Vol 7| Issue 2| 2017 | 70-76.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

FORMULATION DEVELOPMENT AND IN VITRO EVALUATION OF CONTROLLED RELEASE TABLETS OF ALLOPURINOL

Gollapudi Rajesh[1*], Azmeera Ramarao[2], Paladugu Sujitha[3], Md Parveen[4]

[1]Department of Pharmaceutics, Max Institute of Pharmaceutical Sciences, Khammam, Telangana, India.
[2]Department of Pharmaceutical Analysis, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India.
[3]Department of Pharmaceutical Analysis, Max Institute of Pharmaceutical Sciences, Khammam, Telangana, India.
[4]Department of Pharmaceutics, Max Institute of Pharmaceutical Sciences, Khammam, Telangana, India.

ABSTRACT

Developing oral Controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce toxic concentration on oral administration. Hence, it is a challenging task to formulate a suitable dosage form for Controlled delivery of highly water-soluble drugs. Allopurinol selectively and competitively inhibits the hepatic enzyme hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Because of its high solubility, short half-life and therapeutic use in such diseases, it is considered as an ideal drug candidate for the design of oral Controlled release dosage form. It has been studied that a tablet containing eudragitl100,s100, ethyl cellulose and xanthan gum for oral delivery of Allopurinol has been formulated with greater significance; hence it was decided to check the *in-vitro* drug-polymer study in formulating a Controlled release tablet for Allopurinol. A wide range of polymers was selected for formulating the tablets. A semi synthetic polymer Eudragit (RSPO, L-100,S100). Powder blends for different formulations were prepared by mixing the required quantity of drug with the polymer. Eudragit(RSPO, L-100,S-100) were used in different proportions with drug (1:1 and 1:0.5), polyvinyl pyrolidone as binder and microcrystalline cellulose was used as diluents. Wet granulation method was employed for blending of drug with polymers in the given ratio as 9 formulations. The prepared powder blends were then compressed into tablets using the necessary excipients. The tablets were evaluated for hardness, thickness, friability and drug content and were subjected to a 10 hour *in vitro* drug release studies (USP dissolution rate test apparatus II, 50 rpm, 37^0C $\pm 0.5^0$C) using 0.1N hydrochloric acid for first 2hrs, phosphate buffer, pH 6.8 as a dissolution medium (900ml) for the next 8 hrs. The amount of Allopurinol released from the tablet formulations at different time intervals was estimated using a UV spectroscopy method. The formulations that showed a considerable retardation of the drug release are considered promising.

Key words: Allopurinol, Eudrgits.

INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the

Corresponding Author :- **Gollapudi Rajesh** Email:- rajeshgollapudi@yahoo.com

minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity [1-15]. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms [16-27].

MATERIALS AND METHODS

Materials

Allopurinol was gift sample from SD Fine labs, Mumbai ltd, India. Eudragit, Polyvinyl pyrolidine, Microcrystalline cellulose, Aerosil, Megnesium stearate, Isopropyl alchol from Research Lab,Mumbai, India and all other reagents used were of analytical grade and obtained from S.D. Fine chemicals. Mumbai, India.

METHODS

Preparation of granules

The granules were prepared by wet granulation method. This method involved use of appropriately selected tablet additives which would act as binders for the mixtures of drug and other tablet excipients.

Compression of Powder Blends Into Tablets

After evaluation of powder blend the sustained release matrix tablets were prepared by wet granulation method using (8mm diameter, round flat faced punches) multiple punch tablet compression machine (Cadmach Machinery Ltd., Ahmedabad, India). Each tablet contained 50 mg of Allopurinol, the batch size for each formulation was 100 tablets [28-35].

EVALUATION OF CONTROLLED RELEASE TABLETS

Appearance

The tablets were visually observed for capping, chipping, lamination and colour.

Physicochemical characteristic

Dimension (Thickness and Diameter)

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a Vernier caliper.

Tablet Hardness

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2

Friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows, [36-44]

% F = (Initial Wt. - Final Wt. / Initial Wt.) x 100

Drug content of Allopurinol

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar. Then an accurately weighed quantity of powder equivalent to 20 mg of drug was transferred to a 100 ml volumetric flask. Few ml of water was added and shaken for 15 min. Volume was made up to 100 ml with distilled water. The solution was filtered through Whatmann filter paper. 5 ml of the filtrate was diluted to 100 ml with 0.1N hydrochloric acid. Then absorbance of the resulting 10 µg/ml solution was recorded at 205.5 nm. Content uniformity was calculated using formula –

% Purity = 10 C (Au / As) ---------- (9)

Where C - Concentration,

Au and As - Absorbance's obtained from standard preparation and assay preparation respectively.

Weight Variation

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight [45-57]

In-Vitro Dissolution Studies

The in vitro dissolution was carried out using USP type II dissolution apparatus was determined using USP Dissolution testing apparatus type-II (Paddle method; Veego Scientific VDA-8DR, Mumbai, India).

Dissolution medium: 0.1N hydrochloric acid for first 2 hours.

The tablets were placed in the dissolution medium and the apparatus was run. At intervals of 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours 5 ml aliquots were withdrawn and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatman filter paper (No.41). 5 ml of sample was diluted to 10 ml 0.1N Hydrochloric acid for first 2 hours and then with pH 6.8 phosphate buffer for next 8 hours and absorbance of these solutions was measured at 316nm, 322 nm using a Shimadzu-1700 UV spectrophotometer. Drug

concentrations in the sample were determined from standard calibration curve. The release data were calculated by using PCP disso V3 software [58,59].

Release Kinetics.

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as Zero order, First order, Higuchi and Korsmeyer- Peppas.

STABILITY STUDY

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titiled "Stability testing of New Drug Substances and Products (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions

Long-Term Testing: 25^{0} C ± 2^{0} C / 60% RH ± 5% for 12 Months

Accelerated Testing: 40^{0} C ± 2^{0} C / 75% RH ± 5% for 6 Months

Stability studies were carried out at 40^{0} C / 75% RH for the optimized formulation for 3 months. The matrix tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, drug content and In vitro drug release.

RESULTS AND DISCUSSION

Evaluation of Extended Release Tablet

Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

Physical characteristic

The physical characteristic of Allopurinol sustained release matrix tablets (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

Dimension (Thickness and Diameter)

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations were found to be 8.0±0.0 mm and thickness ranged between 4.10±0.12 to 4.18±0.1mm.

Tablet Hardness

A difference in tablet hardness reflects difference in tablet density and porosity. Which in turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of tablets was found to be in the range of 5.50±0.447 kg/cm^2 to 6.16±0.683 kg/cm^2. This indicates good tablet strength.

Percent Friability

Percentage friability of all the formulations was found between 0.284±0.008 to 0.454±0.054%. This indicated good handling property of the prepared SR tablet.

Weight Variation

A tablet is designed to contain a specific amount of drug. When the average mass of the tablet is 300 mg the Pharmacopoeial limit for percentage deviation is ± 5 %. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the Pharmacopoeial specifications.

Drug content of Allopurinol :

The content of active ingredients in the formulation was found to be between 98.54±1.7 to 100.86±1.2 % w/w, which is within the specified limit as per IP 2007(i.e. 90-110% w/w).

***In-vitro* dissolution studies**

Allopurinol is a water soluble drug its release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the sustained release tablet was a key factor in controlling the drug release.

Various Extended release formulations were formulated with rspo,L100,S100) polymer alone; polyvinyl pyrolidone as binder and microcrystalline cellulose was used as diluents.

When cumulative % drug release plotted versus time, it was observed that, for three of the polymers used, an increase in polymer concentration induce a decrease in the release rate.

Table 1. Composition of Allopurinol ER tablet

Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8	F9
Allopurinol	100	100	100	100	100	100	100	100	100
Eudragit RSPO	30	15	30	-	-	-	30	-	-
Eudragit L100	30	15	-	15	30	15	-	30	-
Eudragit S100	-	-	30	15	30	15	-	-	30
MCC	183	213	183	213	183	213	213	213	213
PVP	5	5	5	5	5	5	5	5	5
Aerosil	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	300	300	300	300	300	300	300	300	300

*All the quantities are expressed as mg per tablet

Table 2. Dissolution data of formulations

Time (hours)	Dissolution medium	% Drug release Of F1	% Drug release OfF2	% Drug release Of F3	% Drug release Of F4	% Drug release Of F5	% Drug release Of F6	% Drug release Of F7	% Drug release Of F8	% Drug release Of F9
0	0.1 N HCl pH 6.8 phosphate bufffer	0	0	0	0	0	**0**	0	0	0
0.5		0.45	0.16	0.69	1.56	1.44	**3.59**	4.00	0.45	0.05
1		1.38	1.27	1.85	3.47	2.31	**7.88**	5.21	1.84	1.21
2		2.06	2.66	4.40	7.07	2.83	**14.79**	6.71	3.41	2.89
3		11.06	9.43	17.17	31.10	11.56	**40.03**	26.19	25.98	22.96
4		20.82	16.32	31.66	48.53	20.88	**55.42**	44.07	42.79	38.09
5		30.05	23.15	42.41	59.28	30.39	**67.35**	53.46	57.82	47.38
6		43.39	30.17	53.76	67.66	43.22	**75.85**	62.78	71.72	71.80
7		47.64	36.74	59.12	69.47	50.77	**83.01**	66.41	74.69	75.66
8		57.24	43.20	64.40	76.13	59.17	**86.79**	89.87	91.03	86.94
9		63.72	49.76	70.40	79.07	67.87	**93.27**	97.30	104.57	95.99
10		75.60	54.20	76.54	85.07	80.83	**98.31**			

*****All values are expressed as mean ±SD, n=3.

Table 3. Different kinetic models for Allopurinol ER matrix tablets (F1 to F9)

Code	Zero order		First order		Higuchi		Peppas		Best fit model
	R^2	K_0 mg/h^{-1}	R^2	K_1 (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	n	
F1	0.9474	10.063	0.8592	0.1938	0.8334	23.8548	0.9830	1.9166	Peppas
F2	0.9700	9.4137	0.9021	0.1766	0.8712	23.6698	0.9656	1.7465	Zero-order
F3	0.9820	8.2020	0.9157	0.1455	0.8820	21.6151	0.9781	1.5340	Zero-order
F4	0.8785	10.209	0.7772	0.1920	0.8285	24.6881	0.7632	1.2412	Zero-order
F5	0.9664	9.1268	0.9041	0.1668	0.8594	22.8722	0.9841	1.7415	Peppas
F6	0.9724	4.6413	0.9471	2.0504	0.8364	13.945	0.9798	1.4375	Zero-order
F7	0.9699	8.3884	0.9632	0.1422	0.9049	22.3442	0.9419	1.4277	Zero-order
F8	0.9757	8.6500	0.9669	0.1507	0.9154	23.0754	0.9460	1.3418	Zero-order
F9	0.9641	8.1897	0.9469	0.1388	0.8782	21.6680	0.9519	1.6487	Zero-order

Fig 1. % Drug Release Of Formulations(F1,F2,F3)

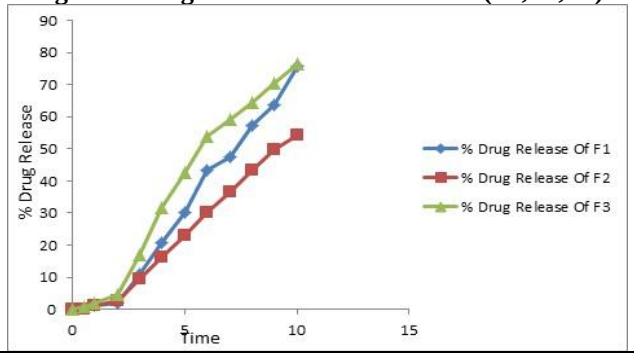


Fig 2. % Drug Release Of Formulations(F4,F5,F6)

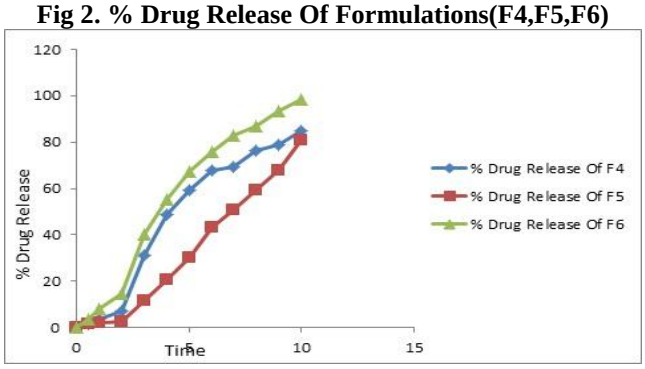
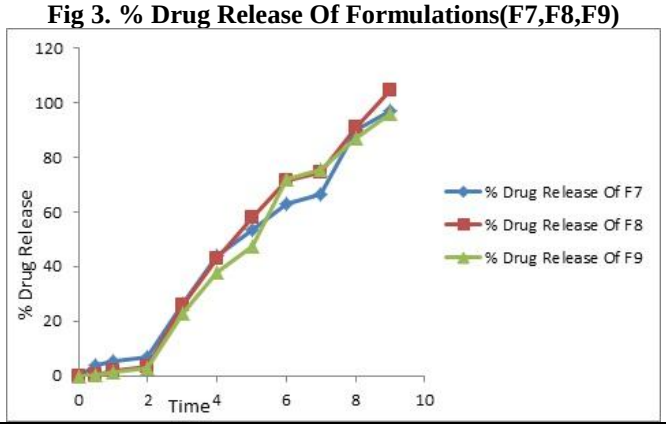


Fig 3. % Drug Release Of Formulations(F7,F8,F9)



SUMMARY

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form. Developing oral Controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and are likely to produce toxic concentration on oral administration. Hence, it is a challenging task to formulate a suitable dosage form for Controlled delivery of highly water-soluble drugs.

Allopurinol selectively and competitively inhibits the hepatic enzyme hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Because of its high solubility, short half-life and therapeutic use in such diseases, it is considered as an ideal drug candidate for the design of oral Controlled release dosage form. It has been studied that a tablet containing eudragitl100,s100, ethyl cellulose and xanthan gum for oral delivery of Allopurinol has been formulated with greater significance; hence it was decided to check the *in-vitro* drug-polymer study in formulating a Controlled release tablet for Allopurinol.

A wide range of polymers was selected for formulating the tablets. A semi synthetic polymer Eudragit(RSPO, L-100,S100). Powder blends for different formulations were prepared by mixing the required quantity of drug with the polymer. Eudragit(RSPO, L-100,S-100) were used in different proportions with drug (1:1 and 1:0.5), polyvinyl pyrolidone as binder and microcrystalline cellulose was used as diluents. Wet granulation method was employed for blending of drug with polymers in the given ratio as 9 formulations. The prepared powder blends were then compressed into tablets using the necessary excipients. The tablets were evaluated for hardness, thickness, friability and drug content and were subjected to a 10 hour *in vitro* drug release studies (USP dissolution rate test apparatus II, 50 rpm, 37^0C $\pm0.5^0$C) using 0.1N hydrochloric acid for first 2hrs, phosphate buffer, pH 6.8 as a dissolution medium (900ml) for the next 8 hrs. The amount of Allopurinol released from the tablet formulations at different time intervals was estimated using a UV spectroscopy method. The formulations that showed a considerable retardation of the drug release are considered promising.

CONCLUSION

Controlled Release tablets of Allopurinol were successfully prepared by using different hydrophilic and hydrophobic polymers as the release retarding materials by Wet Granulation method.

REFERENCES

1. Lachman L, Liberaman HA and Kanig JL. The Theory and practice of Industrial Pharmacy (3rd Edn), Varghese Publishing House Bombay, 430.
2. Gennaro AR. Remington, The Science and Practice of Pharmacy, 19th Edition, 1995, 1662.
3. Chien YW. Novel drug delivery system, Revised and expanded, 1992, 139-140.
4. Shargel L and Andrew BC. Applied Biopharmaceutics and Pharmacokinetics, 174.
5. Bankers GS and Rhodes CT. Modern Pharmaceutics, Marcel Dekker, New York, 1995, 575.
6. Agis K, Treatise on controlled drug delivery Marcel Dekker, Inc. NewYork, 70, 199 - 203.
7. Lachman L and Liberaman HA. Pharmaceutical Dosage Forms Tablets,Marcel Dekker Inc., New York, 2, 1980, 246.
8. Remingtons. The Science & Practice of Pharmacy, Lippan Cott,Williams & Wilkins, Baltimore, Maryland, 1995, 721 - 752.

9. Swain K, Chowdary KA. Design and Evaluation of Gastroretentive Formulation of Theophylline", M. Pharm. Thesis submitted to Berhumpur University, Berhumpur, Orrissa, 2003.
10. Telikapalli P, Patel MM, Sheth MN, Gohel MC and Chauhan GM. Sustained Release Formulation of Verapamil Hydrochloride using Hydrophilic Matrices. *The Eastern Pharmacist*, 1995, 185 - 187.
11. Drug facts and comparisons- part of wolters kluwer healt, 2004, 704-705.
12. Brahmankar DM, Karwa RM, Jaiswal SB. Cellulose matrix for controlledrelease of Ketorolac tromethamine. *Indian Drugs,* 33(3), 1996, 120 - 123.
13. Nath BS, Venkatesh, Hiremath D. Formulation and Evaluation of SustainedRelease Dosage from of Therophylline using a Combined Hydrophobic and Hydrophilic matrix. *Ind. J. Pharm. Sci*., 62(1), 2000, 33 - 36.
14. Kondaiah A and Prakash K. Design of Controlled Release Non erodible PolymerMatrix Tablets of Theohylline Using Sintering Technique. *Indian J. Pharma. Sci.*, 64(3), 2001, 239 - 243.
15. Aithal KS and Udupa N. Controlled Fluoride Release Tablets using Methyl Cellulose and Hydroxy Propyl Methyl Cellulose. *The Indian Drugs*, 31(7), 1991, 298 - 301.
16. Telikapalli P, Patel MM, Sheth MN, Gohel MC and Chauhan GM. Sustained Release Formulation of Verapamil Hydrochloride using Hydrophilic Matrices. *The Eastern Pharmacist*, 1995, 185 - 187.
17. Rangaiah, KV, Madhusudahn S and Verma PRP. Sustained release of Theophylline from HPMC and Eudragit tablets. *Indian drugs,* 32, 1995, 543-7.
18. Ju RTC, et al. Drug release from hydrophilic matrices . A mathematical model based on the polymer disentanglement concentration and the diffusion layer. *J. pharm. Sci.,* 84, 1995, 1464-77
19. Salomen JL, Doelkar E and Buri P. Sustained release of water solubledrug from hydrophillic compressed dosage forms, *pharm. Ind.*, 41(8), 1979, 799-802.
20. Papadimitriou E, Buckton G and Efentakis M. Probing the mechanism of swelling of HPMC matrices. *Int. j. Pharm.*, 98, 1993, 57-62.
21. Hogan JE. Hydroxy propyl methyl cellulose sustained release technology. *Drug. Dev. Ind. Pharm.,* 15(6-7), 1989, 957-999.
22. Khatua MK., Dutta J, Prasad R and Dutta PK.. Study on chitosan-amine oxide bulk matrices for controlled release of cefaclor. *Indian Drug*s, 40(1), 2003, 34.
23. Pandey VP, *et al*. Formulation and release characteristic of sustained release diltiazem hydrochloride tablet. *Ind. J. Pharm. Sci.*, 65(1), 2003, 44-48.
24. Nagoji KEV, Srinivasa R, Vijaya S and Rao MEB. Scientific oral presentation pharmaceutical technology 55th IPC Chennai.
25. Abraham MA and Shirwaikar. Formulation of Multilayered Sustained Release Tablets using Insoluble Matrix System. *Indian J. Pharm. Sci.*, 59 (6), 1997, 312 - 315.
26. Misra AN and Baweja JM. Modified Guar Gum as Hydrophilic Matrix for Controlled Release Tablets. *Indian Drugs,* 34(4), 1997, 216 - 223.
27. Ruckmani K, Agul B, Jaykar B and Ghosal SK. Sustained Release of Nifedipine from Eudragit Matrix Tablets. *The Eastern Pharmacist*, 1995, 137 - 139.
28. Haririan I, Ghaffari A, Mohammed PM. Formulation of controlled Release Matrix Tablets of Isosorbide Dinitrate. *Indian J. Pharm. Sci*, 63(1), 2001, 24-29.
29. Bhalla HL and Sanzgere YD. Improvised controlled release tablet of Salbutamol sulphate. *Indian J. Pharma, Sci,* 49, 1989, 22 - 25.
30. Nellore RV, et al. Development of Metoprolol tartrate extended release matrix tablet formulations for regulatory policy consideration. *J. of Controlled Release,* 50 (1-3), 1989, 247 - 56.
31. Cheng HL, et al. In-vitro and in-vivo studies of Diclofenac Sodium controlled release matrix tablets. *J. Pharm. Sci.*, 47, 1995, 360 - 364.
32. Murali GV, Mohan B, Sheshasayana A and Ramana MKV. Preparationand Evaluation Indomethacin -Ethyl Cellulose Polymer Matrix Systems. *The Eastern Pharmacist*, 2000, 113 - 114.
33. Farid DJ, Sadeg Shoberi N, Hassani M and Nokhodehi. Sustained Release Formulations of Nifedipine. *Indian J. Pharm. Set.*, 60(6), 1998, 375 - 378.
34. American Society of Health System Pharmacist. Bethesda, Maryland and Spring House Corporation, Spring House, Pennsylvania, 638 - 640.
35. Tripati KD. Essentials of medical pharmacology, 4th edition, updated reprint, 2001.
36. Website -http//www.edruginfo.com.
37. Website - http//www.medscape.com.
38. United States Pharmacopeia, 946-948, Maryland USA.
39. Indian Pharmacopoeia Vol. 1st, The controller of Publication Delhi, 1996.

40. The Merck Index. encyclopedia of chemicals, drugs and Biological Merck and C. INC Runway, New Jersey, USA, 1989.
41. Martindale. The Extra Pharmacopoeia, 33, 2001, 332 - 33.
42. British Pharmacopoeia, British Pharmacopoeia commission London Vol 2nd, 1993.
43. Lachman L, Liberaman HA and Kanig JL. The Theory and practice of Industrial Pharmacy, Varghese Publishing House Bombay, 296 - 302.
44. Indian Pharmacopoeia. The Controller of Publication Delhi, 1996, A -80, A -84.
45. Data sheet from Information for health professionals, Roche Products Ltd.
46. Hand Book of Pharmaceutical Excipients. 4th edition American Pharmaceutical Association.
47. Goldstein AM, Alter EN, Seaman JK, Guar gum. In: Whistler RL, editor."Industrial gums, polysaccharides and their derivatives, New York, 1973, 303 - 21.
48. www.degussa.com.
49. British Pharmacopoeia London: The Stationary Office, 2002.
50. Martin A. Physical Pharmacy, New Delhi, 1996, 313 - 316.
51. United States Pharmacopoeia, 2000 Edition.
52. Nish D, Poddar SS, Shajahan AA. Development of Matrix and coated units for pH - Independent Release, 2003.
53. Hosseinali T, Seyed AM, Tina B. Preparation of Sustained-Release Matrix Tablets of Aspirin with Ethylcellulose, Eudragit RS100and Eudragit S100 and Studying the Release Profiles and their Sensitivity toTablet Hardness. *Iranian Journal of Pharmaceutical Research*, 2003, 201-206.
54. Al Taani BM, Tashtoush BM. Effect of Microenvironment pH of Swellable and Erodable Buffered Matrices on the Release Characteristics of Diclofenac Sodium. *AAPS Pharm Sci Tech*, 4(3), 2003, 43
55. Woodcock BG, Asthana O, Wanchel M, Rietbrock N. Methods Find. *Exp. Clin. Pharmacol*, 5(8), 1983, 537 - 41.
56. Mattila J, Mantyla R, Taskinen J, Mannisto P. Drug Metabolism and Pharmocokinetics. *Eur. J.*, 10, 1985, 133 - 138.
57. Krishnanaiah YSR, Latha K, Nageshwar Rao L, Karthikeyan RS, Bhaskar P, Satyanarayana V. Development of Colon Targeted Oral Guar Gum Matrix Tablets of Albendazole for the Treatment of Helminthias. *Indian J. Pharm. Sci.*, 65(4), 2003, 378 - 385.
58. Hango R, Vetrichelvan T, Kavimani S, Jayakar and Mullaicharm AR. Studies on Matrix Tablets of Glibenclamide Using Chitosan. *Indian Drugs*, 32(12), 1995, 578 - 582.
59. Ganguli N, Jayaswal SB, Singh J and Varma MM. Controlled Release Dosage Forms of Glibenclamide. The Eastern Pharmacist, 2(3), 1992, 117 - 118.