1.9
F8	2.76	> 24 hrs.	121 ± 2.5
F9	2.66	> 24hrs.	99 ± 1.0

Hence, the differentiating factor to choose the optimal formulation was taken as the drug release criterion in 24 h buoyancy period.

Swelling studies

Swelling of tablets is a direct indication of amount of water uptake by the tablets. Water uptake studies showed that formulation with high percentage of HPMC imbibed more water and were swollen to greater extent than formulation with low percentage of HPMC. The formulations with HPMC K4M and HPMC K100M showed significant swelling and good tablet integrity. The formulations with HPMC K100M showed higher swelling compared to formulations with K4M, K15M. The swelling index

of the tablets increases with an increase in the polymer viscosity grades. The percentage water uptake of the formulations ranged from 80±3.2 to 138±1.9% [Table 4]. The formulation F7 shows maximum swelling index.

In-vitro drug release studies

The results of *in-vitro* dissolution studies are given in Table 5. Though formulations F1, F2 and F3 showed good release characteristics, more than 90% of drug was released before 16 hr period which is undesirable, while, formulations F4-F6 showed less than 90% drug release even after 12 hr. The presence of HPMC K4M increased the release rate and extent compared to

Table 5. Cumulative percent drug release of designed formulations (F1- F9)

Sampling Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	34.45	14.68	10.45	21.31	28.03	20.2	32.1	15.02	7.3
2	37.45	27.96	4.27	25.35	33.27	32.4	36.84	20.15	9.9
3	42.33	38.66	24.25	34.97	36.22	39.8	42.75	24.45	15.9
4	47.9	50.57	34.43	40.44	42.16	45.2	46.23	30.2	21
5	53.78	61.02	45.12	47.15	46.36	51.6	49.81	37.3	22.9
6	58.68	73.11	56.1	54.97	50.16	62.8	54.12	43.2	30
8	66.92	85.38	68.85	65.54	54.24	69.23	61.23	55.02	38
10	75.36	91.01	76.01	78.1	62.52	72.5	68.12	69	47
12	85.21	96.14	80.14	80.12	68.99	80.12	74.12	77	55.01
16	96.12	97.72	92.1	84.16	76.12	86.23	82.78	85.4	72.89
20	-	-	98.27	86.13	86.56	91.02	94.25	91.7	89
24	-	-	-	88.14	94.14	93.45	97.1	95.6	99.01

HPMC K15M and K100M. By comparing three different grades of HPMC (K4M, K15M and K100M), we concluded that low-viscosity grade HPMC K4M provided better release characteristics and showed good *in-vitro* buoyancy [3]. Formulations F9 were chosen as optimal based on the ability of it to sustain drug release up to 24 hr period as evident from Table 5 and Fig. 2.

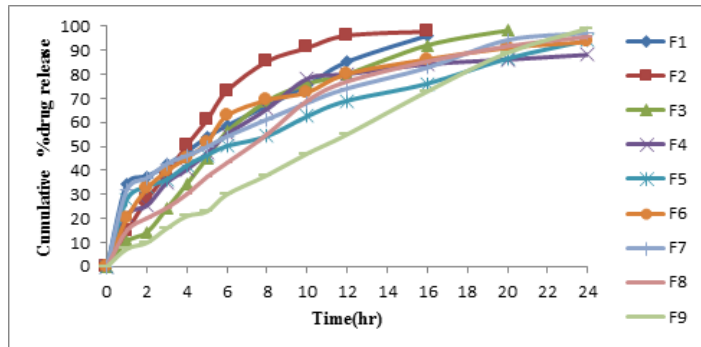


Fig. 2. *In-vitro* drug release profiles of designed formulations (F1-F9) of alprazolam

Drug release kinetics

The *in-vitro* drug release data of the optimized formulation (F9) was fitted in to zero order, first order, Higuchis model and

Korsmeyer-peppas model and the values of slope, intercept and r^2 were calculated in each case. Optimized formulation F9 fitted best for Korsmeyer – Peppas equation with r^2 value of 0.992. The ‘n’ values of Korsmeyer–Peppas model for the best formulations were in the range of 0.45–0.85. Therefore, the most probable mechanism of release was non-Fickian diffusion or anomalous diffusion.

4. CONCLUSION

The floating tablets of alprazolam were prepared by direct compression method based on effervescent approach using different grades of HPMC (HPMC K100M, HPMC K15M and HPMC K4M). The addition of gel forming polymer (HPMC) and gas generating agent sodium bicarbonate along using citric acid was essential to achieve *in vitro* buoyancy. Formulated tablets gave satisfactory results for various physicochemical evaluations for tablets like tablet dimensions, hardness, weight variation, floating lag time, total floating time, content uniformity and *in vitro* drug release. Formulation F9 gave better sustained drug release and floating properties in comparison to other formulations. The most probable mechanism that the release patterns of the formulations followed was non-Fickian diffusion or anomalous diffusion.

Table 6. Kinetics of *in-vitro* release from optimized formulation F9

Formulation code	Zero order R2	First order R2	Higuchi kinetics R2	Korsmeyer–Peppas	
				N	R2
F9	0.990	0.819	0.976	0.85	0.992

REFERENCES

- [1] Sudheer, P.; Kumar, H.; Thomas, L. and Nethravathi, D. R. Floating microspheres - An excellent approach for gastric retention. *Journal of Pharmaceutical Research* **2015**, 14(4), 71-80.
- [2] Sarojini, S.; Manavalan, R. An overview on various approaches to Gastroretentive dosage forms. *International Journal of Drug Development & Research* **2012**, 4(1), 1-13.
- [3] Rao, G.K.; Mandapalli, P.K.; Manthri, R.P.; Reddy, V.P. Development and *in-vivo* evaluation of gastroretentive delivery systems for cefuroxime axetil. *Saudi Pharmaceutical Journal* **2013**, 21, 53–59.
- [4] Gharti, K.P.; Thapa, P.; Budhathoki, U.; Bhargava, A. Formulation and *in-vitro* evaluation of floating tablets of hydroxypropyl methylcellulose and polyethylene oxide using ranitidine hydrochloride as a model drug. *Journal of Young Pharmacists* **2012**, 4(4), 201-208.
- [5] Mohd, A.; Aslam, A.; Khan, P.; Bano, S.; Siddiqi, K.S. UV-absorption and fluorimetric methods for the determination of alprazolam in pharmaceutical formulation. *Arabian Journal of Chemistry* **2013**, 6, 369–378.
- [6] Hamidovic, Ajna. “Alprazolam.” Gale Encyclopedia of Mental Disorders. **2003**. *Encyclopedia.com*. 2 Jun. 2016 <<http://www.encyclopedia.com>>.
- [7] Nanjwade, B.K.; Adichwal, S.A.; Nanjwade, V.K.; Gaikwad, K.R.; Thakare, S.A.; Manvi, F.V. Development and Evaluation of Gastroretentive Floating Tablets of Glipizide Based on Effervescent Technology. *Drug Metabolism & Toxicology* **2012**, 3(3), 1-5.
- [8] Pawar, H.A.; Dhavale, R. Development and evaluation of gastroretentive floating tablets of an antidepressant drug by thermoplastic granulation technique. *Beni -suef university journal of basic and applied sciences* **2014**, 3, 122-132.
- [9] Rosa, M.; Zia, H.; Rhodes, T. Dosing and testing *in-vitro* of a bioadhesive and floating drug delivery system for oral application. *Int J Pharm.* **1994**, 105, 65-70.
- [10] Gambhire, M.N.; Ambade, K.W.; Kurmi, S.D.; Kadam, V.J.; Jadhav, K.R. Development and *in vitro* evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. *AAPS Pharm Sci Tech.* **2007**, 8(3), E1-E9.
- [11] Jaimini, M.; Rana, A.C.; Tanwar, Y.S. Formulation and evaluation of famotidine floating tablets. *Current Drug Delivery* **2007**, 4, 51–5.
- [12] Tripathi, K.D. Essentials of Medical Pharmacology; 5th edition; Jaypee Brothers Medical Publishers (P.) LTD, New Delhi, 588-598.