ejpmr, 2019,6(2), 382-388

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND CHARACTERISATION OF SUSTAINED RELEASE MATRIX TABLETS OF ATAZANAVIR

Bharathi A.*, S. Durga Saranya, J. Sushma Roj, Chandra Sekhar Naik and Madhavi Kiran S.

Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India.

***Corresponding Author: Bharathi A.**
Department of pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India.

Article Received on 20/11/2018 **Article Revised on 11/12/2018** **Article Accepted on 02/01/2019**

ABSTRACT

The objective of present study is to develop a pharmaceutically stable sustained release matrix tablets of Atazanavir and perform the pre compression and post compression parameters and also *in-vitro* evaluation studies of developed formulation. In this investigation the sustained release matrix tablets of Atazanavir were prepared by direct compression method using different polymers like Guar gum, Xanthan gum and Sodium alginate in various concentrations. All the formulations showed acceptable pharmacopiea standards. In this investigation formulation F8 have extended the drug release upto 12hrs. Model fitting analysis for formulation F8 fitted in the zero order, first order, higuchi and peppas plots. The n values obtained from peppa's equation suggested that drug release was followed by non fickaiann diffusion mechanism. Successful formulation was found stable after evaluation for all parameters when kept for 30 days at room temperature at 40^0c.

KEYWORDS: Atazanavir, Sustained Release Tablets.

INTRODUCTION[1,2,3,4,5,6,7,8,9]

Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic fir an extended period of time.

The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Physician can achieve several desirable therapeutics advantages by prescribing sustained release dosage form. Since, the frequency of drug administration is reduced, patient's compliances can be improved and the drug administration can be made more convenient as well. The blood level oscillation characteristics of multiple dosing form of conventional dosage form is reduced, because more even blood level is maintained in the design of sustained release dosage form. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drug can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients. Overall, increased administration of sustained release dosage form gives increased reliability.

Sustained Release: SRF's describes the slow release of a drug substance from a dosage form to maintain therapeutic response for extended period of time. Time depends on the dosage form. In oral form it is in hours, and in parenterals it is in days and months. *Ex*: Aspirin SR, Dextrin SR.

Advantages

- Decreased local and systemic side effects.
- Better drug utilization.
- Improved efficiency in treatment.

Disadvantages

- Decrease systemic availability in comparison to immediate release convention as dosage forms.
- Retrieval of drug is difficult in case of toxicity in case

of toxicity, poisoning or hypersensitive reaction.

- Reduced potential for dosage adjustment of drug normally administered in varying strengths.

Potential Advantage of Sustained Release Dosage Form

✓ Avoid patient's compliance problem due to reduced frequency of dosing.

✓ Blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced because a more even blood level is maintained.

✓ Employ a less total drug.

✓ Minimize or eliminate local or systemic side effects.

✓ Minimize drug accumulation with chronic dosing.

✓ Obtained less potential of reduction in drug activity with chronic use.

✓ Improved efficiency in treatment.

- Cure or control condition more promptly.
- Improved control of condition *i.e.* reduced fluctuation in drug level
- Improved bioavailability of some drugs.

✓ Make a use of special effects, sustained release aspect for relief of arthritis by dosing before bedtime.

✓ Overall, administrations of sustained release form enable increased reliability of therapy.

Recent Trends in Sustained Drug Delivery System: Sustained release dosage forms are categorized as

1. Single unit dosage form.
2. Multiple unit dosage form.
3. Mucoadhesive system.

Matrix System: The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant support to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered.

- The chemical nature of support (generally, the support are formed by polymeric net).
- The physical state of drug (dispersed under molecular or particulate form or both).
- The matrix shape and alteration in volume as a function of time.
- The route of administration (oral administration remains the most widely used but other route are adaptable).
- The release kinetic model.

Advantages of Matrix System

The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out.

- With proper control of manufacturing process, reproducible release profiles are possible.
- There is no risk of "dumping" of a large part of dose, through the structure makes the immediate release of a small amount of active principle unavoidable.
- Their capacity to incorporate active principle is large, which suits them to delivery of large dosage.

MATERIALS

Atazanavir procured from Aurobindo pharma limited, provided by SURA LABS. All the other ingredients such as Guar Gum, Xanthan gum, Sodium alginate, Sodium alginate, Talc and MCC PH-102 were purchased from Merck Specialities Pvt Ltd, Mumbai, India. All the ingredients used were of analytical grade.

Formulation Procedure[10]

Different formulations (F1-F9) were prepared by direct compression method. Table 1 shows composition of each formulation. The formulations are composed of polymers Guar gum, Xanthan gum and Sodium alginate in various concentrations. All powders were passed through through sieve no ≠ 60. Weigh accurate amounts of excipients and atazanavir All the ingredients were mixed thoroughly by triturating upto 15 min .The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Table. 1: Formulation composition for tablets.

Formulation Code	Atazanavir	Guar Gum	Xanthan gum	Sodium alginate	Mg. Stearate	Talc	Total tablet weight
F1	150	30	-	-	6	6	300
F2	150	60	-	-	6	6	300
F3	150	90	-	-	6	6	300
F4	150	-	30	-	6	6	300
F5	150	-	60	-	6	6	300
F6	150	-	90	-	6	6	300
F7	150	-	-	30	6	6	300
F8	150	-	-	60	6	6	300
F9	150	-	-	90	6	6	300

All the quantities were in mg

METHODS

Analytical method development[11,12,13,14,15]

Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in pH 6.8 phosphate buffer. UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

Preparation calibration curve

100mg of Atazanavir pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using pH 6.8 phosphate buffer (100µg/ml).From this 10ml was taken and make up with 100 ml of pH 6.8 phosphate buffer (10µg/ml). The above solution was subsequently diluted with pH 6.8 phosphate buffer to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Atazanavir per ml of solution. The absorbance of the above dilutions was measured at 292 nm by using UV-Spectrophotometer.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients.

Pre-compression Studies

Angle of Repose: Flow property was determined by measuring the angle of repose. Tan (θ) = h / r

Where, θ = Angle of repose, h = Height of heap, r = Radius of pile.

Bulk Density: Bulk density is a ratio of given mass of powder and its bulk volume.

Bulk density = M / V_0

M = Mass of the powder, V_0 = Bulk volume of powder.

Tapped Density: It is generally given by the equation:

Tapped density = M / V_r

M= Mass of powder, V_r = final tapping volume of powder.

Compressibility Index and Hausner Ratio

To measure the unsettled apparent volume, (V_0) and the final tapped volume, (V_f) of the powder after tapping the material until no further volume changes occur .given by the expression as follows.

Compressibility index = 1-Bulk density/ Tapped density × 100

Hausner ratio = Tapped density/ Bulk density

Post-compression Parameters

Hardness: The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in kg/cm^2.

Friability (F): This test is closely related to tablet hardness and designed to evaluate the ability of the to withstand abrasion is determined by the formula.

% friability = (W_1-W_2) / W_1 × 100

W_1 = Weight of tablets before test, W_2 = Weight of the tablets after the test.

Weight Variation Test: Comparison of the weight of the individual tablets (xi) of sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean).

Thickness: The thickness of the tablets was measured by screw gauge. It is expressed in mm.

Content Uniformity: Used to ensure that every tablet contains the amount of drug substances indeed with little variation among tablets with in batch.

In vitro drug release studies[16,17,18,19,20]

The USP type II rotating paddle method was used to study the drug release from the tablet. 900ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued from up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 291 nm and 292 nm using UV-spectrophotometer.

RESULTS AND DISCUSSION

Determination of λ_{max} of Atazanavir 6.8 pH Buffer: The scanning of the 10µg/ml solution of Atazanavir in the ultraviolet range (200-400nm) against 6.8 pH phosphate buffer as blank gave the λ_{max} as 292 nm and it is used for further studies.

Preparation of 6.8-pH Buffer Solution: Dissolve 6.8 g of potassium di-hydrogen phosphate in 250 ml of water and stirred it for 5 min. Dissolve 2 gm of NaOH in 250 ml water. Take 250 ml of potassium di-hydrogen phosphate and to it add 112 ml of NaOH solution in 1000 ml flask and make up a volume up to 1000 ml.

Preparation of Standard Curve of Atazanavir in 6.8 pH Buffer: For the standard graph, Atazanavir 100 mg was accurately weighed and dissolved in 100 ml of of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 6.8 pH Buffer (100µg/ml).From this 10ml was taken and make up with 100 ml of 6.8 pH Buffer (10µg/ml). The above solution was subsequently diluted with 6.8 pH Buffer to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Atazanavir per ml of solution. The absorbance of the above dilutions was measured at 292 nm by using UV-Spectrophotometer.The absorbances, which were found,

are given in Table and the graph plotted of concentration *vs.* a bsorbance is shown in Fig. 1.

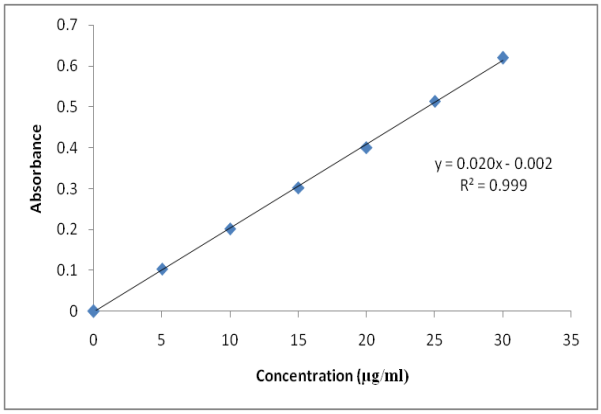

Fig. 1: Calibration of Atazanavir in Phosphate buffer pH 6.8.

Pre-compression Parameters: Pre compression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressability index and hausners ratio. The two most important attributes for the direct compression formula are good flow and good compressability. Inter particulate interactions that influence the bulking properties of a powder with powder flow. A comparison of bulk density and tapped density can give a measure of the relative importance of this interaction in given powder. The powder flow depends on three general areas. The physical property of particle (*ex.* shape, size, compressability), the bulk powder properties (*ex.* size distribution, compaction), and the processing environment(storage, humidity). Pre compression parameter are evaluated, these are mentioned in following Table 2.

Table 2: Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	23.12 ± 0.1	0.45 ± 0.03	0.51± 0.061	11.76 ± 0.58	1.13 ± 0.012
F2	25.53 ± 0.57	0.47 ± 0.06	0.55 ± 0.08	14.54 ± 0.47	1.17 ± 0.032
F3	22.46 ± 0.57	0.53 ± 0.08	0.59 ± 0.011	10.16 ± 0.57	1.11 ± 0.015
F4	26.61 ± 0.63	0.51 ± 0.09	0.60 ± 0.071	15 ± 0.15	1.17 ± 0.021
F5	23.15 ± 0.58	0.48 ± 0.01	0.55 ± 0.08	12.72 ± 0.21	1.14 ± 0.012
F6	27.08 ± 0.51	0.53 ± 0.011	0.61 ± 0.06	13.11 ± 0.35	1.15 ± 0.023
F7	24.38 ± 0.56	0.46 ± 0.08	0.53 ± 0.01	13.20 ± 0.42	1.15 ± 0.031
F8	22.26 ± 0.56	0.50 ± 0.055	0.58 ± 0.08	13.79 ± 0.57	1.16 ± 0.026
F9	26.43 ±1 0.62	0.55 ± 0.07	0.64 ± 0.012	14.06 ± 0.12	1.16 ± 0.056

Post-compression Parameters: Evaluation of tablets was done by studying various parameters like weight variation, thickness, hardness, friability and % drug content and the results were presented in Table 3 and all the results were found to be within the Pharmacopeial standards.

Table. 3: Post Compression Parameters of Tablets.

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	298.95 ±1.22	4.8±0.11	0.45±0.05	4.1±0.05	98.3±0.14
F2	299.15 ± 1.31	4.7±0.15	0.54±0.07	4.2±0.04	99.3±0.13
F3	300.26 ± 0.81	4.5±0.27	0.55±0.02	3.5 ±0.06	98.2±0.15
F4	305.36 ± 1.17	4.7±0.24	0.56±0.04	4.1±0.08	99.2±0.17
F5	297.25 ± 2.02	4.6±0.29	0.48±0.08	3.8±0.09	99.3±012
F6	296.26 ± 2.25	4.7±0.21	0.45±0.02	4.2±0.05	97.2±0.19
F7	302.5 ± 1.15	4.9±0.14	0.51±0.04	3.9±0.03	102.3±0.21
F8	303.63 ± 1.64	4.8±0.13	0.52±0.03	4.1±0.04	103.5±0.14
F9	299.53 ± 1.13	4.5 ± 0.22	0.561 ±0.03	3.8 ±0.02	99.56 ± 0.22

Drug - Excipient Compatibility Study: Drug- excipient compatibility studies were carried out by FT-IR spectroscopy. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components shown in Fig. 2 and 3.

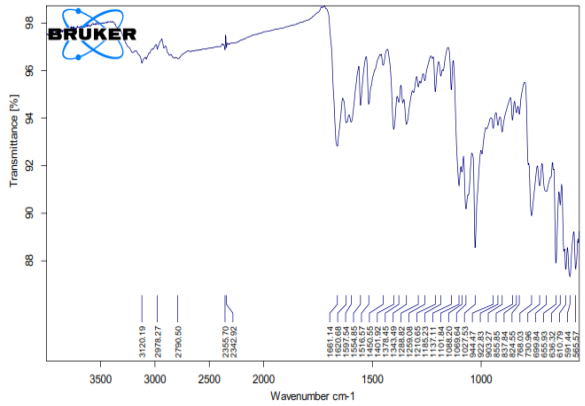

Figure. 2: FTIR Graph Of Pure Drug.

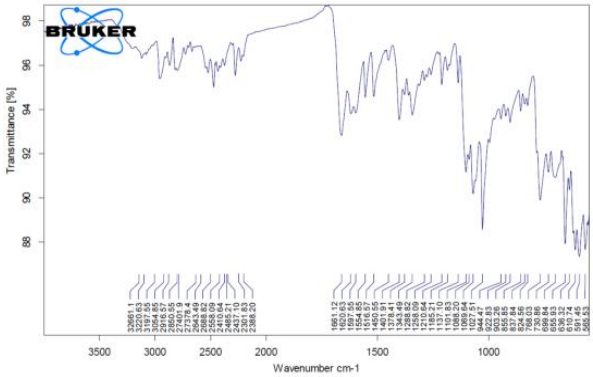

Figure. 3: FTIR Graph Of optimised formula.

***In-vitro* Dissolution Study and Kinetic Modeling of Drug Release:** All the formulations of Atazanavir were subjected to *in-vitro* release studies these studies were carried out using USP type II dissolution apparatus. The dissolution medium consisted of 900 ml of 0.1N Hcl for the first 2h, followed by pH 6.8 for remaining period of time. The release of Atazanavir from sustained release tablet of the various formulations varied according to the ratio and degree of the different polymer. The optimized formulation F8 which releases the Atazanavir in a sustained manner in 1sthr it releases 16.67 % but 99.15% release after 12 h. The *in-vitro* drug release profile of Atazanavir +Guar gum (F1-F_3), Atazanavir + xanthan gum (F4-F6) and Atazanavir + sodium alginate (F7-F9) were shown in Fig. 5, 6 & 7 and Table 10. Formulation F8 has shown the best dissolution profile which is represented in Fig. 8. The kinetic profiles of all formulations were shown in Table 4.

Table. 4. Time vs cumulative prcent drug release for formulations.

Time *(hr)*	% Cumulative Percent Drug Released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	23.46	16.45	12.54	18.26	12.48	10.38	13.24	10.25	7.35
1	40.24	21.38	20.15	32.14	19.81	16.47	20.15	16.67	13.45
2	61.38	32.45	26.72	50.16	25.46	25.49	32.18	23.34	19.46
3	80.15	43.83	39.26	73.54	33.46	31.64	43.56	30.63	23.45
4	99.51	59.64	48.59	88.49	42.15	38.76	55.18	37.41	29.48
5	-	70.15	56.15	99.86	51.49	44.57	63.84	44.95	34.15
6	-	82.47	67.49		62.48	50.15	75.61	50.15	39.46
7	-	99.85	68.53		71.34	55.64	88.43	58.73	44.78
8	-	-	79.34		83.46	61.49	98.43	66.42	49.68
9	-	-	88.63		99.25	70.56	98.36	73.15	56.41
10	-	-	99.34			76.48		81.47	63.34
11	-	-	-			87.52		90.15	71.45
12	-	-	-			98.11		99.15	80.15

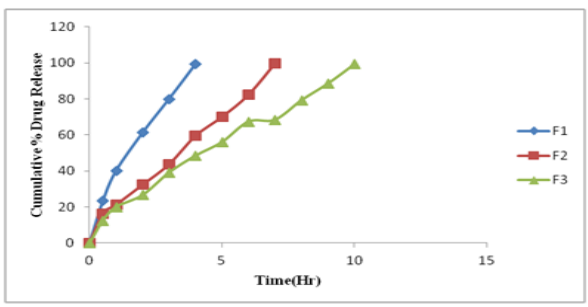

Figure. 4: Dissolution study of Atazanavir tablets (F1 to F3).

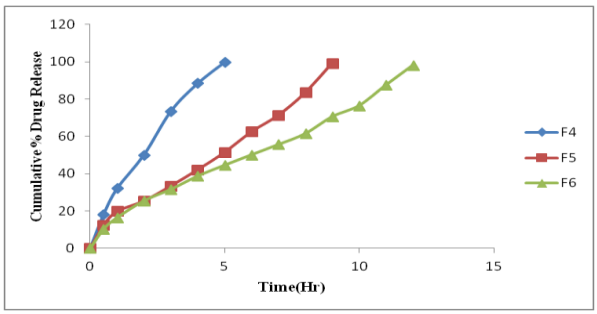

Figure. 5: Dissolution study of sustained Atazanavir tablets (F4 to F6).

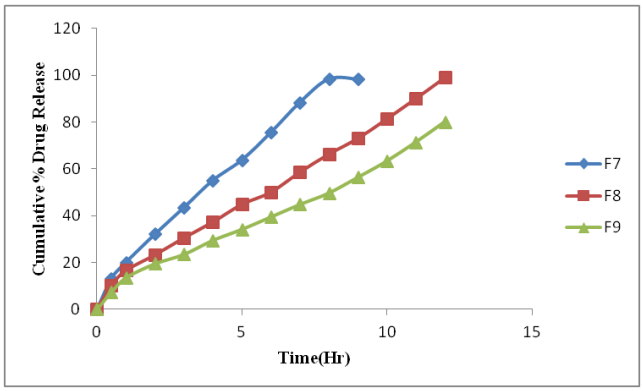

Figure 6: Dissolution study of Atazanavir tablets (F7 to F9)

Table 9.8: Release kinetics data for optimized formulation (F8).

Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	Log (T)	Log (%) Remain
0	0	0			2.000
10.25	0.5	0.707	1.011	-0.301	1.953
16.67	1	1.000	1.222	0.000	1.921
23.34	2	1.414	1.368	0.301	1.885
30.63	3	1.732	1.486	0.477	1.841
37.41	4	2.000	1.573	0.602	1.797
44.95	5	2.236	1.653	0.699	1.741
50.15	6	2.449	1.700	0.778	1.698
58.73	7	2.646	1.769	0.845	1.616
66.42	8	2.828	1.822	0.903	1.526
73.15	9	3.000	1.864	0.954	1.429
81.47	10	3.162	1.911	1.000	1.268
90.15	11	3.317	1.955	1.041	0.993
99.15	12	3.464	1.996	1.079	-0.071

SUMMARY AND CONCLUSION

The sustained release tablet containing Atazanavir matrix were successfully prepared by direct comprssion method. The physiochemical evaluation results for the all formulation trials pass the official limits in angle of repose, bulk density, compressibility index. The prepared tablets were also maintained the physiochemical properties such as thickness, hardness, weight variation, friability.

Increasing the amount of Guar gum and xanthan gum in solid matrix tablet increased the release rate of the drug. The formulation F8 having polymer as sodium alginate optimized formulation which releases the Atazanavir in a sustained manner in first hour it released 16.67 % but 99.15%released after 12 h.

ACKNOWLEDGEMENT

I take this opportunity to acknowledge with deep gratitude the invaluable help of many in completing this project work successfully. I owe a great many thanks to many people for their time and knowledge which helped me accomplish this work.

REFERENCES

1. Altaf AS, Friend DR, MASRx and COSRx. Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003; 1: 102-117.
2. Reddy KR., Mutalik S, Reddy S. AAPS Pharm. Sci. Tech, 2003; 4: 19. 121-125.
3. Mohammed AD et al. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and Hydroxypropyl methyl cellulose. Pharm Dev Tech, 1999; 4: 313-324.
4. Salsa T, Veiga F. Drug Develop. Ind Pharm, 1997; 23: 931.
5. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, inBanker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3rd Ed, Revised andExpanded, Drugs and the Pharmaceutical Sciences., Marcell Dekker, Inc, NewYork, 1995; 72: 575-609.
6. Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery systems Modern Pharmaceutics, 4thed, 2003; 121: 501-502.
7. Lee BJ, Ryu SG, Cui JH, Drug Dev. Ind.Pharm, 1999; 25: 493-501.

8. Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Ed. Modern Pharmaceutics, 3rdEd Marcel Dekker Inc. New York, 1996; 72: 575.
9. Vidyadhara S, Rao PR, Prasad JA. Indian J Pharm Sci., 2004; 66: 188-192.
10. Bogner RH. Bioavailability and bioequivalence of extended-release oral dosage forms. US Pharmacist, 1997; 22: 3–12.
11. Rogers JD, Kwan KC. Pharmacokinetic requirements for controlled-release dosage forms. In: John Urquhart, ed. Controlled-release Pharmaceuticals. Academy of Pharmaceutical Sciences. American Pharmaceutical Association, 1979: 95–119.
12. Madan PL. Sustained-release drug delivery systems, part II: Preformulation considerations. Pharm Manu fact. 1985; 2: 41–45.
13. Wani MS, Controlled Release System-A Review, 2008; 6 1: 56-62.
14. Banker GS, Anderson NR. The Theory and Practice of Industrial Pharmacy: Tablet,Lachman, (3rded) Varghese Publishing House, Bombay, 1990; 3: 293-303.
15. Lee VHL, Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design, Marcel Dekker, INC, and New York, 1987; 2: 16-29.
16. Manish R, Jayesh P, Siahboomi AR. Hydrophilic Matrices for Oral Extended Release: Influence of Fillers on Drug Release from HPMC Matrices. Pharma Times, 2010; 42(04): 67-73.
17. Kumar KP et al. Innovations in Sustained Release Drug Delivery System and Its Market Opportunities. J Chem Pharm Res., 2010; 2 1: 349-360.
18. Brahmankar DM, Sunil B. Jaishwal. "Controlled release medication" chapter 15th in "Bio pharmaceutics and Pharmacokinetics – A Treatise, 1st ed,, 2010; 1: 347- 353.
19. Stanley S. Davis, Formulation strategies for abs windows. Drug Discovery Today, 2005; 10: 249-257.
20. Modi SA et al. Sustained Release Drug Delivery System:A Review.Int J Pharma. Res Dev., 2011; 2(12): 147-160.