INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

FORMULATION, DEVELOPMENT AND OPTIMIZATION OF ALPRAZOLAM 0.5 MG SUSTAINED RELEASE TABLET WITH 12 HOURS RELEASE PROFILE

Ayon Dutta[1]* and Jayanta Chattapadhyay[2]

[1]Department of Pharmaceutics, Bengal School of Technology, Sugandha, Hooghly, Delhi Road, 712102, West Bengal, India.
[2]Department of Pharmaceutical Technology, Bengal School of Technology, Sugandha, Hooghly, Delhi Road, 712102, West Bengal, India.

ABSTRACT

Alprazolam is a Benzodiazepine derivative drug used as an antianxiety drug. Alprazolam 0.5 mg sustained release tablet already available in market but most manufacturers have not reported release profile of their formulation . So, basically marketed Alprazolam 0.5 mg sustained release follows 8 hours release profile. As per comparison of release profile of marketed tablet here developed Alprazolam 0.5 mg sustained release tablet with 12 hours release profile. Total six formulations are developed by using some different rate controlling polymers HPMC (Methocel) K 15 and K 100, PVP K 30, Sodium carboxy methyl cellulose, Acrypol 912G and 971G and other some excepients like lactose , microcrystalline cellulose, dicalcium phosphate, magnesium stearate. Formulations are developed and optimized by changed the ratio of rate controlling polymer. Here mentioned the best two formulation from all formulations. First formulation of best of two follows 8 hours release profile and depending on this profile developed the final formulation by changing ratio of polymers which formulation followed the 12 hours release profile. This 12 hours release profile alprazolam 0.5 mg sustained release tablet not available in market. All formulations are prepared by wet garanulation method. After compression the finished tablet release profile were done by using USP type 1 rotating basket type dissolution apparatus and dissolution medium Phosphate buffer 6.4. Plotted all dissolution kinetic models and swelling index study also done of this tablet. Morphology study of tablets done by using scaning electron microscopy (SEM). Total formulations were prepared according to I.P and follows 3 point assay of I.P.

Keywords: Alprazolam, HPMC, SEM, anxiety and swelling index.

INTRODUCTION

Oral drug delivery system is the most easy and convenient system for oral route. Different types of oral drug delivery system available in market and one of them is sustained release drug delivery system. Sustained release drug delivery system is a system achieved release of drug over an extended period of time. It is a polymer based matrix system consist some hydrophilic polymer. The role of sustained release drug delivery system to deliver the drug at regular time interval and proper site action to maintain therapeutic drug range in plasma. The basic goal of this therapy to achieve a steady state blood level and therapeutically effective for an extended period of time. During long term therapy in case of chronic disease condition if conventional drug delivery are used causes need to administered multiple doses and several demerits are there.

In case of sustained tablet suitable for this type of chronic diseases and give better patient

compliance, always maintain optimum drug level, reduce dose and side effects and maintain the safety margin of high potency of drugs. Sustained release drug delivery system basically accomplished with zero order drug release kinetics that is independent of drug concentration. This type of drug delivery system try to maintain the zero order drug release kinetics and provide the drug in slow first order fashion. Sustained release drug delivery system prepared based on some rate controlling polymer like hydroxyl propyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), carboxy methyl cellulose (CMC), they are all cellulose derivative rate limiting polymer. Those polymers are most preferable polymers for sustained release dosage because of its cost effectivity, broad acceptance, no toxicity and easy for compression. Some factor affects sustained release drug delivery system like molecular size, drug diffusivity, pka ionization constant, drug release rate, stability, action duration, therapeutics window and index. Depend on the sustained release drug delivery system some other delivery system are developed like mucoadhesive drug delivery system and other targeted drug delivery system.

Oral sustained release tablet formed by wet granulation technique and it is a easy and fastest approach for manufacturing of sustained release dosage form. In case of wet granulation technique the main part is mixing of granulating solvent. Most propular solvent is water traditionally used as a solvent for wet granulation technique. Now hydroalcohlic solution also used as a granulating solvent. The most important things is choosing of solvent and mixing proper percentage of solvent during wet granulation technique.

In the present study sustained release dosage form of Alprazolam 0.5 mg has been developed that makes less frequent administering of drug.

Alprazolam is a benzodiazepine derivative drug which affects the chemicals in the brain that may be unbalanced a people with anxiety. Alprazolam is a high potency benzodiazepine classed and is a triazolebenzodiazepine, formed by benzodiazepine with a triazole ring attached to its structure. Basically alprazolam used as antidepressant or antianxiety drug. This drug basically bind with GABA receptor site and it have different location in brain. The triazol ring of alprazolam attached with the GABA receptor zone and that causes given antidepressant activity.

Alprazolam suatained release drug available in market as 0.5 mghowever their release profiles are not declared.Literature survey on alprazolam sustained release formulation revealed 0.5 mg SR tablets have release pattern 8hrs and 24 hrs. To address the need of 12 hrs sustained release profile so that anxiolytic activity last for 12 hrsso that the anxious patient can have 8 to10 hours anxiety free sleep the present aims to develop 12 hrs sustained release profile .

MATERIALS AND METHODS

Materials are used in this study were obtained from industry. The active pharmaceutical ingredient and other excepients were come from Stadmed Pvt.ltd, dumdum, Kolkata. In this study Alprazolam is the active pharmaceutical ingredients. Other excepients used with some rate limiting polymer likeHPMC [K-15M], HPMC [K-100M], dibasic calcium phosphate (DCP), Microcrystalline cellulose (MCC), Polyvinyl pyrollidone K-30 (PVP K-30), Purified Talc, Aerosil, Magnesium Stearate, Sodium Carboxy methyl cellulose (sodium cmc), Isopropyl alcohol(IPA), this all materials which are used to development of this dosage forms, those all materials are supplied by industry(Stadmed pvt.ltd).Instruments are used in this development mentioned in below table(1).

Formulation and development of Alprazolam sustained release tablet

Formulation and development of Alprazolam sustained release tablet with the help of some rate limiting polymer. HPMC K15 and HPMC K100M bothare main rate limiting polymer used in this formulation. These two polymers used in this formulation by changing the ratio of polymer and developed final formulation with 12 hours release profile. This formulation release profile obeys the 3 point assay system according to IP. 3 point assay means:-

1. At 1st point release should be between 20% to 30% of label claim of Alprazolam IP.
2. At 2nd point release should be between 45% to 55% of label claim of Alprazolam IP.
3. At 3rd point release should be not less than 80% of label claim of Alprazolam IP.

Preparation of Alprazolam sustained release tablet

The required amount of drug was taken and gradually mixed with filler and then passes through sieve number 60. Then diluents and disintegrant was gradually mixed with the above mixture and pass through sieve no. 60. The rate limiting polymers of different graded were pass through sieve no. 60 and mixed well with the above mixture. This is the step of dry mixing. Take required amount of binder and dissolved in required quantity of water or isopropyl alcohol and prepared a clear solution with

continuous stirring. Then the binder solution added slowly in dry powder mixture and mixed well. Added extra granulating solution from outside if needed and prepared wet mass or granules. Then the wet mass distributed in a tray and placed in drier at 50-60°C. After drying the large granules are pass through 20 number sieve or milled in multi mill if needed and form small and fine granules. Then check the loss of drying (LOD). Then the granules were lubricated with the help of lubricant. Then the lubricated granules were filled in hopper and set the appropriate punches in compression machine and then compress the granules as tablets.

Formulation of Sustained release dosage forms

Six different formulations F1, F2, F3, F4 and F5, F6 has been made. F1 to F4 are formulation of trial stages, and F5 and F6 are developing stages. F5 is a 8 hours release formulation and this same formulation is used for 12 hours alprazolam0.5 sustained release tablets. F6 is the extended version of F5 formulation. The total formulation are mentioned below Table: 2

Evaluation of Alprazolam sustained release tablet

Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester and also can be measured by other tester like Pfizer tester, Strong cob tester. The hardness was measured in terms of kg/cm^2.

Thickness

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Micrometer screw.

Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss in tablet weight was determined.

% loss =

Initial weight of tablets – Final weight of tablets/Initial weight of tablets*100

Uniformity of Weight

Weigh 20 tablets at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown and none deviates by more than twice that percentage.

In-vitro Dissolution Studies

In vitro drug release profile of matrix tablet is determined with the help of USP dissolution type1 basket type apparatus. In general, a single matrix tablet is placed in dissolution flask which contain 900 ml dissolution medium. The flask is maintained at 37º ± 0.5º C by a constant temperature bath. Phosphate buffer 6.4 used as dissolution medium in this experiment.

Kinetic modelling of drug release

The dissolution profile of all formulation was kinetically shown by using some kinetic equation model like zero order, First order, higuchi model, korsmeyerpeppas models to other kinetic modelling of drug release.

Scanning Electron Microscopy (SEM)

The morphology of the tablet and the internal structure of the tablet when the excepients and the drug are mixed together, this are shown by Scanning Electron Microscopy (SEM) instrument **SEM JEOL MAKE (UK) MODEL- JSM6360.**

Swelling Index study

The swelling index characterizes the rate at which a tablet will dissolute and is also an indicative of the mechanism.The diameter of tablets was taken at intervals of five minutes until maximum diameter was attained with a digital Vernier calliper. Thereafter the swelling indices (SI) were calculated from initial diameter of tablet (D1) and maximum diameter on swelling in water (D2) as expressed below:

$$SI\ (\%) = D2/D1 \times 100$$

Morphological characterization of tablet by scanning electron microscopy

Morphological character of tablet that visible and subvisible particulate matter present in matrix tablet and saw the compactness of the tablet between active pharmaceutical ingredient and excepients. Pharmaceutical manufacturing companies are used high resolution SEM technique for elementally quantify the size and shape of the particles. Here we just studied the morphological structure of alprazolam sustained release tablet in different resolution and saw the compactness structure of the matrix of the tablet

and porosity of the tablet matrix which through dissolution fluid entered in to tablet.

Interpretation of SEM

In those pictures of SEM of tablet surfaces and inner matrix of the tablets are occurred in different process of zooming. 50X and 500 micrometer show the fine tablet surfaces. And 150X, 250X, 350X, 500X those are shows the tablets inner matrixes where the picture shows the compactness of the tablet occurs between API and the excepients. And another shows the pore of matrixes when the dissolution fluid entered in to tablet matrix and swelling occurred depend on the time and swelling increases with time so, porosity increases and the drug release from this pore of matrices. The interpretation of SEM shown by following Figures 1.

Swelling index study of Alprazolam 0.5 mg sustained release tablet

Swelling index indicate that porosity of the tablet increases with time interval due to dissolution fluid entered slowly in to the tablet matrix. Tablet matrix swelled with the connection of dissolution fluid and porosity increases, which induced the drug release with time. Here performed the swelling index study of both 8hrs and 12 hrs release profile alprazolam sustained release tablet.

The diameter of tablets was taken at intervals of five minutes until maximum diameter was attained with a digital Vernier calliper. Thereafter the swelling indices (SI) were calculated from initial diameter of tablet (D1) and maximum diameter on swelling in water (D2) as expressed below: SI (%) = D2/D1 x 100.

The swelling index study determination shown in following Tables: 3 (A and B) and figures 2.

Drug release profile with kinetic graph modelling

Here previewed the drug release profile of both 8hrs and 12hrs drug release profile and calculate the cumulative drug release of the drug. Some other data also be calculated from cumulative drug release.

The drug release profile put in to some kinetic graph model with respect to time ,logCDR, cube root CDR.

Calculation of drug release profile and dissolution kinetics graphs are shown in following Tables: 4 and 5 figures 3.

RESULT AND DISCUSSION

Sustained release tablet of Alprazolam prepared by following the 3 point assay release profile according to I.P. Predicted a idea about the sustained release tablet of alprazolam 0.5 mg and determined the release profile by checked the dissolution profile of any marketed drug. After the market prediction justified that only 8 hrs release profile present in market and depend on this survey report here developed and optimized alprazolam 0.5 mg sustained release tablet with 12 hrs and also 8 hrs release profile using different rate limiting polymers and excepients.

CONCLUSION

The present research work envisages the applicability of Polymers such as HPMCK15M and K100M in the design and development of sustained release tablet formulations of Alprazolam utilizing the factorial design. From the results it was clearly understand that as the retardant (HPMC) concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired sustained release of the drug for longer periods. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be NonFickian Diffusion, Zero order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation F5 may be used once a day administration in the management of anxiety . This may improve the patient compliance by reducing the dosing frequency. which will ultimately improve the therapeutic outcome. We could be able to minimize the per oral cost of the Formulation.

ACKNOWLEDGEMENT

I take this opportunity to express my heartly thanks to all those who have contribute for the success for this research work.

I express my sincere gratitude to my esteemed guide Prof. Dr. Jayanta Chattopadhyay, and supporting industry Stadmed Pvt.ltd for this valuable and meticulous guidance, which help me to achieve my task. His encouragement and constant supervision has motivated me to build up the optimistic attitude towards my dissertation.

I owe my warmest and heartfelt thanks to our beloved Director Prof. Dr. Pranabesh Chakraborty,Bengal School of Technology, for providing us the best of the facility to carry out our project work and has been of constant help throughout our work.

I also thankfull to Stadmed .Pvt.ltd for help to complete me the whole project work.

Table 1: Instrument used and their model/make

S. No.	Instruments	Model/make
1.	Multimill	Salmach Pharmaceutical Pvt.Ltd
2.	Tablet compression machine (rotary)	Cadmad 16 stations compression machine
3.	Hardness tester	Monsanto hardness tester
4.	Friability tester	Scientech SE-275 singe model
5.	Disintegration apparatures	J.S Enterprises
6.	Dissolution apparatures	VEEGO MODEL-VDA-6D

Table 2: Formulation of sustained release dosage form

Code	Formulation											
Formulation	API (Drug)	Methocel/ HPMC [K-15 M]	Methocel/ HPMC [K-100 M]	Lactose I.P	M.C.C I.P	D.C.P I.P	PVP K-30 I.P	Sodium C.M.C	Acrypol 912G/ Acrypol 971G	Aerosil I.P	Purified Talc I.P	Mag. Stearate
	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm	Mg/Gm
F1(8 hr)	0.5/1.0	45/90	32/64	44/88	35/70	*	5/10	*	*	*	2.25/4.5	1.25/2.5
F2 (8 hr)	0.5/1.0	65/130	65/130	55/110	41.9/83	*	7.5/15	*	*	*	3.3/6.6	1.8/3.6
F3 (8 hr)	0.5/1.0	60/120	80/160	*	54/108	56/112	20/40	30/60	*	*	6.0/12	3.0/6.0
F4 (8 hr)	0.5/1.0	*	*	42/84	37/74	37/74	*	*	1)33/66 2)2.5/5.0	*	5.0/10	1.0/2.0
F5 (8 hr)	0.5/1.0	20/40	25/50	*	30/60	30/60	5.0/10	*	*	0.8/1.6	3.0/6.0	1.5/3.0
F6 (12 hr)	0.5/1.0	30/60	40/80	*	35/70	35/70	10/20	*	*	0.8/1.6	3.0/6.0	1.5/3.0

Note:

1) F1 & F2: In two formulations granulating solvents used Isopropyl alcohol I.P and purified water I.P (Hydro alcoholic solution).

2) F3, F4, F5, & F6: Those formulations granulating solvent used only purified water I.P.

Table 3: A)Swelling index study of Alprazolam 0.5 SR tablet (8 hours release)

Time(hrs)	D1(mm)	D2(mm)	Swelling Index
1	7.032	7.5	106
2	7.032	7.9	112
3	7.032	8.2	116
4	7.032	8.5	120
6	7.032	8.7	123
8	7.032	9.0	127

B) Swelling index study of Alprazolam 0.5 SR tablet (12 hours release)

Time(hrs)	D1(mm)	D2(mm)	Swelling Index
1	6.595	6.7	101.5
2	6.595	6.85	103.8
3	6.595	6.9	104
4	6.595	7.1	107.65
6	6.595	7.4	112.20
8	6.595	7.6	115.2
10	6.595	7.9	119.7
12	6.595	8.15	123.5

Table: 4 Alprazolam 0.5 SR tablet with new dissolution profile (up to 12 hrs)

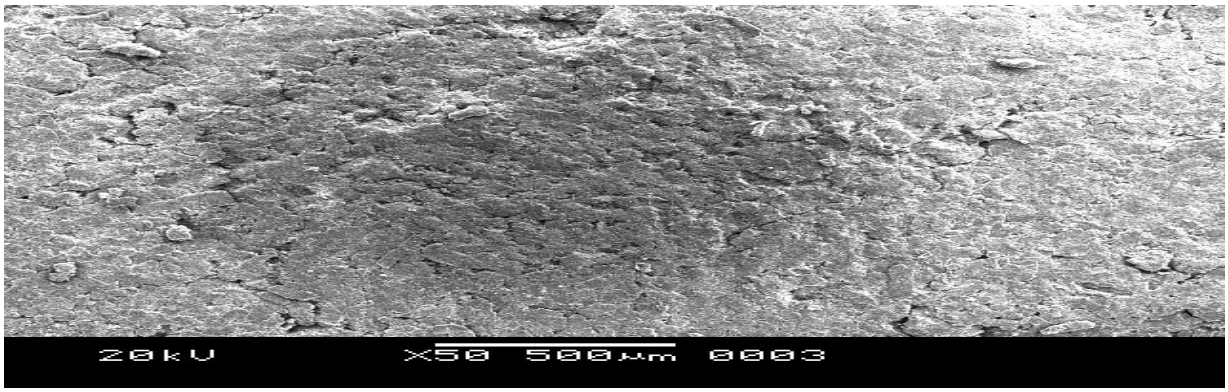
	Initial	Limit
Description	A white coloured , uncoated, circular, 'STADMAD' EMBOSED, scored, flat tablet	
Identification	Positive for Alprazolam.	
Hardness	3.0 kg/cm2	

Diameter	7.031 mm	
Thickness	3.294 mm	
Friability	0.49%	
Average weight	0.15464 g	
Assay:-	Each uncoated tablet contains:-	
Alprazolam IP	Mg/tablet Claim: 0.5 mg/tablet	90% to 110% of label claim of Alprazolam IP
Dissolution (For 1st hour)	20.62%; 24.07%; 22.29%; 21.83%; 23.65% of stated amount	At 1st point release should be between 20% to 30% of label claim of Alprazolam IP. At 2nd point release should be between 45% to 55% of label claim of Alprazolam IP. At 3rd point release should be not less than 80% of label claim of Alprazolam IP.
Dissolution (For 2ndhour)	29.72%; 31.62%; 32.28%; 32.54%; 32.57% of stated amount	
Dissolution (For 3rdhour)	38.04%; 39.52%; 40.12%; 40.06%; 40.15% of stated amount	
Dissolution (For 4thhour)	48.65%; 47.17%; 46.85%; 45.18%; 45.92% of stated amount	
Dissolution (For 6thhour)	54.59%; 57.90%; 55.36%; 57.85%; 58.29%; of stated amount	
Dissolution (For 8thhour)	63.36%;64.76%;65.29%; 62.01%; 65.77% of stated amount	
Dissolution (For 10thhour)	75.75%;74.89%;77.76%;75.86%; 74.86% of stated amount	
Dissolution (For 12thhour)	82.75%;81.76%;82.86%; 81.78%; 81.69% of stated amount	

The same formula of 8hrs release profile is used in this 12 hrs release profile, only change in the ratio of excipients taken.

Table 5: Dissolution release kinetics of Alprazolam 0.5 Sustained release tablets (release 12 hrs)

TIME(hr)	CDR (%)	LOG CDR	LOG TIME	CUBE ROOT CDR	SQUARE ROOT TIME
0	0	0	0	0	0
1	22.49	1.351989	0	2.82269	1
2	31.74	1.501607	0.30103	3.16618	1.414214
3	39.57	1.597366	0.477121	3.407653	1.732051
4	46.75	1.669782	0.60206	3.602416	2
6	56.79	1.754272	0.778151	3.843769	2.44949
8	64.23	1.807738	0.90309	4.004786	2.828427
10	75.8	1.879669	1	4.232105	3.162278
12	82.16	1.91466	1.079181	4.347305	3.464102



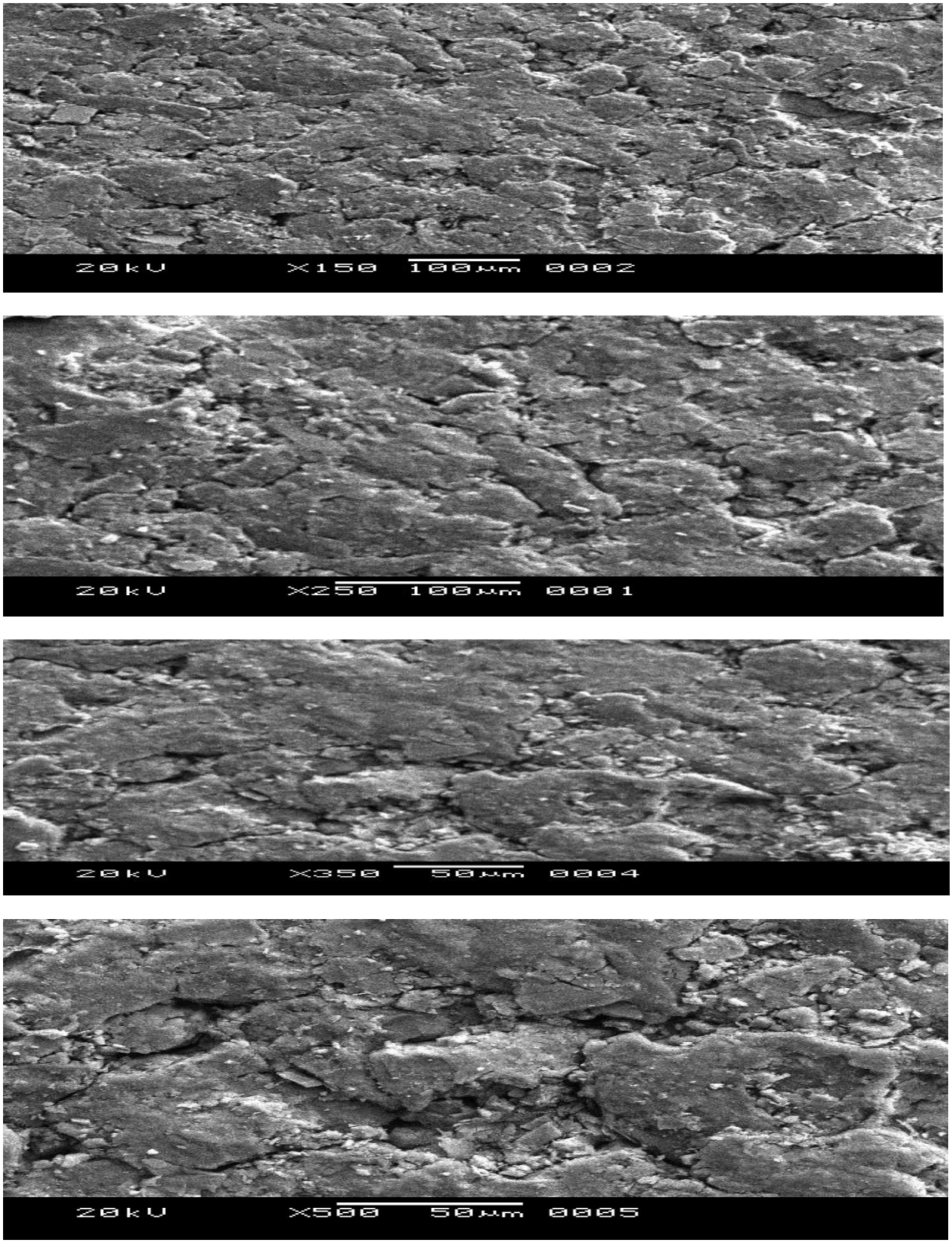


Fig. 1: Morphological characterization of tablet by scanning electron microscopy

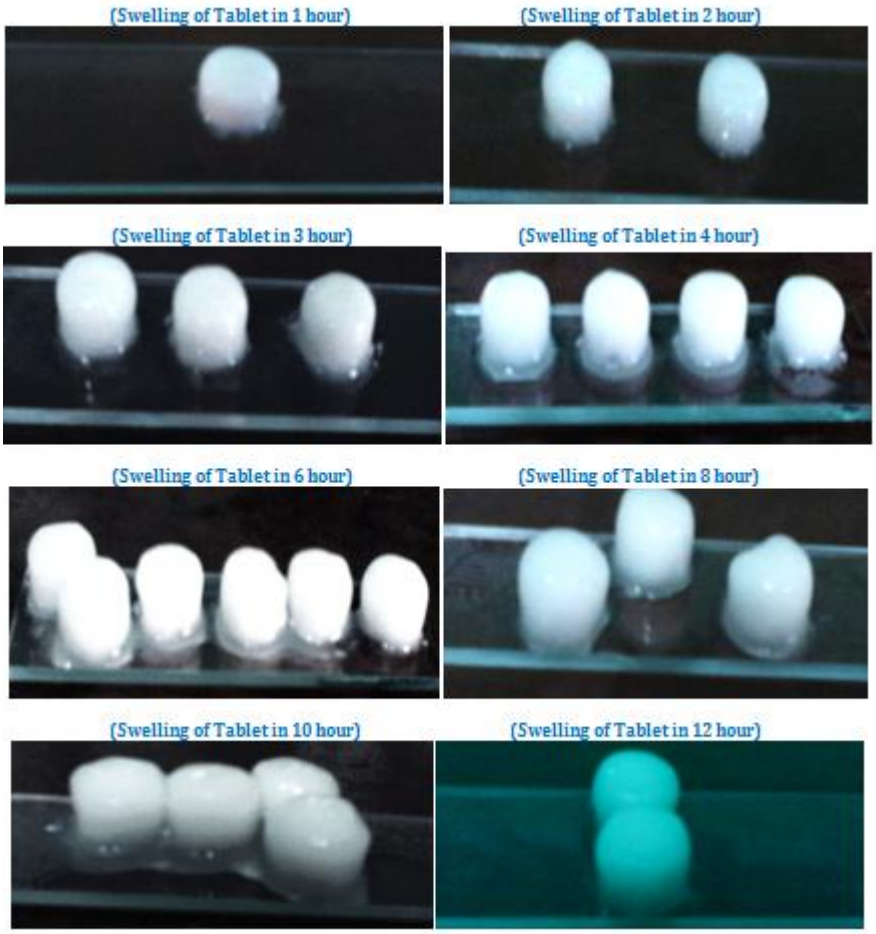
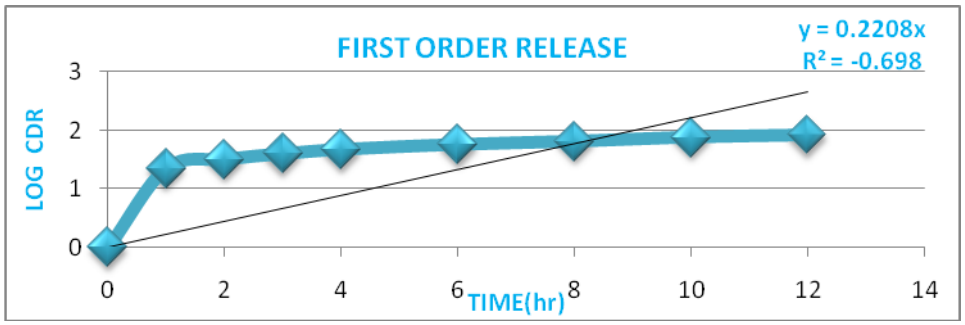


Fig. 2: ALPRAZOLAM 0.5 SR TABLET (RELEASE 12 HOURS)
Swelling Property Increases with Time in Dissolution Fluid



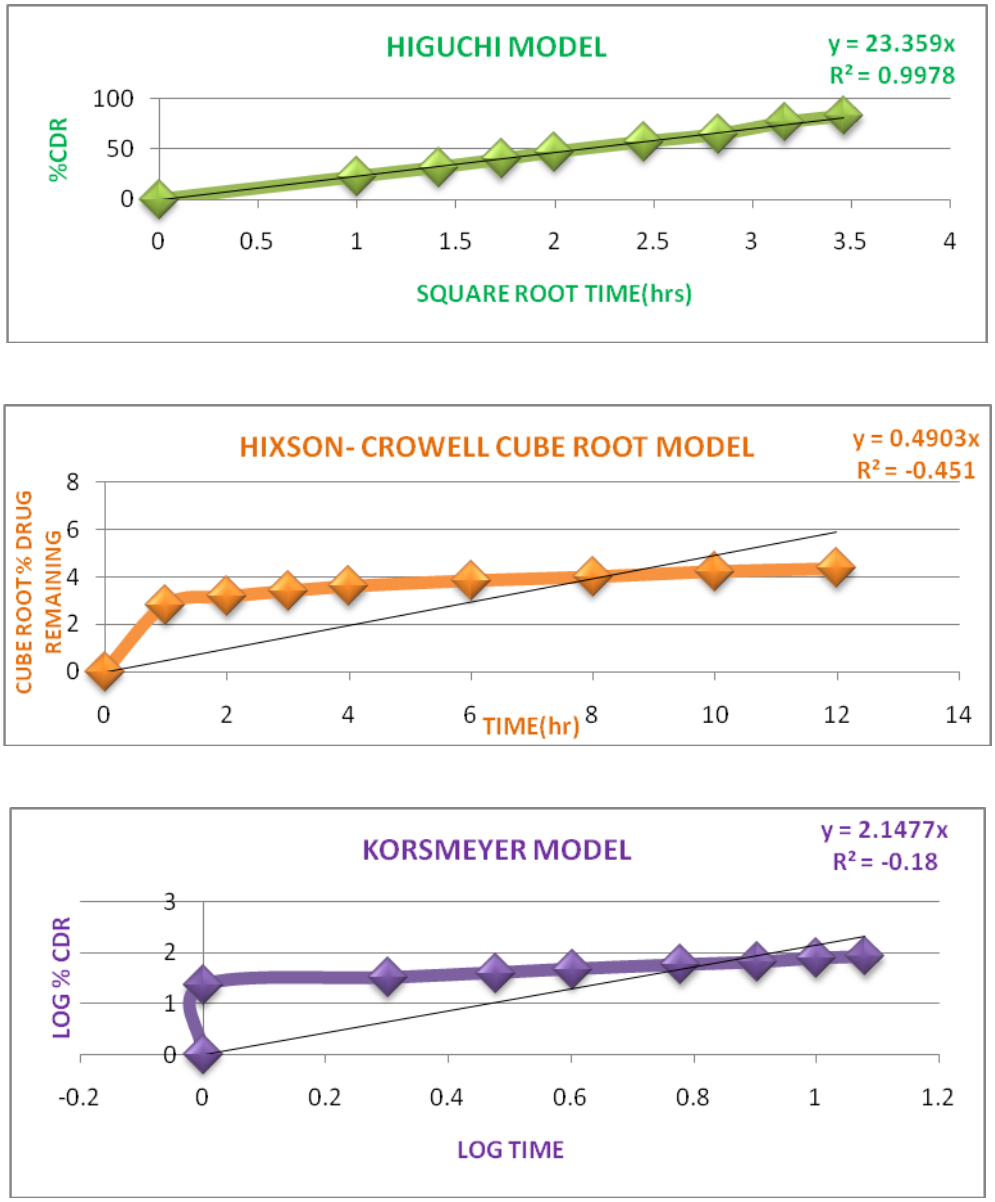


Fig. 3: Graphical Plot Different Dissolution Kinetics Model

REFERENCES

1. Ratilal D and Gaikwad Priti D. An Overview on Sustained Release Drug Delivery System, International Journal of Research and Applied Pharmaceutics. 2011;1701-1708.
2. Ho WH and Lee HLV. Sustained Drug Delivery Fundamentals and Applications. Design and fabrication of oral controlled release drug delivery system. 2nd ed. Marcel Dekker Inc. New York. 1987;373-420.
3. Mohammed AD, James LF, Michael HR, John EH and Rajabi-Siahboomi AR. Release of propranolol hydrochloride from matrix tablets containing sodium carboxy methylcellulose and Hydroxypropyl methylcellulose. Phar Dev Tech. 1999;4:313-324.
4. Venkataraman DSN, Chester A and Kliener L. An overview of controlled release system.Handbook of pharmaceutical controlled release technology. Marcel dekker Inc. 2000;1-30.
5. Basak S, Reddy JB and Mani LK. Formulation and release behavior of sustained release ambroxol hydrochloride HPMC matrix tablet. Indian J Pharm Sci. 2006;68:594-598.
6. Lee VHL. Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design, (2nded)

Marcel Dekker, INC. New York. 1987;16-25.
7. Martínez-González I and Villafuerte-Robles L. Effect of varying the restriction degree of 4-aminopyridine release from HPMC matrices on the mechanism controlling the process. Int J Pharm. 2003;257(1-2):253-64.
8. Salsa T, Veiga F and Pina ME. Oral controlled release dosage form. Cellulose ether polymers in hydrophilic matrices. Drug Develop and Ind Pharm. 1997;23:929-938.
9. Kamboj S, Saroha K, Goel M and Madhu C. Sustained Release Drug Delivery System. An Overview. Journal of Pharmaceutics. 2013;1:169-181.
10. Ratilal D and Gaikwad Priti D. An Overview on Sustained Release Drug Delivery System. International Journal of Research and Applied Pharmaceutics. 2011;1701-1708.
11. Gandhi A and Kumar SL. Recent Trends in Sustained Release Drug Delivery System. International Journal of Applied Pharmaceutics. 2014;1:122-134.
12. Phad Anil B, Mahale NB, Chaudhari SK and Salunke SK. A Sustained Release Drug Delivery System. World Journal of Pharmaceutical Research. 2014;3(5):1377-1390.
13. PatelChirag J and Satyanand T. Novel Sustained Release Drug Delivery: A Modern Review. International Journal of Applied Pharmaceutics. 2014;1:115-119.
14. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics. 1983;2:25-35.
15. Gwen MJ and Joseph R. Sustained and Controlled Release Drug Delivery System. Modern Pharmaceutics Journal of Applied Sciences. 2002;507-510.
16. Vinay K, Prajapati SK, Girish C, Mahendra S and Neeraj K. Sustained Release Matrix Type Drug Delivery System: A Review. World Journal of Pharmacy and Pharmaceutical Sciences. 2012;1:934-960.
17. Khyati P, Upendra P, Bhavin B, Ghansyam P and Dhiren D. Extended Release Oral Drug Delivery System. International Journal of Pharmaceutical Research and Biomedical Sciences. 2012;2:1-26.
18. Rao Raghavendra NG, Raj Prasanna Richard K and Nayak S. Review on Matrix Tablet as Sustained Release. International Journal of Pharmaceutical Research and Allied Sciences. 2013;2:1700-1717.
19. Kumar Sampath KP, Bhowmik D and Srivastava S. Sustained release drug delivery system potentials. International Journal of Pharmaceutics. 2010;2:751-754.
20. Misa R, Waghmare A and Aqueel S. Matrix tablet. A Promising Technique for Controlled drug delivery. Indo American Journal of Pharmaceutical Research. 2013;3:3791-3805.