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Design and evaluation of hydrophilic matrix-based sustained release tablets of alprazolam

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ABSTRACT

In this study an attempt was made to design and evaluate oral sustained release matrix tablets of alprazolam using Methocel K15M CR and Methocel K4M Premium as the release rate retardant polymers. Tablets were prepared by direct compression method. Tablets were evaluated for parameters such as weight variation, hardness, friability and drug content.. *In vitro* release studies were performed using USP type I apparatus in 500 mL of phosphate buffer pH 6.0 at 100 rpm for 16 hours. The release kinetics was analyzed using the zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the matrix tablets. *In vitro* release studies revealed that percent drug release decreased with increase of polymer loading. Based on the dissolution data comparison with innovator brand all the formulations were found to similar with innovator brand. The drug release profiles of the optimized formulations were well controlled and uniform throughout the dissolution studies. All the formulations were checked for stability as per ICH guidelines and formulations were found stable during the study.

INTRODUCTION

Conventional tablets are the most popular and available oral solid formulations that are preferred by physicians and patients. But conventional tablet formulations are not ideally suited to some drugs having *short plasma half-life.* High frequency of dosing of immediate release tablets of drug having *short plasma half-life* is really a problem that can be solved by designing sustain release dosage form.

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects [1]. Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view [2]. Moreover, it has been shown that the suitable combination of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form [3]. Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance [4]. The polymers selected for the present study were Methocel K15M CR and Methocel K4M Premium. These polymers provide pH-dependant &pH independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms [5].

Alprazolam is used mainly in the treatment of anxiety disorders and panic disorder. Anxiety disorders and panic disorder are very common diseases where the patients have to take medicine regularly. Immediate release alprazolam tablets are generally prescribed for administration up to four doses per day for the treatment of anxiety and more than four doses per day for the treatment of panic disorder. Such high frequency of dosing may be bothersome and can adversely affect patient stability. Further, breakthrough anxiety can be a problem in current dosing method. Sustained release dosage form of Alprazolam can provide better patient compliance and prolonged action against these two major diseases.

In the present study an initiative was taken to formulate alprazolam sustained release tablet by using of two release retarding polymers Methocel K15M CR and Methocel K4M Premium. Methocel K15M CR and Methocel K4M Premium are semi synthetic derivative of cellulose. They are swellable and hydrophilic polymer. They are suitable to use as a retardant

material in SR matrix tablets, as they are nontoxic and easy to handle [6]. Matrix tablets prepared using Methocel polymer on contact with aqueous fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix [7]. The tablets were prepared by conventional direct compression technique and their physical parameters and *in vitro* release characteristics were evaluated. Stability of tablets (potency and drug release) was also studied to find out any excipients-drug interaction in the formulation.

MATERIALS AND METHODS

Materials

Alprazolam (Lake Chemicals Ltd., India), Methocel K4M premium , Methocel K15M CR (Colorcon Asia Pvt. Ltd.), Microcrystalline Cellulose (Avicel PH 101) (Mingtai Chemical, Taiwan), Magnesium Stearate (Novochem GmbH Germany) Colloidal Silicon Dioxide (Aerosil 200) (Degussa AG , Germany), Allura Orange Lake (Neelikon Food. Dyes and Chemicals Ltd. India). HPLC grade Acetonitrile, HPLC grade Methanol, Monobasic Potassium Phosphate, Dibasic Potassium Phosphate, Potassium Hydroxide (Scharlab S.L., Spain), Tetrahydrofuran, Phosphoric Acid (Merck K Ga A, Germany)

Preparation of matrix tablet

Drug, polymers and other excipients were weighed separately for 200 tablets for each formulation as shown in Table-1. The proposed formulations were coded as F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9 & F-10. The tablets were prepared by direct compression technology. Required amount (for 200 tablets) of the drug (alprazolam), polymer (Methocel K4M premium and Methocel K15M CR), filler (Avicel PH 102) and Allura Orange Lake were weighed and passed through mesh # 40 into a SS bowl and mix it by hand for 10 minutes. Magnesium stearate and colloidal silicon dioxide (Aerosil 200) were then mixed with the blended granules. Blended granules were then compressed using "Mini Compress" machine equipped with 8.0 mm round punch and die set. After compression, all the preparations were stored in double polythene bags at room temperature for further study.

Evaluation of Granules

Granules from all the formulation were evaluated for bulk density, compressibility index, total porosity, angle of repose, moisture content and hausner ratio.

LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by tap density tester. Initial volume and tapped volume of 2 gm of granules were observed and LBD, TBD, compressibility index and hausner ratio were calculated from the following equations:

LBD = Weight of the powder / Volume of the packing. ---------- (1)

TBD = Weight of the powder / Tapped volume of the packing. -(2)

Carr's index (%) = [(TBD LBD) X 100]/TBD ----------(3)

Hausner Ratio = Tapped Density / Bulk Density ----------(4)

Total porosity was determined by measuring the volume occupied by a selected weight of powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space (V)

$$\text{Porosity}\ (\%) = (V_{bulk} \; V) / V_{bulk} \times 100 \quad \text{----------(5)}$$

The angle of repose of granules was determined by following granules through the funnel freely to surface. The radius (r) and height (h) of the powder cone was measured and angle of repose was calculated using the following equation

$$\text{Angle of repose}, \theta = tan^{-1} (h/r) \quad \text{----------(6)}$$

Moisture content of granules was determined using Mettler Karl Fischer Titrator.

Evaluation of Tablets

All the prepared tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods. The average weights and percentage deviation were calculated by weighing 20 tablets from each brand by an analytical weighing balance (AY-200, Shimadzu, Japan). The crushing strength was determined with an Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland). Ten tablets of each brand were weighed and subjected to abrasion by employing a Veego friabilator (VFT-2, India) to determine friability.

HPLC Analysis of alprazolam: Shimadzu HPLC-Prominence integrated with PDA detector was used for the analysis. The chromatographic system consisted of a LC-20 AT pump, The Separation was achieved from C8 column (Kromasil C_8 250 × 4.6 mm, 5µ, England) at ambient temperature with a mobile phase consisting of Buffer (0.025 M orthophoshoric acid): Acetronitrile: Tetrahydrofuran (ratio: 60: 35: 5) at a flow rate of 1.0 ml/min. The drug analysis data were acquired and processed using LC solution (Version 1.2, Shimadzu, Japan) software running under Windows XP on a Pentium PC. The method was

Table No. 1: Composition of alprazolam matrix tablets (mg/tablet)

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Alprazolam	1	1	1	1	1	1	1	1	1	1
Methocel K15M CR	56	56	56	56	40	48	64	40	48	64
Methocel K4M Premium	0	12	24	36	12	12	12	24	24	24
Aerosil 200	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Avicel PH-102	139	127	115	103	143	135	119	131	123	107

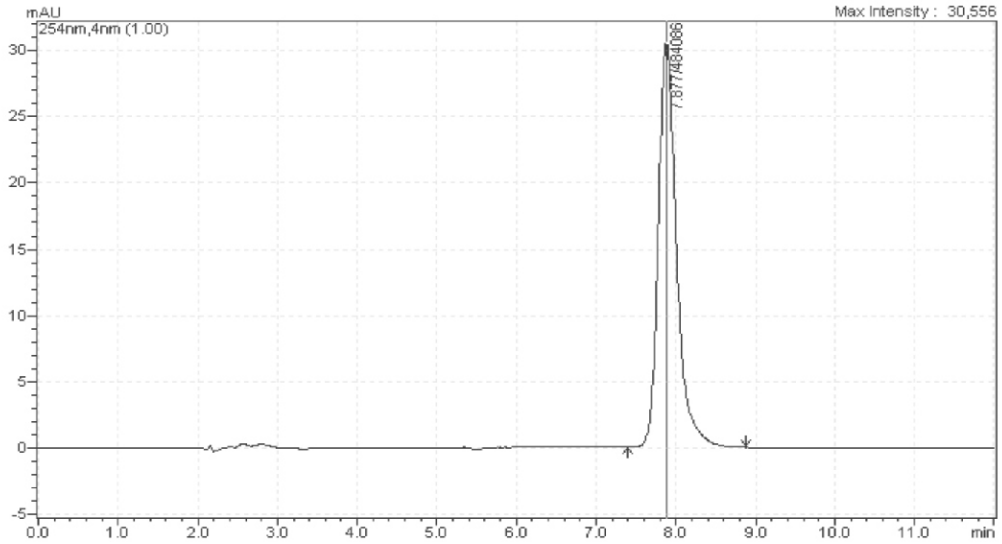

FIG. 1: Chromatogram of standard alprazolam

validated for the parameters like system suitability, selectivity, linearity, accuracy, precision and robustness. The retention time was about 8 minutes both for standard solution and sample solution (Figure 1).

Assay

Sufficient quantity of finely powdered tablet sample (Equivalent to 1.0 mg of alprazolam) was dissolve in 100 ml diluting solution by sonicating for 2 minutes. The solution was allowed to cool & filtered through whatman filter paper. Again filtrate of this solution was passed through 0.2µ disk filter. The samples were analyzed by a validated HPLC method.

Content uniformity

10 intact tablets from each formulation (F-1 F-10) were placed in 10 volumetric flasks. Tablets were disintegrated in 2 ml water and dissolved in 100 ml diluting solution. The solution was then allowed to cool & filtered through membrane filter paper. Again the filtrate of the solution was passed through 0.2µ disk filter. The samples were analyzed by a validated HPLC method.

In Vitro Release Studies

In vitro dissolution study was performed in 500ml Phosphate Buffer (pH 6.0±0.1). The temperature of the medium was set to 37 ± 0.5°C. Apparatus I (Basket) was used and the rpm (rotation per minute) was set to 100. After 1hr, 2hr, 4hr, 8hr, 10hr, 12hr & 16hr definite volume (5ml) of aliquots were collected for analysis which were then replaced with equal volume of fresh dissolution medium. The samples were analyzed by High Performance Liquid Chromatography (HPLC) method.

Drug release kinetics

The drug release data were fitted to models representing zero order (cumulative amount of drug released vs. time), first order (log percentage of drug unreleased vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), and Korsmeyer's equation (log cumulative percentage of drug released vs. time) kinetics to know the release mechanisms [8-10].

The following equations were used to fill the model :

$$C = K_0 t \text{----------} \quad (7)$$

$$Log\, C = Log\, C_0 - kt/2.303 \text{ ---------} \quad (8)$$

$$Q = K\sqrt{t} \text{----------} \quad (9)$$

$$Q_0^{1/3}\ Q_t^{1/3} = k_{HC}\,\mathbf{x}\,t \text{----------} \quad (10)$$

$$Q/Q_0 = Kt^n \text{----------} \quad (11)$$

Where, C_0 = Drug concentration at t = 0, C = the amount of drug un-dissolved at t time Q_0 = Initial amount of the drug in the tablets, Q_t = the amount of drug release in time t k = corresponding release rate constant, n = The diffusion exponent that depends on the release mechanism.

If $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5 < n < 1$, the release follows a non-Fickian diffusion or anomalous transport [11]. The drug release follows zero order drug release and case II transport if n=1. But when n>1, then the release mechanism is super case II transport. This model is used in the polymeric dosage form when the release mechanism is unknown or more than one release phenomena is present in the preparation.

Stability studies

Stability studies were done according to ICH guidelines to assess the drug and formulation stability [12]. All the formulations were subjected to stability study at 40 ± 2ºC and 75 ± 5% RH for 90 days. The samples were evaluated for physical changes, hardness, friability, drug content and percentage drug release during the stability studies. The assay of stressed alprazolam matrix tablet was carried out by High Performance Liquid Chromatography (HPLC) method.

RESULTS AND DISCUSSION

Characterization of granules

Physical properties of the granules of different proposed formulations (F-1 to F-10) were shown in Table 2. The results of LBD ranged from 0.419±0.03 to 0.449±0.02 g/ml. The results of

Table No. 2: Physical properties of the prepared granules of different formulations

Formulation	Loose Bulk Density (LBD) (gm/ml)	Tapped Bulk Density (TBD) (gm/ml)	Carr's Index (%)	Hausner ratio	Total Porosity (%)	Angle of Repose (°)	Moisture content (%)
F-1	0.419±0.03	0.509±0.02	17.682±0.02	1.215±0.02	17.65± 0.06	27.19±0.02	5.2125
F-2	0.431±0.04	0.526±0.03	18.060±0.03	1..220±0.03	17.03±0.04	26.74±0.03	5.1104
F-3	0.434±0.02	0.506±0.03	14.229±0.02	1.166±0.04	16.31±0.03	28.36±0.02	5.3102
F-4	0.445±0.04	0.529±0.05	15.879±0.02	1.189±0.03	14.53±0.01	27.81±0.01	4.9857
F-5	0.439±0.03	0.521± 0.03	15.739±0.03	1.187±0.04	15.62±0.01	26.54±0.03	5.1098
F-6	0.442±0.02	0.519±0.03	14.836±0.03	1.174±0.01	13.58±0.01	28.44±0.03	5.2569
F-7	0.441±0.02	0.532±0.04	17.105±0.04	1.206±0.02	16.98±0.01	26.91±0.01	5.1152
F-8	0.431±0.02	0.529±0.01	18.526±0.02	1.227±0.04	13.63±0.01	28.11±0.03	5.2351
F-9	0.444±0.03	0.544±0.04	18.382±0.02	1.225±0.02	15.65±0.02	27.51± 0.04	4.9314
F-10	0.449±0.02	0.527±0.03	14.801±0.03	1.174±0.03	16.47±0.04	27.69± 0.02	5.1265

Table No. 3: Properties of the prepared tablets of different formulations

Formulation	Average weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kp)	Friability (%)	Assay (mg/tab)	content uniformity (mg/tab)
F-1	200±2.5%	8.00	3.77±0.01	11.6±0.05	0.27	1.0557	1.0118
F-2	200±2.5%	8.00	3.81±0.02	11.5±0.06	0.29	1.0424	1.0123
F-3	200±2.5%	8.00	3.69±0.02	11.1±0.04	0.32	1.0616	1.0154
F-4	200±2.5%	8.00	3.65±0.01	11.4±0.03	0.18	1.0266	1.0118
F-5	200±2.5%	8.00	3.79±0.01	11.5±0.04	0.17	1.0532	1.0156
F-6	200±2.5%	8.00	3.80±0.01	11.4±0.08	0.35	1.0687	1.0129
F-7	200±2.5%	8.00	3.59±0.02	11.2±0.04	0.23	1.0763	1.0134
F-8	200±2.5%	8.00	3.68±0.01	11.3±0.07	0.44	1.0105	1.0114
F-9	200±2.5%	8.00	3.84±0.02	11.7±0.05	0.39	1.0211	1.0137
F-10	200±2.5%	8.00	3.67±0.03	11.4±0.02	0.41	0.9917	1.0172

angle of repose (<30^0) indicated good flow properties of the granules. This was further supported by lower Carr's index (14.229±0.02 to 18.526±0.02%) and Hausner ratio (1.166±0.01 to 1.264±0.03) values. The percentage porosity values (13.58±0.01 to 17.65±0.06%) of the granules indicated that the packing of the granules might range from close to loose packing and also further confirming that the particles were not of greatly different in sizes. The results indicated that the granules possessed satisfactory flow properties and compressibility properties.

Physicochemical evaluation of matrix tablets

The results of physical parameters (weight, hardness, thickness and friability) and drug content of the prepared matrix tablets are shown in Table 3. The thickness of the tablets were found between 3.59±0.02 to 3.84±0.02 mm, hardness of the tablets ranged from 11.1±0.04 to 11.7±0.05 Kp and friability ranged from 0.17 to 0.44%. The weight variations of prepared tablets (200±2.5%) complied with the pharmacopoeial specifications. The drug content of every formulation was found about to 100% of labeled content. Good uniformity of content of alprazolam showed uniform drug distribution. So, it can be said that physical properties and drug content of the compressed matrix tablets were satisfactory.

***In vitro* release study**

The release profiles of different formulations (F-1 to F-10) of alprazolam matrix tablets are shown in Fig. 1. All dissolution data are based on the actual drug content of the test tablets as calculated from the assay results. The result showed that the drug release from the tablet was sustained for 16 hr. The drug release profiles were well controlled and uniform throughout the dissolution studies. HPMC polymers form viscous gelatinous layer (gel layer) upon exposure to aqueous medium by undergoing rapid hydration and chain relaxation and this gel layer acts as the barrier to release of drug and as a result drug release was prolonged.

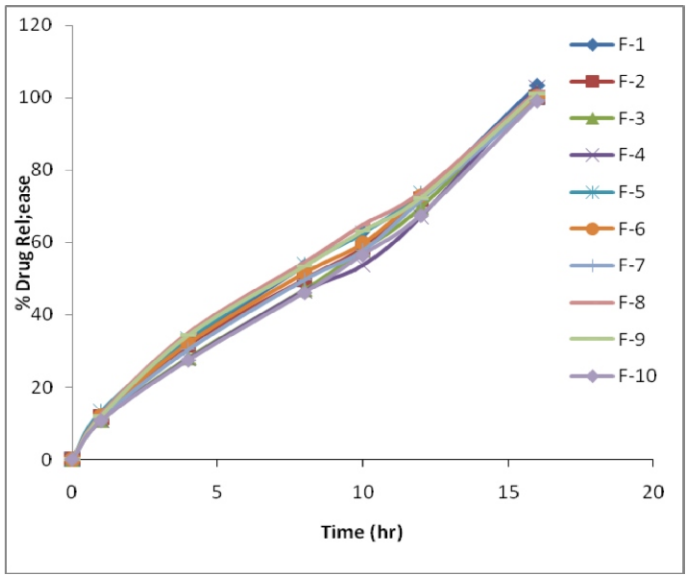

Fig: 1 Drug release from different formulations (F-1 to F-10)

Table No. 5: Drug release rate parameters (Time in hr)

Formulation	T25%	T50%	T80%	MDT
F-1	2.794	7.258	13.867	7.932
F-2	2.917	7.700	14.873	8.469
F-3	3.202	8.232	15.616	8.959
F-4	3.301	8.657	16.644	9.495
F-5	2.568	7.106	14.170	7.966
F-6	2.822	7.510	14.587	8.287
F-7	3.034	7.863	14.995	8.583
F-8	2.598	6.905	13.399	7.615
F-9	2.728	7.163	13.785	7.861
F-10	3.294	8.513	16.207	9.284

Drug release kinetics

The data from table 4 shows that all the formulations were best fitted to Zero order, First Order, Korsmeyer-Peppas and Hixson-Crowell. To confirm the drug mechanism, the data were fitted into KorsmeyerPeppas equation. All the formulations showed exponent (n) values ranging from 0.706 to 0.772, indicating anomalous / non- Fickian transport as if $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5 < n < 1$, the release follows a non-Fickian diffusion or anomalous transport [11].

Successive fractional dissolution time

Successive fractional dissolution time ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$) of ten formulations (F-1 to F-10) of alprazolam matrix tablets were summarized in table 5.$T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ were changed due to the change of polymers ratio. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa.

Comparison of dissolution data

Difference factor (f1), similarity factor (f2) and dissolution efficiency (%DE) were calculated to compare the dissolution profile with innovator brand [12-13]. Difference factor f1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \times (t_2 - t_1)} \times 100$$

Table No. 4: Y-equation (Y = aX+b) and correlation co-efficient (R2) from different plots of formulation F-1 to F-10

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson- Crowell	
	K_0	R^2	K_1	R^2	K_h	R^2	n	R^2	K_{HC}	R^2
F-1	6.069	0.992	-0.044	0.992	24.39	0.943	0.726	0.996	0.131	0.997
F-2	5.86	0.991	-0.042	0.976	23.48	0.936	0.714	0.991	0.123	0.988
F-3	5.925	0.99	-0.04	0.979	23.49	0.916	0.734	0.988	0.119	0.99
F-4	5.88	0.98	-0.036	0.979	23.18	0.896	0.719	0.984	0.111	0.988
F-5	5.886	0.991	-0.044	0.988	23.82	0.955	0.681	0.994	0.13	0.994
F-6	5.892	0.991	-0.043	0.979	23.68	0.942	0.708	0.993	0.126	0.99
F-7	5.849	0.992	-0.041	0.975	23.4	0.934	0.728	0.991	0.122	0.987
F-8	5.996	0.99	-0.046	0.993	24.31	0.957	0.709	0.997	0.134	0.996
F-9	5.932	0.989	-0.044	0.994	23.98	0.952	0.718	0.996	0.129	0.996
F-10	5.778	0.99	-0.038	0.984	22.91	0.915	0.73	0.986	0.114	0.993

Table No. 6: Comparison of dissolution (f1, f2 and %DE) data with innovator brand

Pair Comparison	f2	f1	%DE
IB			56.88
F-1	93.30	1.33	56.15
F-2	71.52	5.13	53.99
F-3	64.62	7.59	52.17
F-4	59.10	9.40	51.12
F-5	84.72	2.47	56.21
F-6	76.86	3.91	54.86
F-7	69.08	6.05	53.40
F-8	90.58	1.80	57.33
F-9	87.80	2.35	56.18
F-10	60.41	9.74	50.94

Table No 7: Potency of different formulations (F-1 to F-10)

Formulation	Initial potency (mg/tab)	Potency after 90 days (mg/tab)
F-1	1.0557	1.0716
F-2	1.0424	1.0422
F-3	1.0616	1.0394
F-4	1.0266	1.0278
F-5	1.0532	1.0672
F-6	1.0687	1.0481
F-7	1.0763	1.0349
F-8	1.0105	1.0387
F-9	1.0211	1.0342
F-10	0.9917	1.0118

similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The following equations were used to calculate difference factor (f1), similarity factor (f2) and dissolution efficiency (%DE) Where n is the number of time points, Rt is the dissolution value of reference product at time t and Tt is the dissolution value for the test product at time t.

Table 6 shows the f1, f2 and % DE values of different brands in respect of innovator brand. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 to15 and f2 is between 50 to 100 (FDA, 1997). All the formulations seem to be best similar to the innovator brand for higher f2 and lower f1 value. % DE of all the brands is close to the innovator brand..

Stability study

Potency of different formulations (F-1 to F-10) after 90 days is summarized in table 7. The assay of stressed alprazolam matrix tablets at 40°C+75%RH was carried out by High Performance Liquid Chromatography (HPLC) method. The assay of alprazolam found 1.0118 to 1.0716 mg/tablet.

CONCLUSION

The present study was undertaken with an aim to design oral sustained-release tablets of alprazolam for once daily administration for the therapy of anxiety. It can be concluded that the present study indicates that the oral sustained release tablets of alprazolam provides a better option for development of a once daily formulation of the drug. Success of the *In vitro* drug release studies recommends the product for further in vivo studies.

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