Development and Evaluation of Alprazolam Controlled Release tablets

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Abstract

Twenty three different tablet formulations of alprazolam were prepared using Polymer like hydroxypropylmethyl cellulose (HPMC K4M, HPMC K15M and HPMC K100M) in the concentration of 5 – 50 % of total weight of tablets and combination of HPMC K15M and HPMC K100M with ethyl cellulose (EC) was formulated by using wet granulation method. Drug formulation containing 1.0 mg, 1.5 mg, 5 mg, 10 mg and 15 mg alprazolam per tablet maintaining constant HPMC K15M concentration was also developed.

The in-vitro dissolution studies of the formulated and marketed product in USP type II apparatus showed that the drug release is dependent upon the drug: polymer ratio; also molecular weight of the polymer and solubility of loaded drug. With increasing concentration and molecular weight of polymer, drug release was found to be decreased. When formulating the tablets the method used whether direct compression or wet granulations also affect the release of the drug from matrix. Wet granulation method by using 40 % HPMC K15M in combination with 5 % EC was found to be most suitable controlled release alprazolam tablet as drug release was found to be appreciable in this formulation. When loading dose of alprazolam was increased, drug release was found to be tremendously decreased because of the poor solubility of alprazolam in water. When one-way ANOVA was applied for various formulated and marketed tablets it was found that there is no significant difference ($p > 0.05$) in drug release rate among formulation similarly model independent methods was also applied such as similarity and dissimilarity factor and found that there is no significant difference between these formulations. Key Words: *Controlled release, Alprazolam, Polymers, Dissolution, HPMC.*

Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceuticals products of different dosage forms .The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration, patient compliance, and cost effectiveness [1].

Controlled release dosage forms (CRDF) can be defined as prolonged action formulations, which provide continuous release of medicaments at a predetermined rate and predetermined time [2]. The main advantages of controlled drug delivery systems are maintenance of therapeutically optimum drug concentrations in the plasma through zero order release without

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significant fluctuations and elimination of the need for frequent single dose administrations [3]. Different types of CRDF systems are prepared depending on this behavior of the polymers and the method of drug release from these polymers differs upon its design and its physiochemical characteristics. Alprazolam is a short-acting drug in the benzodiazepine class used to treat anxiety disorders and as an adjunctive treatment for depression [4].

Pharmacokinetic data: Bioavailability- 80-90%, Metabolism - Hepatic, Half-life - 6-12 hours and Excretion- Renal

Alprazolam is readily absorbed from the gastrointestinal tract. The peak plasma concentration is achieved in 1-2 hours. Most of the drug is bound to plasma protein, mainly albumin.

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a pre-designed manner. Because of low costs and ease of fabrication, one of the most common approaches to get controlled release is to embed a drug in a hydrophobic matrix such as wax, polyethylene, polypropylene, and ethyl cellulose or hydrophilic matrix such as hydroxypropylcellulose, HPMC, methylcellulose, sodium carboxymethyl cellulose (sodium CMC) [5]

Polymer used in the formulation of controlled release Alprazolam is HPMC of various grades (HPMC-K4M, HPMC- K15M and HPMC- K100M) and EC. The use of hydrophilic polymers in preparation of CRDF is considered as simple because of its gel forming properties in contact with water. The gel formation of the polymer is the barrier for controlling drug transport from the dosage form to outer environment. In addition the integrity of polymer in water and its gel strength is dependent upon its molecular size, polymer relaxation temperature and hydrophilicity of the polymer [6].

As water insoluble excipients, EC can effectively control the release of an active by modifying the size and length of the diffusion path. In this role, it is typically used in combination with a water-soluble active, water-soluble excipient such as a HPMC cellulose ether and poly ethylen glycol (PEG) . By varying excipient ratio and the particle size, a wide variety of release rate profiles can be achieved [7] [8] [9].

Materials and Methods

Materials

Alprazolam (Chacko suns chemicals, India), HPMC K4M, HPMC K15 M (Feicheng Ruitai fine chemicals, China), Ethyl Cellulose (Samsung fine chemicals, Shaghai China), Starch (Shital chemicals, India), Microcrystalline Cellulose Powder PH 101 [(MCCP)(Sigachi Chemicals India)], Magnesium Stearate (Varsh Chemicals, India), Purified Talc (Niclon Chemicals, India), Aerosil (Rutocel, Beijing), were obtained from Lomus Pharmaceuticals Pvt. Ltd. (Gothatar, Kathmandu Nepal) as a gift sample. HPMC K100M (Dow chemicals) was obtained from Research Lab of Pharmacy department, Kathmandu University, Dhulikhel Nepal and Market Product (Alpras, Torrent India) was purchased from Delhi, India and coded as RT.

Equipments and Instrument

Tray Drier - Global Enterprises, India, Tablet Compression machine: 16 stations rotary tablet compression machine – Cadmach India, Balance for dispensing - OHAUS , USA, Analytical Balance – Scaltec Germany , UV Spectrophotometer – Shimadzu, Japan (UV – 2450), USP Dissolution Apparatus – Electro lab, Moisture Balance – Scaltech Germany , Friability Tester – Electro lab Friabilator , Hardness Tester – Campbell, India, Vernier Caliper - Mitutoya Corporation, Japan.

Method

Formulation by Dry granulation method

Two different formulations using Dry granulation method were prepared. For each batch Polymer was passed through 40#. Starch and MCCP were passed through 60 #. Alprazolam, excipients and polymer was mixed manually in SS tray for 15 minutes which was passed through 14 #. The powder so obtained was mixed with lubricants (Magnesium Stearate, Purified Talc) which were initially passed through 100 #. Then the powder blend was mixed in poly bag for 10 minutes and finally compressed in tablet compression machine with die size of 8.0 mm. Content uniformity test was performed and found to be out of limit so in-vitro dissolution test was not done. The results are summarized in the Table2.

Formulation by nonaqueous granulation method

Twenty-one different formulations using wet granulation method were prepared. For each batch Polymer was passed through 40#. Starch and MCCP were passed through 60 #. Alprazolam was dissolved in alcohol and the polymer were dispersed in methylene chloride Then the drug, excipients and polymer was mixed manually in stainless steel (SS) tray for 15 minutes to form a wet dough mass which was passed through 14 #. The granules so obtained were initially dried in air for 5 minutes and semi-dried granules were passed through 20 # followed by final drying at 50 ^{o}C in tray drier for 15 minutes. The Purified Talc, Magnesium Stearate, was sieved through 100 #. Then the lubricants was added to the granules and mixed in double lined poly-bag for 10 minutes. Finally granules were compressed in tablet compression machine with die size of 8.0 mm. The tablets were tested for the physical characteristics and in vitro dissolution rate. Composition for formulation of Alprazolam tablet by using hydrophilic polymer and combination of hydrophilic and hydrophobic polymer are summarized in Table1.

Table 1(a)

Composition of Controlled release Alprazolam Tablets

Ingredients (mg/tab)	ACR-01	ACR-02	ACR-03	ACR-04	ACR-05	ACR-06	ACR-07	ACR-08	ACR-09	ACR-10	ACR-11	ACR-12
Alprazolam	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Alcohol (µl)	10	10	10	10	10	10	10	10	10	10	10	10
Starch	157	157	157	145.5	145.5	145.5	122.5	122.5	122.5	99.5	99.5	76.5
MCCP PH 101	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	11.5	-	-	23	-	-	46	-	-	-	-	-
HPMC K15M	-	11.5	-	-	23	-	-	46	-	69	-	92
HPMC K100M	-	-	11.5	-	-	23	-	-	46	-	69	-
Ethyl Cellulose	-	-	-	-	-	-	-	-	-	0	0	0
Purified Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4
Aerosil-200	1	1	1	1	1	1	1	1	1	1	1	1

Total weight (mg)	230	230	230	230	230	230	230	230	230	230	230	230

Table 1(b)

Composition of Controlled release Alprazolam tabets

Ingredients (mg/tab)	ACR-13	ACR-14	ACR-15	ACR-16	ACR-17	ACR-18	ACR-19	ACR-20	ACR-21	ACR-22	ACR-23
Alprazolam	1.5	1.5	1.5	1.5	1.5	1	5	10	15	1.5	1.5
Alcohol (µl)	10	10	10	10	10	7.5	37.5	75	112.5	10	10
Starch	76.5	53.5	53.5	65	65	77	73	68	63	76.5	76.5
MCCP PH 101	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	-	-	-	-	-	-	-	-	-	-	-
HPMC K15M	-	115	-	92	-	92	92	92	92	92	92
HPMC K100M	92	-	115	-	92	-	-	-	-	-	-
Ethyl Cellulose	0	0	0	11.5	11.5	-	-	-	-	-	-
Purified Talc	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4
Aerosil-200	1	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	230	230	230	230	230	230	230	230	230	230	230

Evaluation of Tablets

The tablets were evaluated for their physicochemical parameters such as weight variation, hardness, thickness, friability, assay, content uniformity, in-vitro dissolution.

Assay Method

Twenty tablets from each batch were sampled, weighed and crushed to a fine powder and quantity equivalent to 1.5 mg of Alprazolam was dissolved in 25 ml of 0.1 N HCl solutions and volume was made 100 ml with same solvent and sonicated for 15 minutes. Then the solutions were filtered through whatman filter paper and 10 ml of solution was diluted to 25 ml with 0.1 N HCl solutions. The absorbance of this final solution and the same concentration of standard Alprazolam solution were compared at wavelength 260 nm. The results are summarized in the Table 2.

Content Uniformity Test

10 tablets from each batch were dissolved individually in 25 ml of 0.1 N HCl solutions and volume was made 100 ml with same solvent and sonicated for 15 minutes. Solutions were filtered through whatman filter and 10 ml of solution was diluted to 25 ml with 0.1 N HCl. Standard solution of Alprazolam of same concentration was compared with sample solution at wavelength 260 nm. The results are summarized in the Table 2.

Dissolution Tests

USP apparatus II was used to test the dissolution profiles of the reference product and formulated products in 500 ml 0.1 N HCl as medium at 37 $\pm$ 0.5 ^{o}C with paddle speed 50 rpm [38]. 10 ml of sample was drawn at every hour and equal volume of medium was replaced into each of the dissolution jars after each sampling to maintain the sink condition. Absorbance of each filtrate sample was measured and compared with the same concentration of standard solution in UV spectrophotometer at wavelength 260 nm. The dissolution data of all the formulated and reference products are summarized in Table 3.

Table 2 Physical characteristics (Mean ± SD) of formulated controlled release Alprazolam tablets

Formulation	Average weight[a] (mg)	Hardness[b] (Kg/cm^2)	Thickness[a] (mm)	Diameter[a] (mm)	Friability[a] (%)	Assay[c] (%)	Content Uniformity[b] (%)
ACR- 01	230.40 ± 4.51	6.95 ± 0.90	0.00 ± 0.00	0.00 ± 0.00	0.06	96.32 ± 1.50	100.40 ± 3.59
ACR- 02	230.20 ± 4.45	6.1 ± 0.57	0.00 ± 0.00	0.00 ± 0.00	0.04	102.67 ± 1.09	99.08 ± 4.11
ACR- 03	230.05 ± 3.22	5.65 ± 0.53	0.00 ± 0.00	0.00 ± 0.00	0.16	101.64 ± 0.96	100.18 ± 4.20
ACR- 04	228.65 ± 3.99	7.01 ± 1.18	0.00 ± 0.00	0.00 ± 0.00	0.18	96.87 ± 0.43	99.98 ± 4.52
ACR- 05	230.55 ± 3.49	5.75 ± 0.54	0.00 ± 0.00	0.00 ± 0.00	0.09	97.45 ± 0.47	98.84 ± 2.78
ACR- 06	230.00 ± 4.38	6.8 ± 0.67	0.00 ± 0.00	0.00 ± 0.00	0.09	97.98 ± 1.59	99.34 ± 4.59
ACR- 07	229.45 ± 3.64	6.46 ± 0.59	0.00 ± 0.00	0.00 ± 0.00	0.15	100.88 ± 0.77	99.34 ± 4.34
ACR- 08	231.10 ± 4.35	6.25 ± 0.79	0.00 ± 0.00	0.00 ± 0.00	0.21	101.35 ± 0.04	99.08 ± 4.63
ACR- 09	229.80 ± 3.33	7.15 ± 0.75	0.00 ± 0.00	0.00 ± 0.00	0.04	97.91 ± 0.64	101.44 ± 4.52
ACR- 10	229.40 ± 3.34	7.1 ± 0.88	0.00 ± 0.00	0.00 ± 0.00	0.19	97.24 ± 0.48	99.69 ± 3.47
ACR- 11	230.75 ± 2.57	7 ± 0.85	0.00 ± 0.00	0.00 ± 0.00	0.07	97.74 ± 1.16	101.13 ± 5.08
ACR- 12	230.65 ± 4.10	7.75 ± 0.63	0.00 ± 0.00	0.00 ± 0.00	0.11	98.97 ± 1.29	98.49 ± 4.90
ACR- 13	230.50 ± 2.27	7.8 ± 0.54	0.00 ± 0.00	0.00 ± 0.00	0.27	99.48 ± 0.53	97.97 ± 4.20
ACR- 14	229.05 ± 3.85	7.95 ± 0.50	0.00 ± 0.00	0.00 ± 0.00	0.12	99.40 ± 2.41	100.41 ± 4.61
ACR- 15	229.50 ± 4.20	7.15 ± 0.67	0.00 ± 0.00	0.00 ± 0.00	0.064	97.26 ± 0.63	100.05 ± 3.08
ACR- 16	228.95 ± 3.44	8.5 ± 0.53	0.00 ± 0.00	0.00 ± 0.00	0.04	98.08 ± 1.47	98.03 ± 4.55
ACR- 17	229.45 ± 4.06	8.55 ± 0.55	0.00 ± 0.00	0.00 ± 0.00	0.03	99.99 ± 1.51	100.39 ± 4.39
ACR- 18	229.00 ± 1.63	8.4 ± 0.52	0.00 ± 0.00	0.00 ± 0.00	0.13	99.26 ± 2.56	100.33 ± 2.06
ACR- 19	229.00 ± 1.87	8.4 ± 0.46	0.00 ± 0.00	0.00 ± 0.00	0.09	99.09 ± 2.11	99.51 ± 2.93
ACR- 20	230.00 ± 1.47	8.45 ± 0.44	0.00 ± 0.00	0.00 ± 0.00	0.07	97.97 ± 1.54	100.21 ± 3.51
ACR- 21	226.00 ± 1.65	8.2 ± 0.63	0.00 ± 0.00	0.00 ± 0.00	0.06	97.39 ± 0.86	100.14 ± 1.87
ACR- 22	230.00 ± 2.02	9.1 ± 0.46	0.00 ± 0.00	0.00 ± 0.00	0.14	106.57 ± 2.74	108.57 ± 22.53
ACR- 23	231.00 ± 2.04	9 ± 0.47	0.00 ± 0.00	0.00 ± 0.00	0.18	98.01 ± 1.52	107.00 ± 26.12

[a]n = 20, [b]n = 10, [c]n = 30

Mathematical Modeling of Drug Release Profile

The dissolution data obtained for formulated products and reference product were analyzed using various mathematical models.

Zero Order Kinetics

Zero order reaction is defined as a reaction in which the rate does not depend on the concentration terms of reactant. This is the ideal method of drug release to achieve prolonged pharmacological action. The equation for zero order kinetic is represented as follows,

$$Q_1 = Q_o + k_o t \quad \text{..... (1)}$$

Where, Q_1 = Amount of drug dissolved in time t, and

Q_o = Initial amount of drug in the solution, which is often zero and K_o is the zero order release constant. Average of Qo- Q_1 was calculated and a graph of Qo- Q_1 versus time't' was plotted for each formulation.

First Order Kinetic Model

First order process is defined as a reaction in which the rate of reaction depends on the concentration of one reactant. i.e. greater the concentration, faster the reaction. The pharmaceutical dosage forms containing water-soluble drugs in porous matrices follow first order release kinetics, and can be expressed by the equation

$$\log Q_1 = \log Q_o + \frac{kt}{2.303} \quad \text{..... (2)}$$

Here also, average of log Q_o/ Q_t was calculated and graph of log Q_o/ Q_t versus time't' was plotted for formulation , which show 12 hours release. The degree of correlation (R^2) obtained after passing the trend line with y-intercept which was then used to determine whether or not the release from the different formulation are following the first order or not.

Higuchi and Korsmeyer – Peppas Model

Both the Higuchi model and Korsmeyer – Peppas model is obtained from power law proposed by Ritger and Peppas as stated in equation (3);

$$\frac{M_t}{M} = kt^n \quad \text{..... (3)}$$

The fitness of data to Higuchi equation was assessed by determining the correlation coefficient between square root of time and M_t / M_∞. Plot of M_t / M_∞ versus $t^{1/2}$ gives a straight line with a slop of k_H, Higuchi dissolution rate constant.The fitness of data to Korsmeyer – Peppas model was assessed by determining the correlation coefficient between log (M_t / M_∞) and log of time, t. Plot of log (M_t / M_∞) versus log of time till the 60 % of drug is released will be a straight line with a slope of n and the intercept value of log k. anti-log of log k gives the value of k. "n" is release exponent of different geometrical symmetry.

Table 3(a) *In-Vitro* Dissolution of formualted and marketed controlled release Alprazolam tablets

Alprazolam	Polymer Content			Formulation	Cumulative % of Drug Released (Mean ± SD; n = 6) (hour)																	
	HPMC		EC		1			2			3			4			5			6		
(mg)	Grade	(%)	(%)																			
1.5	K4M	5	-	ACR- 01	89.23	±	0.39	96.13	±	1.05												
1.5	K15M	5	-	ACR- 02	87.68	±	0.88	95.48	±	0.65												
1.5	K100M	5	-	ACR- 03	85.32	±	0.67	95.10	±	1.33												
1.5	K4M	10	-	ACR- 04	70.83	±	1.19	78.24	±	0.71	87.52	±	0.98	97.80	±	1.57						
1.5	K15M	10	-	ACR- 05	68.15	±	0.80	74.23	±	1.41	86.01	±	0.18	95.11	±	1.17						
1.5	K100M	10	-	ACR- 06	67.01	±	1.16	76.92	±	1.61	84.92	±	1.36	94.82	±	1.15						
1.5	K4M	20	-	ACR- 07	62.11	±	0.89	69.80	±	0.64	76.60	±	0.91	80.92	±	0.72	88.32	±	0.32	96.02	±	0.26
1.5	K15M	20	-	ACR- 08	56.03	±	1.25	64.19	±	0.95	76.30	±	0.85	78.19	±	0.52	83.17	±	0.49	95.07	±	0.85
1.5	K100M	20	-	ACR- 09	53.33	±	0.82	62.18	±	1.28	75.09	±	0.70	76.35	±	1.33	81.63	±	0.80	93.19	±	2.60
1.5	K15M	30	-	ACR- 10	47.60	±	1.17	56.12	±	0.67	63.31	±	1.48	69.99	±	0.77	76.43	±	1.03	80.29	±	1.20
1.5	K100M	30	-	ACR- 11	45.04	±	0.96	52.12	±	1.50	60.01	±	0.80	67.16	±	0.21	73.14	±	0.73	79.32	±	1.81
1.5	K15M	40	-	ACR- 12	31.11	±	1.02	47.38	±	0.76	56.16	±	1.29	67.20	±	0.94	73.39	±	0.36	77.27	±	0.21
1.5	K100M	40	-	ACR- 13	30.20	±	0.95	45.29	±	0.64	55.32	±	0.54	64.13	±	0.61	73.01	±	0.71	76.16	±	1.99
1.5	K15M	50	-	ACR- 14	23.11	±	1.01	30.15	±	0.42	39.93	±	1.37	40.17	±	1.39	48.17	±	0.45	50.93	±	0.74
1.5	K100M	50	-	ACR- 15	21.09	±	1.06	29.66	±	0.94	37.18	±	0.85	40.09	±	1.26	47.09	±	0.08	48.63	±	1.09
1.5	K15M	40	5	ACR- 16	29.70	±	0.71	45.36	±	0.50	51.23	±	0.49	59.08	±	1.33	63.09	±	2.67	68.43	±	1.03
1.5	K100M	40	5	ACR- 17	28.36	±	0.93	43.15	±	0.74	49.15	±	0.93	57.33	±	1.20	61.11	±	1.40	66.39	±	1.45
1	K15M	40	-	ACR- 18	29.13	±	1.43	45.38	±	0.98	53.77	±	0.86	63.74	±	1.08	70.43	±	4.05	74.21	±	0.24
5	K15M	40	-	ACR- 19	10.78	±	1.24	18.29	±	1.03	21.66	±	0.76	26.80	±	0.99	33.56	±	1.84	44.32	±	0.40
10	K15M	40	-	ACR- 20	0.00	±	0.00	0.00	±	0.00	13.41	±	1.05	15.12	±	0.79	18.68	±	0.76	23.96	±	0.77
15	K15M	40	-	ACR- 21	0.00	±	0.00	0.00	±	0.00	0.00	±	0.00	0.00	±	0.00	10.64	±	0.87	15.40	±	1.08
1.5	-	-	-	RT	25.89	±	1.10	40.15	±	1.67	51.67	±	0.95	54.32	±	0.72	62.05	±	0.52	69.29	±	1.00

Table 3 (b) *In-Vitro* Dissolution of formulated and marketed controlled release Alprazolam tablets

Alprazolam	Polymer Content			Formulation	Cumulative % of Drug Released (Mean ± SD; n = 6) (hour)																	
	HPMC		EC																			
(mg)	Grade	(%)	(%)		7			8			9			10			11			12		
1.5	K4M	5	-	ACR- 01																		
1.5	K15M	5	-	ACR- 02				s														
1.5	K100M	5	-	ACR- 03																		
1.5	K4M	10	-	ACR- 04																		
1.5	K15M	10	-	ACR- 05																		
1.5	K100M	10	-	ACR- 06																		
1.5	K4M	20	-	ACR- 07																		
1.5	K15M	20	-	ACR- 08																		
1.5	K100M	20	-	ACR- 09																		
1.5	K15M	30	-	ACR- 10	89.01	±	1.04	96.39	±	0.20												
1.5	K100M	30	-	ACR- 11	86.09	±	1.10	93.25	±	1.41												
1.5	K15M	40	-	ACR- 12	86.29	±	0.76	91.26	±	0.75	94.54	±	1.72	97.08	±	0.68	99.27	±	1.51			
1.5	K100M	40	-	ACR- 13	83.28	±	0.91	90.22	±	0.25	93.29	±	0.52	96.45	±	1.51	98.52	±	1.63			
1.5	K15M	50	-	ACR- 14	59.33	±	0.77	65.93	±	1.94	71.19	±	0.69	78.33	±	1.07	81.95	±	0.71	86.09	±	0.69
1.5	K100M	50	-	ACR- 15	57.39	±	0.89	63.51	±	2.02	69.38	±	0.59	75.01	±	0.32	80.36	±	0.61	83.66	±	0.95
1.5	K15M	40	5	ACR- 16	73.53	±	0.62	77.36	±	1.05	81.33	±	1.33	84.36	±	0.35	89.50	±	0.74	96.07	±	1.37
1.5	K100M	40	5	ACR- 17	71.33	±	0.40	76.09	±	1.03	80.01	±	0.81	82.11	±	1.72	85.07	±	1.48	92.51	±	0.84
1	K15M	40	-	ACR- 18	83.98	±	1.02	88.64	±	1.41	90.32	±	0.71	92.99	±	0.93	95.82	±	1.46	97.87	±	1.08
5	K15M	40	-	ACR- 19	50.73	±	1.32	58.87	±	1.05	64.53	±	1.08	70.43	±	1.19	74.39	±	0.45	81.85	±	1.22
10	K15M	40	-	ACR- 20	27.47	±	0.66	30.73	±	1.22	35.57	±	1.50	40.36	±	0.40	48.50	±	0.52	52.42	±	1.25
15	K15M	40	-	ACR- 21	21.49	±	1.68	23.58	±	0.89	28.90	±	0.42	31.58	±	1.82	35.65	±	1.08	37.51	±	1.51
1.5	-	-	-	RT	70.49	±	0.78	75.98	±	1.24	82.95	±	1.97	85.47	±	0.71	89.21	±	1.32	97.07	±	0.77

Results and Discussion

Evaluation of Physiochemical properties of Controlled release Alprazolam Tablets

Each formulated tablets were characterized by various physico-chemical properties such as weight variation, hardness, thickness, friability, assay and content uniformity. The average tablet weight was found to be in the 217 – 240 mg (230 mg) target. The average tablet hardness was 5.0 – 9.5 kg (8 kg/cm^2 target). Content uniformity of tablet was 91.92 – 109.94 % and assay of tablet was 96.32 – 103.30 %. The results are given in Table 2.

In Vitro Drug Release

Dissolution test of reference tablet and all tablets formulated by wet granulation were conducted at 37 ^oC using USP Apparatus 2 (Paddle) at a rotation speed of 50 RPM. The dissolution medium consisted of 500 ml of 0.1 N HCl solution (pH = 1.1). A 10 ml sample was taken from the medium at 1, 2, 3, 4, 5, 6, 7, 9, 10, 11 and 12 h. and equal volume of medium was replaced into each of the dissolution jars after each sampling. Each sample was filtered through 10 µm filter prior to analysis. The amount of drug release was determined by ultraviolet spectroscopy [10].The dissolution release specification were as follows: less than 45 % release at 2 h, 45 – 65 % release at 4 h, 75 – 90 % release at 8 h, and greater than 90 % release at 12 h [38].The dissolution profile of marketed tablets tested by using USP dissolution apparatus II (paddle) at 37 ± 2° C and 50 rpm 500ml 0.1 N HCl was shown in Figure1.

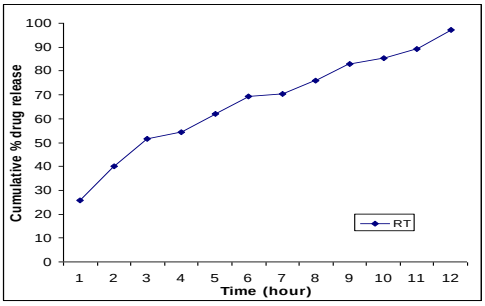

Figure1 Drug release profile of marketed SR Alprazolam Tablet.

Effect of Polymer concentration

HPMC K4M

In tablet formulations containing hydrophilic polymers like HPMC, the release of active drug is controlled by the rate of formation of a partially hydrated gel layer of the tablet surface formed upon contact with aqueous gastric media following ingestion and the continuous formation of additional gel layers [38].Formulation ACR-01, ACR–04, ACR–07 contained HPMC K4M in increasing order A comparison of their dissolution profile is given in Figure 2

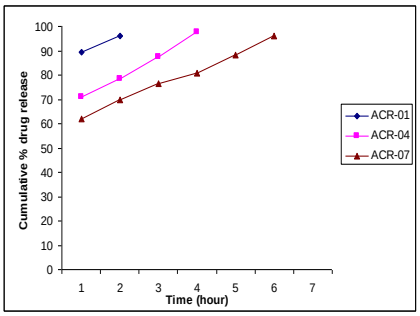

Figure 2 Drug release profile of formulation ACR 01, ACR 04 and ACR 07 using 5 %, 10 % and 20 % HPMC K4M as polymer respectively.

This profile indicates that increase in percentage of HPMC increases the dissolution time. The difference in drug release profile is clearly observed. In formulation ACR 01

about 96 % of drug was released within 2 hour which contains only 5 % HPMC K4M of the total weight of Tablet. In formulation ACR 04 about 98 % of drug was released within 4 hours and this formulation contains exactly double concentration of polymer than the formulation ACR 01. In Formulation ACR- 07 Containing 30 % of HPMC K4M about 96 % of drug was released within 6 hours.

HPMC K15M

Formulation ACR- 02, ACR-05, ACR-08, ACR-10, ACR-12, and ACR- 14 contained 5 %, 10 %, 20 %, 30 %, 40 % and 50 % HPMC K15M respectively of the total weight of tablets. A comparison of their dissolution profile is given in Figure 3.

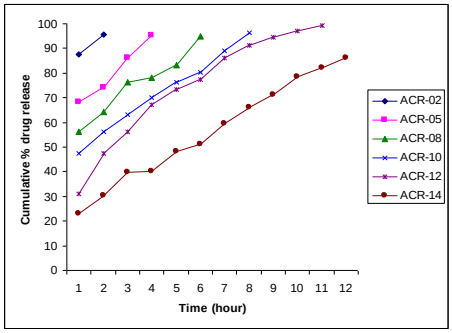

Figure 3 Drug release profile of formulation ACR 02, ACR 05, ACR 08, ACR 10 and ACR 12 using 5 %, 10 %, 20 %, 30 %, 40 % and 50 % HPMC K15M as polymer respectively.

In formulation ACR-02 about 95 % of drug was released within 2 hour, in formulation ACR-05 about 95 % of drug was released within 4 hours, in Formulation ACR-08 about 96 % of drug was released within 6 hours, in formulation ACR-10 about 96 % of drug was released at 8 hour and in formulation ACR-12 about 99 % of drug was released at 11 hour and in formulation ACR-14 about 86.0 %of drug was released which indicates that increase in percentage of HPMC increases the dissolution time. The release of the drug was found to be appreciable in the case of formulation ACR-12.

HPMC K100M

Formulation ACR- 03, ACR-06, ACR-09, ACR-11, ACR-13 and ACR-14 contained 5 %, 10 %, 20 %, 30%, 40 % and 50% HPMC K100M respectively of the total weight of tablets. A comparison of their dissolution profile is given in Figure 4

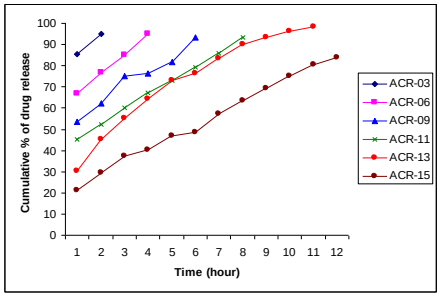

Figure 4 Drug release profile of formulation ACR-03, ACR-06, ACR-09, ACR-11, ACR-13 and ACR-15 using 5 %, 10 %, 20 %, 30 %, 40 % and 50 % HPMC K100M as polymer respectively.

In formulation ACR-03 about 95 % of drug was released within 2 hour, in formulation ACR-06 about 95 % of drug was released within 4 hours, in Formulation ACR-09 about 93 % of drug was released within 6 hours, in formulation ACR-11 about 93 % of drug was released at 8 hour and in formulation ACR-13 about 98 % of drug was released at 11 hour and in formulation ACR-15 about 84 % of drug released at 12 hour, the release of the drug was found to be appreciable in the case of formulation ACR-13.which indicates that increase in percentage of HPMC increases the dissolution time and retards the drug release. The difference in drug release profile is clearly observed.

Effect of various types Hydrophilic polymer at same concentration

Drug release from the formulation ACR-01, ACR-04, ACR-07 using HPMC K4M, formulation ACR-02, ACR-05, ACR-08, ACR-10, ACR-12, ACR-14 using HPMC K15M and formulation ACR-03, ACR-06, ACR-09, ACR-11, ACR-13, ACR-15 using HPMC K100M were found to be in different even Same concentration of HPMC were incorporated in these formulation .These formulation indicates that increasing polymer concentration retard the drug release. The drug release profiles of these formulations have been shown in Figure given below.

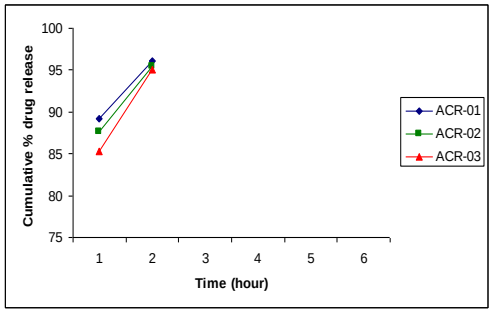

Figure 5 Drug release profile of formulation ACR 01

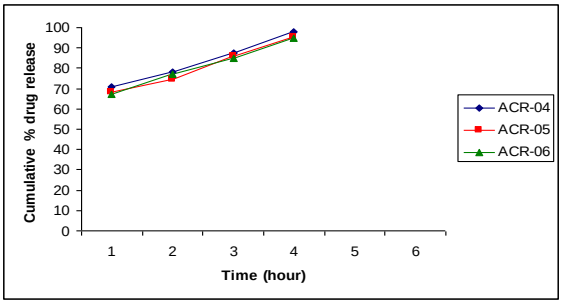

Figure 6 Drug release profile of formulation ACR 04, ACR 02 and ACR 03 using 5% HPMC K4M, HPMC K15M ACR 05 & ACR 06 using 10 % HPMC K4M, HPMC K15 M and HPMC K100M respectively.

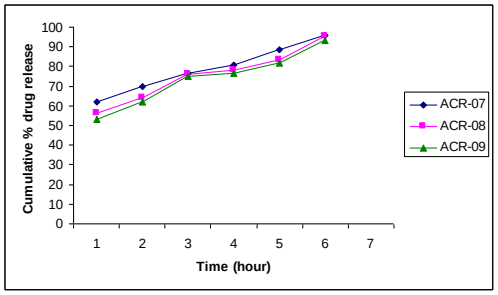

Figure 7 Drug release profile of formulation ACR 07

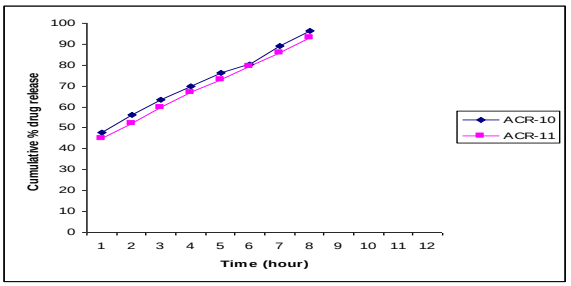

Figure 8 Drug release profile of formulation ACR 10, ACR ACR 08 & ACR 09 using 20% HPMC K4M, HPMC K15M 11 using 30 % HPMC K15 M and HPMC K100M respectively. & HPMC K100M respectively.

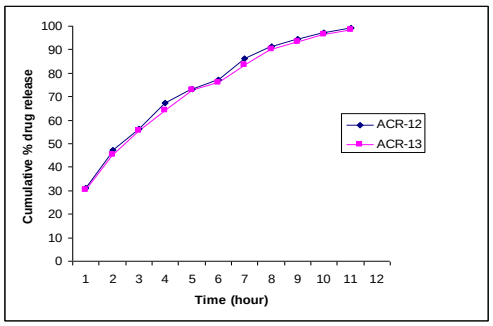

Figure 9 Drug release profile of formulation ACR 12

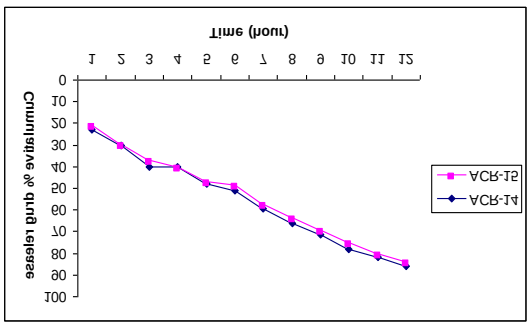

Figure 10 Drug release profile of formulation ACR 14, ACR 15 and ACR 13 using 40 % HPMC K15M, HPMC K100M using 50 % HPMC K4M, HPMC K15 M and HPMC K100M respectively. respectively.

Hydrophilic with Hydrophobic polymer

The dissolution profiles of various formulation (ACR-16 and ACR-17) by using 40 % hydrophilic polymer (HPMC K15M, HPMC K100M), in combination with hydrophobic

polymer, 5 % EC respectively are shown in Figure 3.12. In these formulations low concentration of Ethyl cellulose was incorporated in the formulation containing HPMC to see the change in the release profile of the drug from the matrix. Incorporation of Ethyl cellulose was found to control the drug release. In formulation ACR-16 about 96 % of drug was released within 12 hour and in formulation ACR-17about 92 % of drug was released within 12 hours,

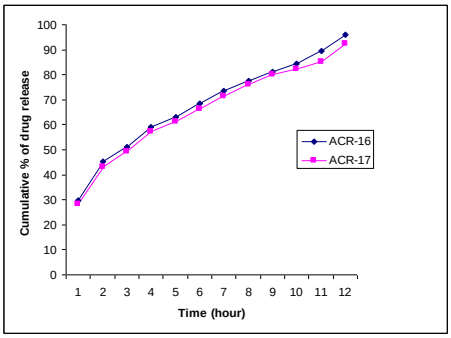

Figure 11 Drug release profile of formulation ACR-16 and ACR-17 using HPMC K15 M (40%) and HPMC K100M (40%) in Combination with 5 % EC respectively.

Effect of Drug loading on release profile

Formulation ACR-18, ACR-12, ACR-19, ACR-20 and ACR-21 contained 1.0, 1.5, 5.0, 10.0 and 15.0 mg Alprazolam respectively and each formulation contained 40 % HPMC K15M.Dissolution study was performed to see the effect of drug loading on release profile of these formulations and have been shown in following Figure which indicates that increasing the loading dose of alprazolam causes decrease in drug release having constant HPMC concentration.

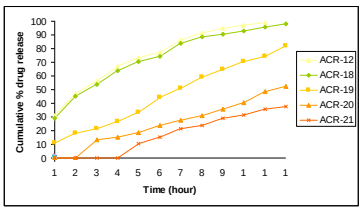

Figure 12 Drug release profile of formulation ACR 12, ACR 18, ACR 19, ACR 20 and ACR 21 containing 1.0 mg, 1.5 mg, 5 mg, 10 mg, and 15 mg alprazolam.

Comparison of dissolution profile of formulated product with marketed product

In formulation ACR-16 drug released was about 29 % in 1 hour and 96 % within 12 hour and in formulation ACR-17 drug released was about 28 % in 1 hour and about 92 % within 12 hours. Similarly, in marketed Tablet drug released was 26 % in 1 hour and 97 % within 12 hours. And drug release profile of these formulated and marketed products can be compared from the following Figure.

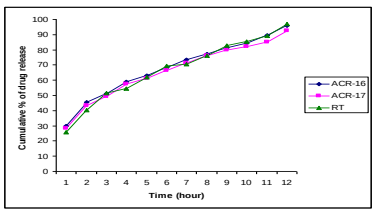

Figure 13 comparison of Drug release profile of formulated product ACR-16 and ACR-17 with marketed Product.

Drug Release Kinetics

The drug release data from the formulated and marketed tablets were fitted to various kinetics equations following Zero order, First order, Higuchi model and Korsmeyer-Peppas

equations.and presented in Table 4. The correlation coefficient obtained from curve fitting into different kinetic equation suggested that most of the formulations were found to follow either Higuchi or Korsmeyer-peppas model and some of formulation were found to follow Zero order and 1st order. The release exponent "n" value for the different formulations ranged from 0.48 – 1.41. The release kinetics from reference Tablets was best fitted with Higuchi model with R^2 value 0.9916. Formulation ACR-04 and ACR-20 were found to follow 1st order kinetics with R^2 value 0.9993 and 0.989 respectively. Only formulation ACR-19 was found to follow Zero order kinetics with R^2 value 0.9895.Regression coefficient of drug release profiles of ACR-12, ACR-13, ACR-14, ACR-15, ACR-16 and ACR-17 obtained with Higuchi model are all greater than 0.96.

The release exponents "n" of these six formulations are in between 0.6836 to 0.8614 followed anomalous transport ($0.5<n<1.0$) indicating both diffusion and swelling controlled release [11]. Regression coefficient of drug release profiles of ACR-05 ACR-06, ACR-07, ACR-08, ACR-09, ACR-10, ACR-11, ACR-18 and ACR-21 obtained with Korsmeyer Peppas model are all above 0.96. The release exponent "n" values of these formulations are in between 0.48 to 0.64 except formulation ACR- 21 with n value 1.41 showed Super-Case-II transport [12]. The formulations ACR-18 showed n value less than 0.5. The drug diffusion partially through a swollen matrix and water-filled pores in the formulations could be the reason for smaller value of release exponent ($n<0.5$).

Statistical Analysis

One way ANOVA was applied to the various formulated tablets to find out any significant difference between release profiles of these formulations. The formulation ACR-12 and ACR-13 containing 40 % HPMC K15M and 40 % HPMC K100M with dissolution profile up to 11 hours was tested and found that there is no significant difference ($p > 0.05$) in drug release rate between these two formulations. Similarly formulation ACR-16, ACR-17 containing 40 % HPMC K15M and 40 % HPMC K100M with 5 % EC on both formulation with dissolution profile up to 12 hours was tested and found that no significant difference ($p> 0.05$) in drug release rate was found between formulation ACR-16 and ACR- 17.

Similarity and Dissimilarity Factor

Models independent methods were used to test the dissimilarity factor f_1 and Similarity factor f_2 of the various formulated and reference tablets. According to this method, a product is considered to be similar when its f_2 value lies within 50 -100 and f_1 within 0 -15. When formulation ACR-12 and ACR-13 were compared by similarity factor and value was found to be 79.07 and it indicates that there is no significant difference between formulation ACR-12 and ACR-13.Similarly, Similarity factor between formulation ACR-16 and ACR-17 was 70.935 and it also indicates that there is no significant difference between these formulations.

Finally formulation ACR-16 was compared with reference tablet with similarity factor and value was assessed by 68.93 which indicate that there is no significant difference between these two formulations. Dissimilarity factor f_1 between formulation ACR-12 and ACR-13 was calculated and value was found to be 1.837 which indicates there is no significant difference between these two formulations. Formulation ACR-16 and ACR-17 was also tested by dissimilarity factor and value was found to be 3.227 and found that there no significant difference between these two formulation. Finally formulation ACR-16 and reference tablet was compared by dissimilarity factor and value was 3.053 and it also indicates that there is no significant difference between these two formulations.

Table 4 Drug release kinetics of formulated and marketed controlled release Alprazolam tablets

Formulation	Zero Order Model		First Order Model		Higuchi Model		Peppas Model	
	k (% hr^{-1})	R^2	k (% hr^{-1})	R^2	k (% hr^{-1})	R^2	n	R^2
ACR 04	29.369	-5.0831	0.1080107	0.9993	52.867	0.9711	0.5037	0.9978
ACR 05	28.503	-4.1164	0.1146894	0.9903	51.232	0.9606	0.5181	0.9981
ACR 06	28.496	-4.3691	0.1139985	0.9951	51.252	0.9897	0.543	0.9971
ACR 07	19.483	-3.7954	0.0840595	0.991	42.287	0.9805	0.5636	0.9954
ACR 08	18.817	-2.0623	0.0983381	0.9536	40.676	0.9624	0.575	0.9929
ACR 09	18.414	-1.673	0.103635	0.9433	39.754	0.963	0.5965	0.9923
ACR 10	14.156	-0.5509	0.0958048	0.9793	34.786	0.9843	0.6111	0.9888
ACR 11	13.668	-0.2838	0.1015623	0.9823	33.51	0.9869	0.6478	0.9889
ACR 12	11.156	0.3313	0.1001805	0.8451	31.676	0.988	0.6836	0.9716
ACR 13	10.984	0.4003	0.1029441	0.8537	31.141	0.9916	0.7113	0.9709
ACR 14	5.7502	0.7948	0.1123864	0.9512	23.365	0.9753	0.8258	0.9663
ACR 15	8.0178	0.8126	0.1149197	0.945	22.63	0.9787	0.8614	0.9617
ACR 16	9.3592	0.2456	0.0868231	0.8739	27.735	0.9933	0.727	0.9682
ACR 17	9.0622	0.2586	0.0877443	0.867	26.855	0.9935	0.7513	0.969
ACR 18	10.157	0.2981	0.0925806	0.8242	30.102	0.9762	0.4828	0.9874
ACR 19	7.0229	0.9895	0.172725	0.9356	19.983	0.8457	0.8449	0.9839
ACR 20	4.0958	0.9625	0.1549919	0.989	11.414	0.7313	1.0261	0.9814
ACR 21	2.9274	0.8708	0.1711129	0.9207	7.9462	0.6002	1.4164	0.9719
RT	9.3125	0.4936	0.1239014	0.8616	27.461	0.9916	0.5004	0.9905

Conclusion

- The release of Controlled release alprazolam tablet depends on the various viscosity grade of HPMC. Increasing the viscosity of polymer retards the drug release.
- Drug release from HPMC-K4M > HPMC-15M > HPMC-K100M.
- Increase in concentration of polymer increases the dissolution time.
- When Aplrazolam loading was increased maintaining HPMC concentration constant the drug release was found to be decreased.
- In formulation when EC in combination with water-soluble HPMC was used the release was found to be decreased.

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