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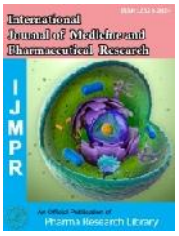

Research Article **Open Access**

Matrix Diffusion Controlled Release Tablets of Repaglinide-Formulation and *In-vitro* Evaluation

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A B S T R A C T

The purpose of present reaserch work was to prepare and evaluate the controlled release tablets of Repaglinide. Direct compression method was used to prepare the tablets using different polymers include Eudragit S-100, Eudragit RSPO, Eudragit RLPO, Eudragit L-100, HPMC K4M and HPMC K15M. Formulations were prepared by varying the amount of polymers. The prepared tablets were (F1-F12) evaluated for both precompression and postcompression parameters. The compatability of drug with polymers is identified by FTIR studies. The resulta obtained showed that the drug is compatible with all the polymers used.

Keywords: Repaglinide, Eudragit S-100, Eudragit RSPO, Eudragit RLPO, Eudragit L-100, HPMC K4M and HPMC K15M, Direct compression method

A R T I C L E I N F O

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1. Introduction

Over the past 30 years, as the expense and complications involved in marketing new entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery of, greater attention has been focused on development of controlled release drug delivery systems. It is generally been recognized that for most disease states, a substantial number therapeutically effective compounds already exists. The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-

release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized" . Several types of modified-release drug products are recognized

- Extended-release drug products. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.
- Delayed-release drug products. A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.
- Targeted-release drug products. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

Oral Controlled Release Drug Delivery Systems

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.

Advantages of Controlled Drug Delivery Systems

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Minimize or eliminate local side effects
- Minimize drug accumulation with chronic dosing.

Disadvantages of Controlled Drug Delivery Systems

- Increased variability among dosage units.
- In vitro – in vivo correlation.
- Toxicity due to dose dumping may occur when more than usual fraction is being released.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- More rapid development of tolerance.
- Need for additional patient education and counseling.

General Design Principle for Controlled – Release Drug Delivery Systems: In the drug delivery system, the pharmacodynamics of active molecules becomes more a function of design and less one of inherent kinetic properties. Therefore, a deep understanding of the design of controlled – release systems of the pharmacokinetics and pharmacodynamics of the drug is required.

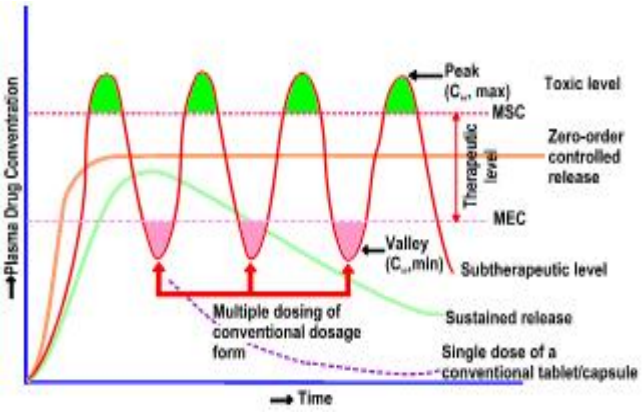


Figure 1

Types of Oral Controlled Release Drug Delivery Systems: A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems
- Diffusion controlled release systems
- Diffusion and dissolution systems
- Osmotically controlled release systems

Gastro retentive drug delivery systems

- Electrically stimulated release devices
- Ion-exchange resins

Factors Influencing the Design and Performance of Sustained Release Products: The design of controlled - release delivery system is subjected to several variables of considerable importance. Among these, the properties of the drug, the route of drug delivery, and the disease being treated and length of the therapy have major importance.

Physicochemical factors

- Aqueous solubility
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size and Diffusivity
- Absorption
- Distribution
- Elimination
- Biological half life and Duration of action
- Side effects and Margin of safety

2. Materials and Methods

Materials: Repaglinide procured from natco pharma, hpmc k4m, hpmc k15m, hpmc k100m, xanthane gum, eudragit l-100, eudragit s-100, magnesium sterate, carbopol, chitosan, talc, microcrystaline cellulose.

Methods

Preformulation studies

Before formulation of drug substances into a dosage form, it is essential that drug and polymer should be chemically and physically characterized. Preformulation studies give the information need to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

Calibration curve of Repaglinide in 0.1 N HCl:

The stock solution of Repaglinide was freshly prepared by dissolving 100 mg of Repaglinide few ml of 0.1 N HCl(5ml) in a 100ml volumetric flask and then make up the solution upto the mark using 0.1N HCl for obtaining the solution of strength 1000µg/ml (stock I). 10ml of this solution is diluted to 100ml with of 0.1 N HCl to obtain a solution of strength 100 µg/ml (stock II). From this secondary stock0.5, 1.0, 1.5, 2.0, 2.5 and 3.0ml, was taken separately in a 10 ml volumetric flask and made up to 10ml with of 0.1 N HCl, to produce 5, 10, 15, 20, 25 and 30µg/ml respectively. The absorbance was measured at 228nm using a UV spectrophotometer. A plot of concentrations of drug versus absorbance was plotted. The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of amount of drug. This procedure is repeated 3 times and the average value will be taken into consideration.

Fourier transform infrared spectrophotometry (FTIR):

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepare were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

Formulation

Preparation of Repaglinide tablets

Direct compression method: Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests.

Pre compression parameters

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$$\mathbf{Tan\ \theta = h/r}$$

Where: θ = Angle of repose
h = Height of the cone
r = Radius of the cone base

Bulk density: Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.15 g powder blend introduced into a dry 100 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the following formula.

$$\mathbf{\rho_b = M / Vo}$$

Where
ρ_b = Apparent bulk density
M = Weight of sample
V = Apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped 500 times initially followed by an additional taps of 750 times until difference between succeeding measurement is less than 2% and then tapped volume, $V_f$was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the following formula.

$$\mathbf{\rho_{tap} = M / V_f}$$

Where ρ_{tap} = Tapped density
M = Weight of sample
V_f = Tapped volume of powder

Carr's index (%)

The compressibility index (carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the carr's index which is calculated using the following formulas:

$$\mathbf{Compressibility\ index = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100}$$

Where ρ_b = Bulk density
ρ_{tap} = Tapped density

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's ratio=Tapped density (ρ_t) / Bulk density (ρ_b)

Where ρ_t tapped density and ρ_b is bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow.

Post compression parameters

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations. Following parameters were evaluated:

Tablet thickness: The thickness in millimeters (mm) was measured individually for 10 pre weighed Tablets by using micrometer (screw gauge). The average thickness and standard deviation were reported.

Weight variation

Twenty Tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of three batches were calculated. It passes the test for weight variation, if not more than two of the individual Tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Tablet hardness: Hardness of Tablet is defined as the force applied across the diameter of the Tablet in order to break the Tablet. The resistance of the Tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of 6 Tablets was determined using Monsanto hardness tester and the average is calculated and presented with standard deviation.

Friability

The friability values of the Tablets were determined using a Roche-type friabilator. Accurately weighed six Tablets were placed in Roche friabilator and rotated at 25rpm for 4 min. The Tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original Tablets. Percentage friability was calculated using the following equation.

$$\textbf{Friability} = ([w_O - w] / w_O) \text{ ò } \mathbf{100}$$

Where; w = weight of the Tablet after 100 revolutions.

w_O = weight of the Tablet at time zero before revolution.

Swelling Index: Swelling index of the dosage form is conducted by using USP dissolution apparatus-II in 900 ml of pH 7.4 phosphate buffer which is maintained at 37±0.5°c, rotated at 50 rpm. At selected regular intervals, the tablet is withdrawn the excess water was blotted with tissue paper. This procedure was repeated until the tablet reaches constant weight. The swelling index was calculated by using following formula

$$\% \text{ swelling index} = \{(W_t) - (W_o) / (W_t)\} \times \mathbf{100}$$

Water uptake: A piece of tissue paper folded twice was placed in a petridish containing 5ml of water. A pre weighed tablet was placed on the paper and time for complete wetting was measured which is characterized by coloring of tablet. R was determined according to the following formula.

$$R = (W_a - W_b / W_b) 100$$

***In vitro* Drug release study:** The drug release was studied using USP type II apparatus at 37 ± 0.5°C and at 50rpm usingthe pH of the dissolution medium was kept for 2 h with 0.1NHCl was prepared by taking 8.5ml of HCl in 1000ml of water. Then, 6.8 g of KH_2PO_4 and 0.8 g of NaOH. were added, adjusting the pH to 6.8. The release rate analysis was done. 1ml of the sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably and analyzed spectrophotometrically. Equal amount of the fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved was calculated.

3. Results and Discussion

The spectra for pure Repaglinide and for the physical mixture of Repaglinide and all the polymers were determined to check the intactness of the drug in the polymer mixture using FTIR – Spectrophotometer by disc method. 1447.77 Aromatic (C=O), 2934 CH3 Streching, 1339.19 CH2 bending, 3306.35 N-H Streching, 1685.30-Cyclic C=0.By observing the IR spectra of pure drug and the all physical mixtures of drug and polymers in figures 4.5 to 4.7 it was found out that none of the above mentioned groups were affected by those polymers. Thus it can be said that there was no interaction between the drug and any of the polymers.

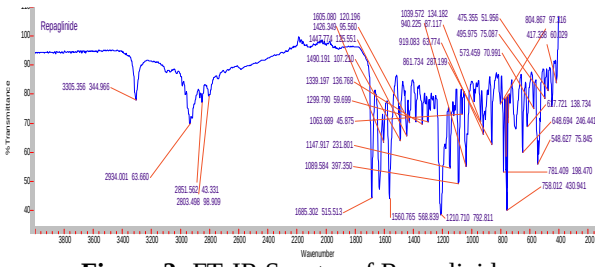


Figure 2: FT-IR Spectra of Repaglinide

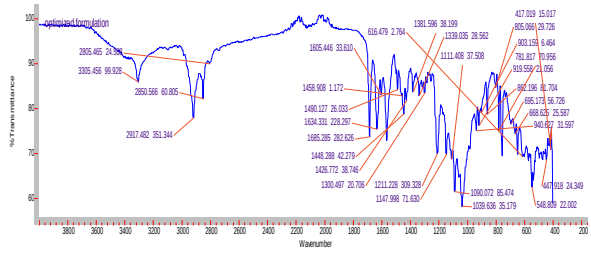
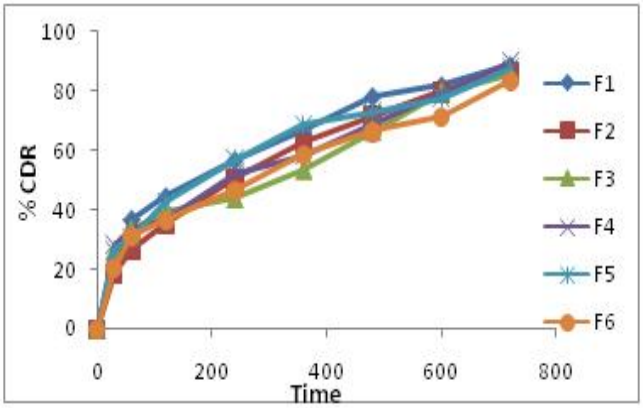
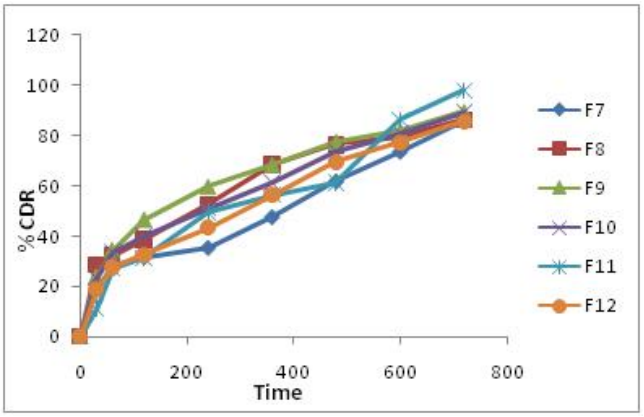


Figure 3: FT-IR spectra of optimized formulation

Bulk density of all formulations was in the range of 0.41gm/cc to 0.48gm/cc. Tapped density of all formulations was in the range of 0.57gm/cc to 0.66gm/cc. Carr's index of all the formulations of with Eudragit and HPMC were between 21.4% and 34.7% respectively, which indicates the flow properties of the powders of all formulations are excellent. Hausner's Ratio of all the formulations of powders with Eudragit and HPMC were between 1.35 and 1.56 respectively which indicates the flow properties of the powders of all formulations are excellent. The powders with ethyl Eudragit had an angle of repose ranging from 31.2 to 35.9 indicates that all of the formlations made with Eudragit had excellent flow properties.



Dissolution graphs of F1, F2, F3, F4, F5 & F6



Drug Release of F7, F8, F9, F10, F11, F12

Table 1: Composition of Formulations of repaglinide containing Eudragit (L-100, RSPO, RLPO, S-100)

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Repaglinide	2	2	2	2	2	2	2	2
Eudragit L-100	4	8	-	-	-	-	-	-
Eudragit RSPO	-	-	4	8	-	-	-	-
Eudragit RLPO	-	-	-	-	-	-	4	8
Eudragit S-100	-	-	-	-	4	8	-	-
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
MCC	66	52	66	52	66	52	66	52
Total weight	75	75	75	75	75	75	75	75

Table 2: Composition of Formulations of repaglinide containing HPMC K4M, HPMC K15M

Ingredients	**F9**	**F10**	**F11**	**F12**
Repaginide	2	2	2	2
HPMC k4M	12	16	-	-
HPMC K15M	-	-	12	16
Magnesium stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
MCC	58	54	58	54
Total weight	75	75	75	75

Table 3: Comprehensive Report on Flow Properties of Powders

Formulation	**Bulk Density* G/cc**	**Tapped Density* G/cc**	**Hausner Ratio**	**Compressibiliy Index %**	**Angle of Repose**
F1	0.427±0.003	0.577±0.00	1.35	30.7	31.2±1.001
F2	0.43±0.036	0.663±0.00	1.54	35.6	31.6±0.5
F3	0.412±0.003	0.646±0.00	1.56	32.75	35.8±0.95
F4	0.423±0.006	0.623±0.00	1.47	33.8	32.6±0.5
F5	0.435±0.001	0.634±0.00	1.45	32.4	33.4±0.4
F6	0.421±0.001	0.652±0.00	1.54	33.4	35.9±0.458
F7	0.423±0.003	0.632±0.00	1.49	33.9	32.3±0.3
F8	0.462±0.004	0.648±0.00	1.40	34.7	34.2±0.34
F9	0.453±0.003	0.655±0.00	1.44	29.4	32.5±0.5

F10	0.441±0.002	0.648±0.00	1.46	21.4	36.8±0.529
F11	0.437±0.002	0.638±0.00	1.45	32.1	33.1±0.624
F12	0.423±0.006	0.623±0.00	1.47	33.8	32.6±0.5

Table 4: Post compression parameters

Formulation code	Hardness (kg/cm^2)	Friability (%)	Avg weight (mg)	Thickness	Swelling index	Water uptake (%)
F1	2.5	0.09	75	1.5	10	20.7
F2	3.0	0.06	75	1.0	25.6	22.4
F3	3.1	0.06	74	1.5	37.8	25.7
F4	3.2	0.11	74	1.5	33.5	29.9
F5	2.8	0.07	75	1..3	24.4	24.4
F6	2.5	0.04	75	1.5	40.9	21.7
F7	2.5	0.08	75	1.6	45.3	30.6
F8	2.3	0.07	76	1.5	33.6	32.5
F9	2.6	0.05	75	1.4	34.6	28.6
F10	2.5	0.04	75	1.5	39.7	27.9
F11	2.5	0.06	74	1.3	23.3	30.8
F12	3.2	0.09	74	1.5	43.7	25.8

Table 5: *In-Vitro* Drug Release Study: Cumulative % Drug Release of F1,F2,F3,F4,F5,F6

Formulation	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	22.62	18.59	26.57	28.36	26.58	20.72
60	36.95	26.59	33.57	33.57	30.57	31.25
120	44.59	35.27	39.84	36.95	42.59	36.59
240	56.85	50.29	44.14	52.29	56.87	46.58
360	66.63	62.57	53.68	58.28	68.52	58.67
480	78.25	71.58	66.59	68.74	72.59	66.27
600	81.89	79.68	79.86	79.48	77.59	71.43
720	88.69	86.57	85.8	89.57	87.48	83.25

Table 6: Cumulative % Drug Release of F7,F8,F9,F10,F11,F12

Formulation	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
30	18.62	28.59	23.87	23.25	11.25	18.97
60	28.57	32.45	34.36	33.57	27.30	27.57
120	31.59	38.64	46.57	40.19	31.24	32.54
240	35.27	52.59	59.67	51.05	49.57	43.29
360	47.58	68.57	68.39	61.29	56.27	56.27
480	61.85	76.38	77.59	73.59	61.20	69.57
600	73.72	79.41	81.98	81.25	86.37	77.45
720	85.65	86.29	89.54	89.37	97.82	85.69

4. Conclusion

The aim of the present study was to develop an controlled release formulation of Repaglinide to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of HPMC were employed as polymers. Repaglinide dose was fixed as 2mg. Total weight of the tablet was considered as 75mg. Polymers were used in the concentration of 12 and 16mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F11) showed better and desired drug release pattern i.e.,97.82 % in 12 hours. It followed zero order release kinetics mechanism.

5. References

[1] Abraham MA and Shirwaikar, "Formulation of Multilayered Sustained Release Tablets using Insoluble Matrix System", Indian J. Pharm. Sci., 1997, 59 (6),312 - 315.

[2] Agis Kydonieus, Treatise on controlled drug delivery Marcel Dekker, Inc. NewYork, 70, 199 – 203

[3] Aithal KS. And Udupa N, "Controlled Fluoride Release Tablets using MethylCellulose and Hydroxy Propyl Methyl Cellulose", The Indian Drugs, 1994, 31(7); 298 - 301.

[4] "American Society of Health System Pharmacist", Bethesda, Maryland and Spring House Corporation, Spring House, Pennsylvania, 638 - 640.

[5] Anna Viridén, Bengt Wittgren, Anette Larsson . Investigation of critical polymer properties for polymer release and swelling of HPMC matrix tablets. European journal of pharmaceutical sciences 2009; 36: 297–309.

[6] Bankers GS and Rhodes CT. Modern Pharmaceutics (3rd Edn.), Marcel Dekker, New York, 1995; 575.

[7] Lachman Leon, Liberaman HA. and Kanig JL, The Theory and practice of Industrial Pharmacy (3rd Edn), Varghese Publishing House Bombay, 430.

[8] Brahmankar DM, Karwa RM, Jaiswal SB, "Cellulose matrix for controlled release of Ketorolac tromethamine", Indian Drugs, 1996 Mar; 33 (3): 120 - 123.

[9] Lachman Leon, Liberaman HA and Kanig JL, The Theory and practice of Industrial Pharmacy (3rd Edn), Varghese Publishing House Bombay, 430.

[10] Lachman Leon and Liberaman HA. Pharmaceutical Dosage Forms Tablets, Marcel Dekker Inc., New York N.Y., 1980; 2: 246.

[11] Lachman Leon, Liberaman HA and Kanig JL, "The Theory and practice of Industrial Pharmacy" (3rd Edn), Varghese Publishing House Bombay, 296 - 302.

[12] Remingtons; The Science & Practice of Pharmacy, 20th Edn., Lippan Cott,Williams & Wilkins, Baltimore, Maryland, 1995; 721 - 752.

[13] Website -http//www.edruginfo.com.

[14] "Essentials of medical pharmacology" -4th edition, updated reprint 2001 by Dr. K. D. Tripathi.

[15] Modi V. S, Thorat Y. S, Dhavale S. C. Formulation and evaluation of controlled release delivery of tramadol hydrochloride using 32– full factorial design. Int. J. ChemTech Res., 2010, 2(1): 669- 675.

[16] Jagan Mohan. S, Kishan V, Madhusudan Rao Y and Chalapathi Rao N.V."Formulation of Controlled Release Levodopa and Carbidopa Matrix Tablets: Influence of Some Hydrophilic Polymers on the Release". Current Trends in Biotechnology and Pharmacy, Volume 3 (2) April - 2009.

[17] Shargel L and Andrew BC. Applied Bio pharmaceutics and Pharmacokinetics (4thEdn.), 174.

[18] Suwannee PP, Tommy H, Tetuya A, Kazunori K, Tamotsu K. A study of hydrophilic cellulose matrix effect of drugs on swelling properties. Chem Pharm Bull 1990, 44(5); 1039-42.

[19] Bhaskaran S, Remiz M. Novel approach to zero order drug delivery via hydrogel for diltiazem hydrochloride. Ind J Pharm Sci 2002; 64(4):357-61.

[20] Shigeru A, Hidenobu A, Ryoichi M, Katsumi I, Hiroshi O. Sustained release matrix using hydroxy propyl cellulose-ethyl cellulose complex as filler and controlling factors of drug release. Chem Pharm Bull 1990; 41(8):1438-43.

[21] J. Siepmann, N.A. Peppas. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose. Advanced Drug Delivery Reviews 2001; 48: 139–157.

[22] Misra AN and Baweja JM, "Modified Guar Gum as Hydrophilic Matrix for Controlled Release Tablets", *Indian Drugs*, April 1997; 34 (4); 216 - 223.