Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/nxr9h624

FORMULATION AND *IN VITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF DEFLAZACORT

Fouzia Sultana[1*], Y. Sirisha[2], K. Nagasree[3]

[1*,2,3]Department Of Pharmaceutics, Samskruti College Of Pharmacy In Ghatkesar, Telangana. 501301.

***Corresponding Author:** Fouzia Sultana
*Department of Pharmaceutics, Samskruti College Of Pharmacy, Ghatkesar, Telangana.
Email Id- fouziasultana.syed@gmail.com

ABSTRACT
In the present work, an attempt has been made to develop controlled release tablets of Deflazacort by selecting different types of polymers Eudragit S 100, Ethyl Cellulose and Hydroxypropyl Cellulose as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F8 formulation showed maximum % drug release i.e., 96.94 % in 12 hours. Hence it is considered as optimized formulation F8 which contains Hydroxypropyl Cellulose (10 mg). Whereas the formulations with Eudragit S 100 showed more retarding with low concentration of polymer.

KEY WORDS: Deflazacort, Eudragit S 100, Ethyl Cellulose, Hydroxypropyl Cellulose and Controlled Release Tablets.

INTRODUCTION
Drug delivery is a technique of delivering medication to a patient in such a manner that specifically increases the drug concentration in some parts of the body as compared to others. The ultimate goal of any delivery system is to extend, confine and target the drug in the diseased tissue with a protected interaction. Every Dosage form is a combination of drug/active pharmaceutical ingredients (APIs) and the non-drug component called excipients/additives. APIs are the actual chemical components used to treat diseases.[1]

Administration of drugs into the body cavities (rectal, vaginal) can be impractical and unfeasible as they can be degraded at the site of administration (e.g., low pH in the stomach) and may cause local irritations or injury when the drug concentration is high at the site of administration. Some APIs are sensitive to the environment and can benefit from reducing the exposure to environmental factors (light, moisture, temperature and pH), or they need to be chemically stabilized due to the inherent chemical instability. APIs mostly have unpleasant organoleptic qualities (taste, smell and compliance), which reduce patient compliance.[2,3] The glidants prevent lump formation by reducing the friction between particles and improve the flowability of the tablet granules or powder. Anti-

adherents stop the powder from sticking to the machines during manufacturing. Lubricants ensure the smooth surface of dosage form, by reducing the friction between the walls of the tablets and the die cavity during ejection. Flavouring agents help to mask the unpleasant odour and colourants are added to aid in recognition and aesthetics.[4] The most common dosage forms comprise tablets, capsules, pills, ointments, syrups and injections. Various routes of drug administration are tabulated in Table 1 and Figure 3. The preferred route of drug administration depends on three main factors: The part of the body being treated, the way the drug works within the body and the solubility and permeability of the drug. For example, certain drugs are prone to destruction by stomach acids after oral administration resulting in poor bioavailability. Hence, they need to be given by the parenteral route instead. Intravenous administration of drugs gives 100% bioavailability. [5]

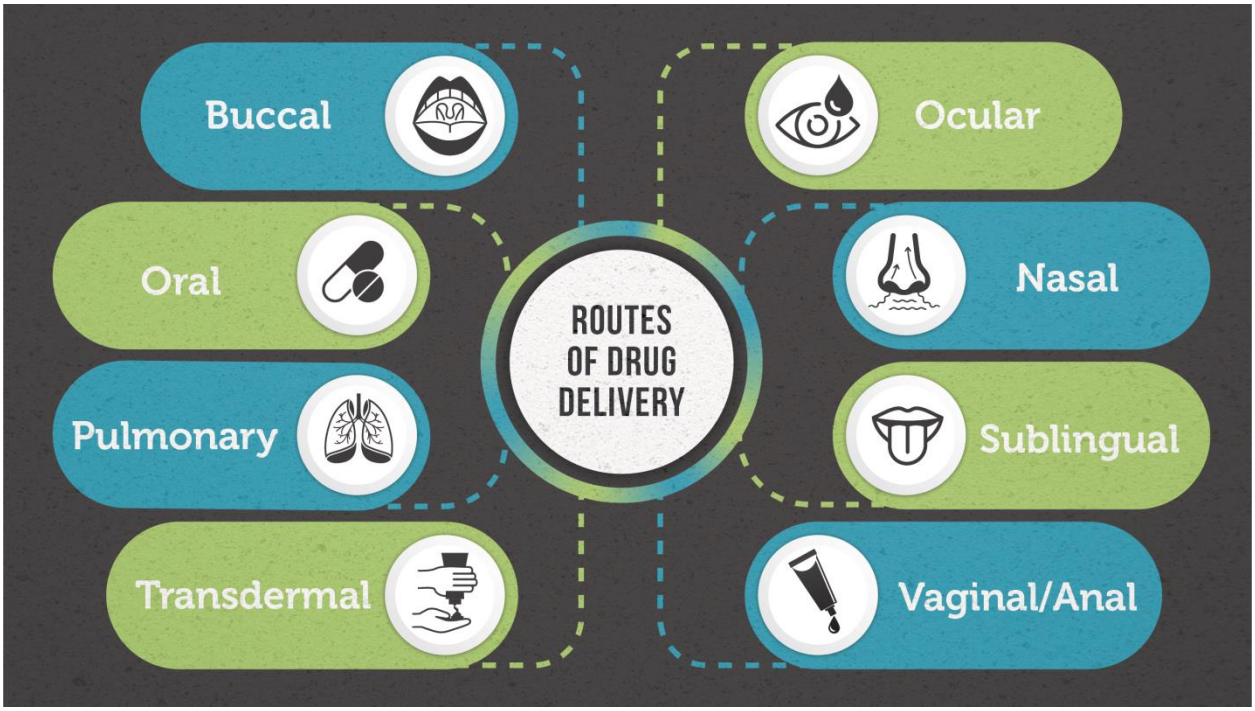


FIG 1.1: Routes of Drug delivery system

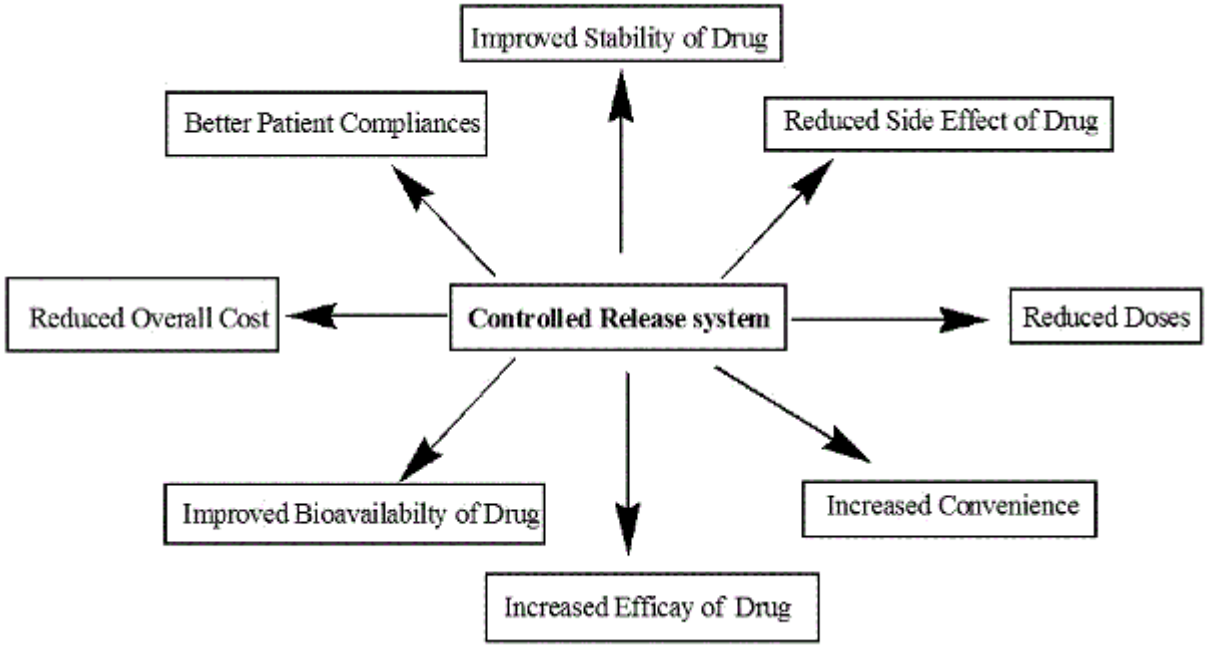
DRAWBACK OF CONVENTIONAL DOSAGE FORM

1) Poor patient compliance: Chances of missing of the dose of a drug.
2) The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.
4) The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur.[6, 7, 8]

Controlled drug delivery is one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time.
The rationale of controlled release dosage form can be summarized as below:

- To provide a location-specific action within the GIT.
- To avoid an undesirable local action within the GIT.
- To provide a programmed drug delivery pattern.
- To increase the rate and extent of absorption/bioavailability.
- To extend the duration of action of the drug.

ADVANTAGES



1] Therapeutic advantage:
Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

2] Reduction in adverse side effects and improvement in tolerability:
Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

3] Patient comfort and compliance:
Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.

4] Reduction in Health care cost:
The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration.
Avoid night time dosing: It also good for patients to avoid the at night time.

5] Economy: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less.[9,10]

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:
1] Dose dumping:
Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2] Less flexibility in accurate dose adjustment:
In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

3] Poor In-vitro In-vivo correlation:
In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so- called 'absorption window' becomes important and may give rise to unsatisfactory drug absorption in-vivo despite excellent in-vitro release characteristics.

4] Increased potential for first pass clearance:
Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating an enzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.

5] Patient variation:
The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patients.
6] Administration of controlled release medication does not permit prompt termination of therapy. Immediate changes in drug levels during therapy, such as might be encountered if significant adverse effects are noted, cannot be accommodated.
7] There is danger of an ineffective action or even absence of it if the therapeutic substance is poorly absorbed from GIT.
8] Therapeutic agents for which single dose exceeds 1 gm, the technical process requirements may make product very difficult or sometimes impossible to prepare.
9] Therapeutical agents which absorbed by active transport are not good candidates for controlled release dosage form e. g. Riboflavin.
10] Economic factors must also be taken into account, since more costly processes and equipments are involved in manufacturing of many controlled release dosage forms.[11]

MATERIALS
Aceclofenac-Provided by SURA LABS, Dilsukhnagar, Hyderabad, Deflazacort Procured From Manus Aktteva Biopharma LLP ,India. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Eudragit S-100 Merck Specialities Pvt Ltd, Mumbai, India,Ethyl Cellulose-Merck Specialities Pvt Ltd, Mumbai, India,Hydroxypropyl Cellulose-Yarrow Chem. Products, Mumbai, India,Lactose-Shakti Chemicals, Mehsana, India,PVP K30 Merck Specialities Pvt Ltd, Mumbai, India,Magnesium stearate-S. D. Fine Chemicals Ltd., Mumbai, India,Talc-S. D. Fine Chemicals Ltd., Mumbai, India

METHODOLOGY
a) Determination of absorption maxima:
100mg of Deflazacort pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

b) Preparation calibration curve:

100mg of Deflazacort pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 10, 20, 30, 40 and 50 µg/ml of Deflazacort per ml of solution. The absorbance of the above dilutions was measured at 244 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

9.2. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. 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, 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 was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Formulation composition for tablets

INGREDIENTS (mg)	**FORMULATION CHART**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Deflazacort	6	6	6	6	6	6	6	6	6
Ethyl Cellulose	5	10	15	-	-	-	-	-	-
Eudragit S 100	-	-	-	5	10	15	-	-	-
Hydroxypropyl Cellulose	-	-	-	-	-	-	5	10	15
Lactose	71	66	61	71	66	61	71	66	61
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	**4**	4	4	4	4	4	4	4	4
Total Tablet Weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULTS AND DISCUSSION

The present study was aimed to developing Controlled release tablets of Deflazacort using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

10.1. Analytical Method

Graphs of Deflazacort were taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 244 nm respectively.

Table 10.1: Observations for graph of Deflazacort in 0.1N HCl

Concentration [µg/mL]	Absorbance
0	0
10	0.149
20	0.258
30	0.357
40	0.472
50	0.589

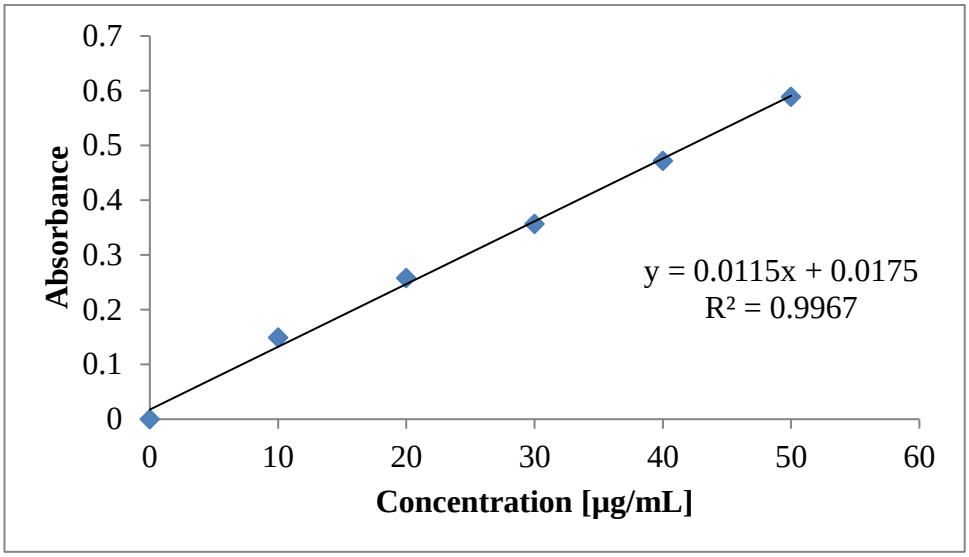


Figure : Standard graph of Deflazacort in 0.1N HCl

Table : Observations for graph of Deflazacort in p H 6.8 phosphate buffer

Conc [µg/ml]	Abs
0	0
10	0.161
20	0.295
30	0.445
40	0.571
50	0.698

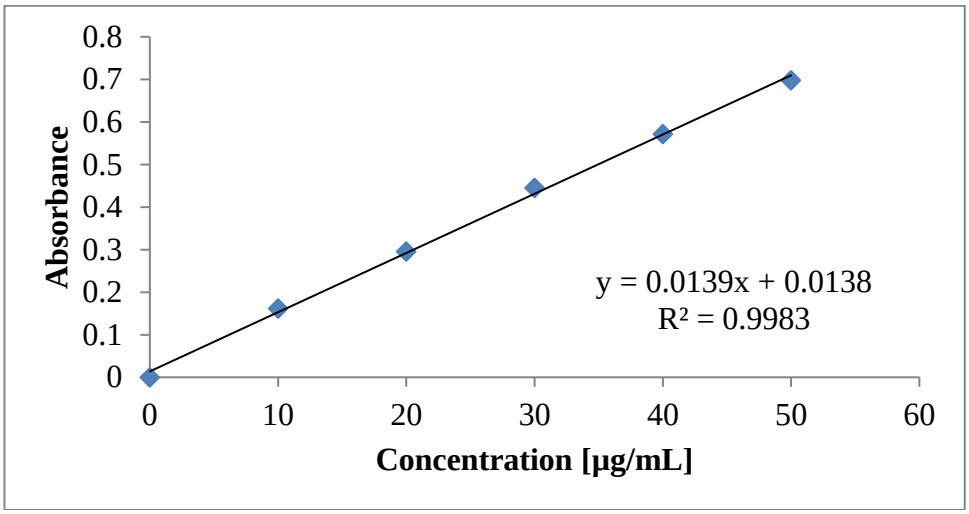


Figure: Standard graph of Deflazacort pH 6.8 phosphate buffer (244 nm)

Preformulation parameters of powder blend

Table : Pre-formulation parameters of Core blend

Table : Pre-compression parameters					
Formulations	**Bulk Density(gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Ɵ)**
F1	0.47±0.001	0.53±0.005	14.11±0.10	1.13±0.011	28.76±0.14
F2	0.44±0.003	0.66±0.003	30.45±0.07	1.55±0.007	5.64±0.20
F3	0.41±0.004	0.59±0.004	18.75±0.09	1.22±0.011	7.01±0.13
F4	0.58±0.004	0.52±0.005	8.27±0.28	1.01±0.010	4.28±0.13
F5	0.55±0.003	0.65±0.002	9.52±0.09	1.14±0.009	31.58±0.24
F6	0.42±0.002	0.58±0.002	19.89±0.11	1.26±0.011	4.22±0.22
F7	0.49±0.004	0.51±0.003	19.33±0.050	1.23±0.010	0.19±0.23
F8	0.56±0.006	0.64±0.005	13.63±0.08	1.14±0.010	2.26±0.07
F9	0.43±0.003	0.57±0.002	18.95±0.12	1.05±0.007	7.03±0.16

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41±0.004 to 0.58±0.004 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.51±0.003 to 0.66±0.003 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 8.27±0.28 to 30.45±0.07 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 1.01±0.010 to 1.55±0.007 indicating the powder has good flow properties.

Quality control parameters for tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table: 10.4. *In vitro* quality control parameters for tablets

Formulation codes	**Average Weight (mg)**	**Hardness(kg/cm^2)**	**Friability (% lose)**	**Thickness (mm)**	**Drug content (%)**
F1	98.32	5.7	0.79	2.03	99.73
F2	97.54	5.4	0.48	2.16	97.42
F3	97.22	5.1	0.12	2.79	99.10
F4	99.15	5.8	0.85	2.32	97.89
F5	98.10	5.5	0.55	2.55	98.55
F6	95.48	5.2	0.28	2.78	97.23
F7	98.39	5.9	0.94	2.11	99.91
F8	97.56	5.6	0.68	2.24	99.62
F9	100.02	5.3	0.33	2.47	98.34

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 10.4. The average tablet weight of all the formulations was found to be between 95.48 to 100.02**.** The maximum allowed percentage weight variation for tablets weighing >100 mg is 5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 2.03 to 2.79.

Hardness and friability: All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 10.4. The average hardness for all the formulations was found to be between **(**5.1 **to** 5.9) Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 10.4. The average percentage friability for all the formulations was between 0.12 to 0.94which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 10.4. The drug content values for all the formulations were found to be in the range of **(**97.23 **to** 99.91 **).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.
All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table : Dissolution Data of Deflazacort Tablets

TIME (hr)	% Cumulative Drug Release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
In dissolution media 0.1 N HCL									
0	0	0	0	0	0	0	0	0	0
1	27.72	19.85	14.62	23.8	27.69	24.72	17.3	16.75	19.35
2	33.39	20.22	18.21	36.4	30.75	37.54	24.4	23.89	25.92
In dissolution media 6.8 Phosphate Buffer									
3	43.75	26.80	23.85	47.3	43.82	49.35	32.6	24.73	33.55
4	56.49	38.35	28.76	53.4	54.46	53.41	38.8	33.27	37.28
5	59.75	43.24	33.93	64.6	65.21	61.46	46.2	38.10	42.10
6	63.12	44.87	34.24	76.5	73.96	68.38	54.4	44.61	48.83
7	74.69	56.42	45.75	83.14	78.43	77.57	57.95	55.46	53.79
8	85.24	59.96	56.36	94.59	82.22	83.26	61.44	63.75	57.97
9	94.14	64.29	67.24		98.43	94.38	65.82	77.51	65.41
10	93.86	76.34	78.10			99.19	74.49	80.28	71.11
11		83.89	80.96				78.20	88.31	72.52
12		88.21	84.75				86.15	96.94	78.63

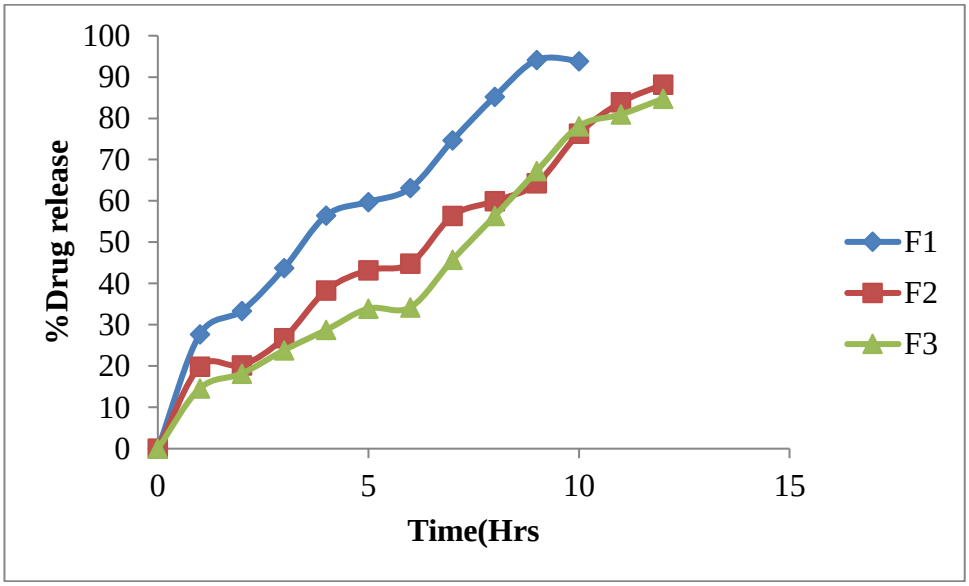


Fig : Dissolution profile of Deflazacort (F1, F2, F3 formulations).

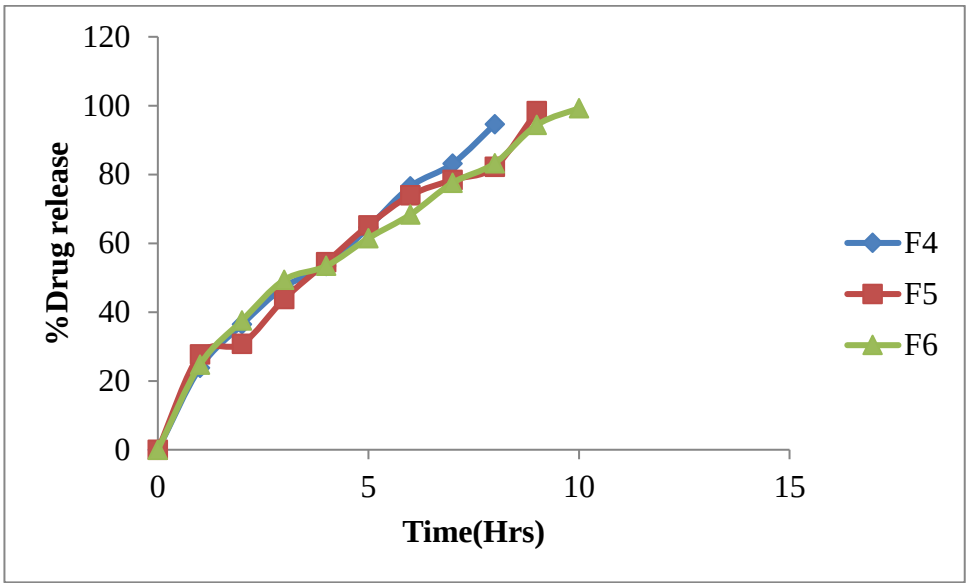


Fig : Dissolution profile of Deflazacort (F4, F5, F6 formulations)

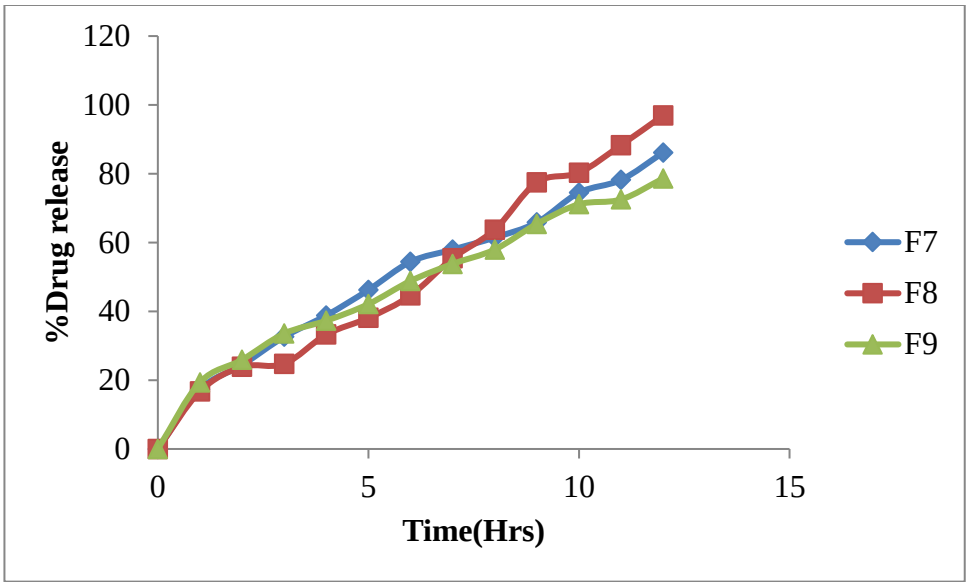


Fig : Dissolution profile of Deflazacort (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Ethyl Cellulose polymer (high concentrations) were able to retard the drug release up to desired time period i.e., 12 hours. The formulations prepared with Eudragit S100 were unable retarded the drug release. They were not shown total drug release. Hence they were not considered.

Whereas the formulations prepared with Hydroxypropyl Cellulose were retarded the drug release in the concentration of 10 mg (F8 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.94 % in 12 hours with good retardation.

From the above results it was evident that the formulation F8 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 10.6: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
16.75	1	1.000	1.224	0.000	1.920	16.750	0.0597	-0.776	83.25	4.642	4.366	0.275
23.89	2	1.414	1.378	0.301	1.881	11.945	0.0419	-0.622	76.11	4.642	4.238	0.404
24.73	3	1.732	1.393	0.477	1.877	8.243	0.0404	-0.607	75.27	4.642	4.222	0.419
33.27	4	2.000	1.522	0.602	1.824	8.318	0.0301	-0.478	66.73	4.642	4.056	0.586
38.1	5	2.236	1.581	0.699	1.792	7.620	0.0262	-0.419	61.9	4.642	3.956	0.686
44.61	6	2.449	1.649	0.778	1.743	7.435	0.0224	-0.351	55.39	4.642	3.812	0.830
55.46	7	2.646	1.744	0.845	1.649	7.923	0.0180	-0.256	44.54	4.642	3.545	1.097
63.75	8	2.828	1.804	0.903	1.559	7.969	0.0157	-0.196	36.25	4.642	3.310	1.332
77.51	9	3.000	1.889	0.954	1.352	8.612	0.0129	-0.111	22.49	4.642	2.823	1.819
80.28	10	3.162	1.905	1.000	1.295	8.028	0.0125	-0.095	19.72	4.642	2.702	1.940
88.31	11	3.317	1.946	1.041	1.068	8.028	0.0113	-0.054	11.69	4.642	2.270	2.372
96.94	12	3.464	1.987	1.079	0.486	8.078	0.0103	-0.013	3.06	4.642	1.452	3.190

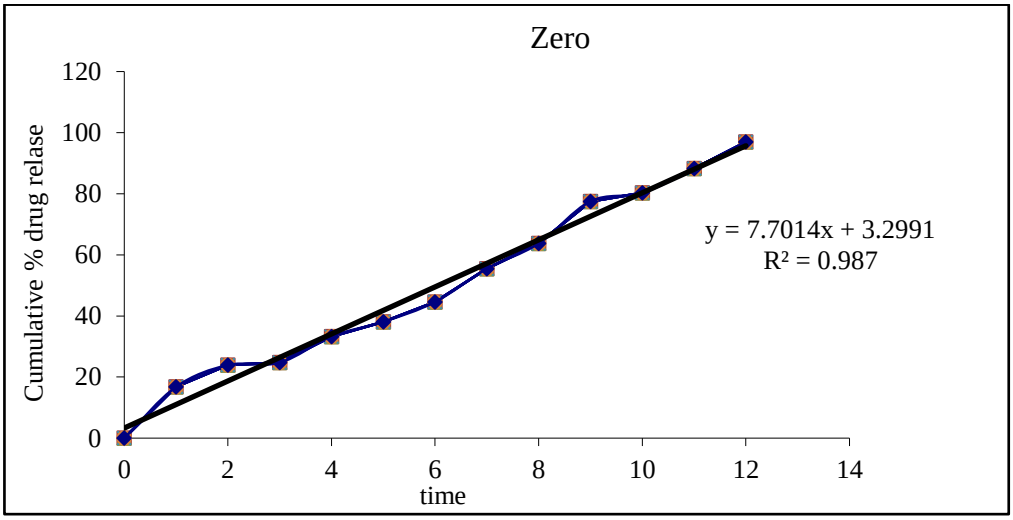


Fig 10.6 : Zero order release kinetics graph

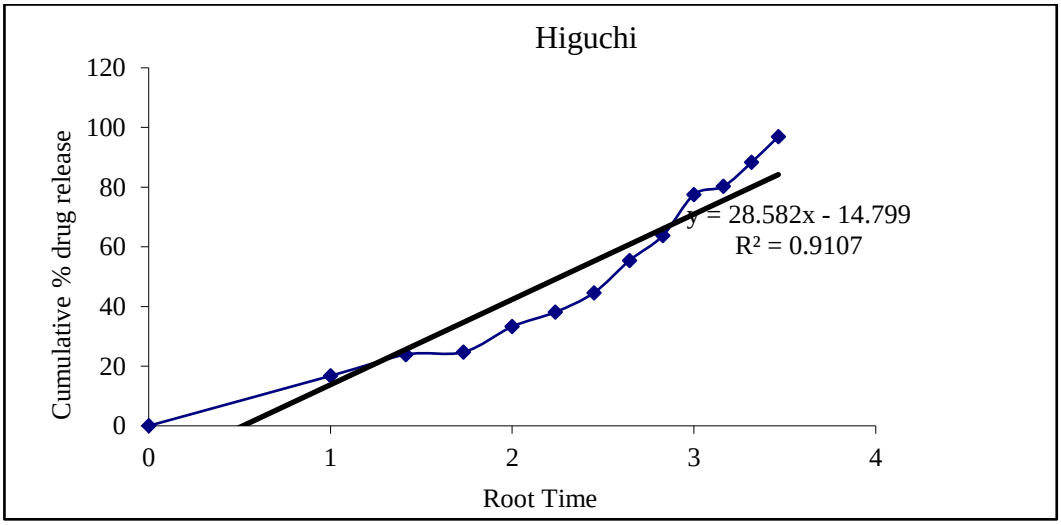


Fig 10.7 : Higuchi release kinetics graph

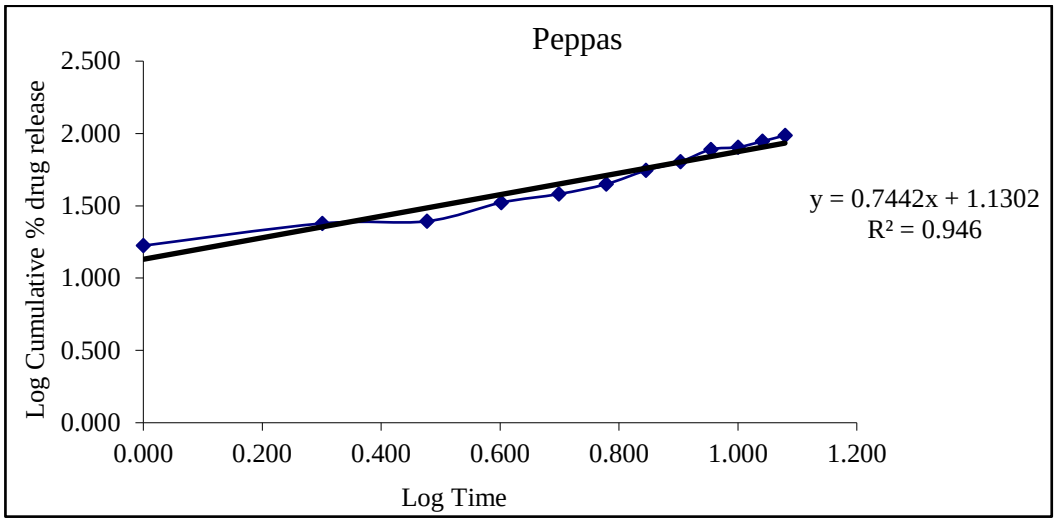


Fig 10.8: Kars mayer peppas graph

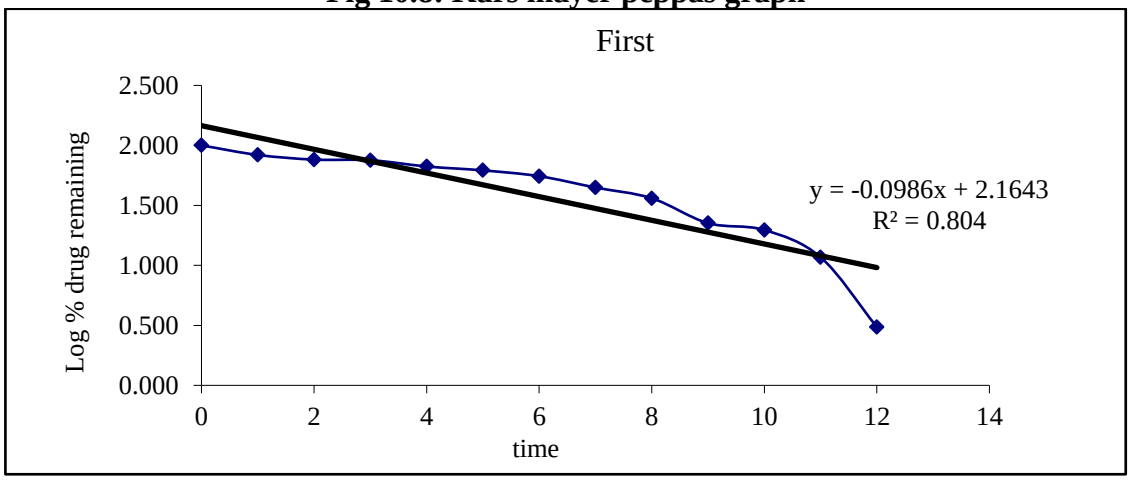


Fig 10.9: First order release kinetics graph

To study the release rate kinetics and the release mechanism of the drug from the tablet formulations, the Optimised *in vitro* drug release data were treated with the mathematical equation such as first order kinetics equation, zero-order kinetics equation

Drug and excipient compatibility studies

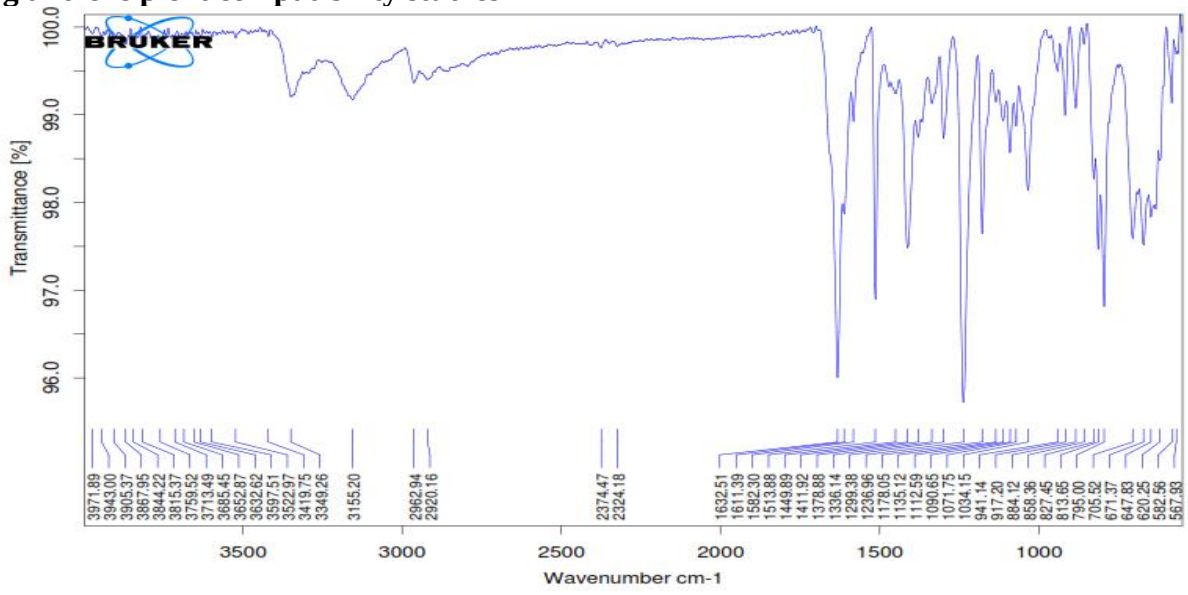


Figure 10.10: FT-IR Spectrum of Deflazacort pure drug

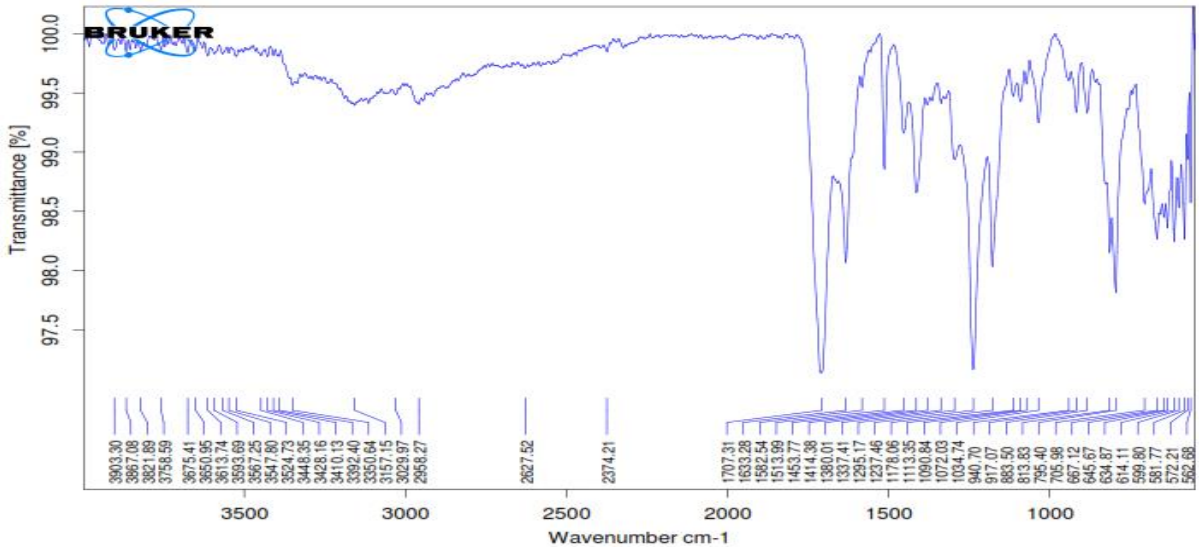


Figure 10.11: FT-IR Spectrum of Optimised Formulation

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra.

CONCLUSION:

The aim of the present study was to develop controlled release formulation of Deflazacort to maintain constant therapeutic levels of the drug for over 12 hrs. Eudragit S 100, Ethyl Cellulose and Hydroxypropyl Cellulose were employed as polymers. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 5, 10 and 15mg concentration. Compatibility study revealed that there was no interaction between the drug and the excipients in the formulation. The pre-compression and the post compression parameters are found to be within the limits. 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 (F8) showed better and desired drug release pattern i.e., 96.94 % in 12 hours. It contains the polymer Hydroxypropyl cellulose as sustained release material. It followed Zero order release kinetics mechanism.

FUTURE SCOPE

Deflazacort from test tablets showed prolonged release and may be able to sustain the therapeutic effect. This can be further proved by pharmacodynamic study and *In vivo* pharmacokinetic study.

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.