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THE FORMULATION AND *IN-VITRO* EVALUATION OF NICARDIPINE SUSTAINED RELEASE TABLETS USING NATURAL POLYMERS

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ABSTRACT

The objective of the present work is to design and formulate a new sustained release formulation for Nicardipine. The antihypertensive drug is given orally either as immediate release or as an extended release tablet twice or thrice a day. In order to reduce this frequency of administration, new sustained release formulations of Nicardipine were designed using natural polymers like guar gum, xanthum gum and the semisynthetic polymer HPMC. The tablets were prepared by wet granulation method using different polymers, their various combinations and in varying concentrations. The granules and the formulations were evaluated for their conformity to various physico-chemical parameters using official procedures. The *in-vitro* studies were done using pH 6.8 phosphate buffer medium for 12 hours duration. All the granules showed excellent pre-compression parameters of flow, density and compressibility. Out of all the formulations, the F7 formulation showed excellent sustained release profile with 94.7% of the drug being released over a period of 12 hours. This would ensure better therapeutic efficacy and patient compliance.

INTRODUCTION

Hypertension has been implicated as a risk factor in a number of ailments such as spontaneous intracerebral hemorrhage, sickle cell anemia, type 1 diabetes, fractures, diabetic neuropathy, renal disease etc.[1-5] The silent killer disease is rapidly becoming a worldwide health crisis and is usually difficult to diagnose early as it shows no early symptoms.[6] The disease requires a lifestyle change and the patient should be highly compliant if he wants to manage the disease effectively. Nicardipine HCl is a dihydropyridine calcium channel blocker used for blocking the transmembrane Ca^{+2} channels and cause coronary and peripheral vasodilatation. Its primary use is for the management of angina pectoris, Hypertension and cardiovascular diseases.[7] The drug has a short half life of 2-4 hours, hence, has to be given at a frequency of thrice daily in 30 mg. individual doses. As this requires a high patient compliance, the drug is associated with patient disobedience. The objective of most of the therapeutic regimens is to rapidly raise the plasma concentration to the required drug level and then to hold it constant for the desired duration of treatment. The extent to which this situation can be achieved depends on many factors, including the minimum effective concentration of the drug, the level at which side effects occur, the dose administered , the rate of drug release from the dosage form , the rate of elimination and the frequency of dosing[8]. Provided that the dose size and

frequency of administration are correct, therapeutic 'steady state' levels of the drug can be achieved rapidly and maintained by the repetitive administration of conventional oral dosage forms. To improve Nicardipine's patient compliance, development of a novel drug delivery system (NDDS) having dual benefits of better efficacy and patient compliance is needed. The NDDS of sustained release dosage form corresponds to the same. Sustained release dosage form is a specialized controlled release formulation that tends to release the drug in a predetermined, phased manner that maintains an effective drug plasma level and has minimum side effects.[9] The objective of the present study is to design and formulate a sustained release formulation of Nicardipine that had to capacity to release the drug in a progressive, controlled manner over a period of 12 hours. The formulations were designed using different concentrations of natural gums such as Guar gum, [10] xanthum gum [11,12,13,14] and certain semi-synthetic polymers such as Hydroxypropyl methlycellulose (HPMC).[15, 16, 17] The studies were further aimed at conducting *in-vitro* performance of the intended formulations.

Materials and Methods:

Materials:

The drug Nicardipine was provided by Chandra labs, Hyderabad, India. The rest of the excipients such as Guar gum, xanthum gum, isopropyl alcohol, Polyvinylpyrrolidone, Microcrystalline cellulose, Magnesium stearate, talc and HPMC were purchased from S.D. Fine Chemicals. Ltd, Mumbai, India. All other reagents used were of analytical grade.

Experimental Methods:

Compatibility Studies of Drug & Polymers: Prior to the development of the dosage forms the pre-formulation study was carried out. Hence infrared spectra of pure drug and the physical mixture of drug and polymers were taken. Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 150 cm^{-1} in a Shimadzu FT-IR spectrophotometer. The figures above illustrate that the functional groups like C-O stretch with the observation range of 1150-1085 has peaks at 1102.28 in pure drug and 1119.97 in optimized formulation. Similarly the functional group C-N has a peak range of 1342-1240 has peaks at 1243.63 in pure drug (Fig 1) and 1274.01 in optimized formulation (Fig 2). The functional groups in both the pure drug and optimized formulation are found. Hence it can be concluded that the pure drug is compatible with the excipients used in the study.

Preparation of The Standard Calibration Curves Of Nicardipine:

Standard calibration linearity curve of Nicardipine in pH 6.8 Phosphate buffer: Nicardipine (100mg) was dissolved in 10ml of methanol and volume was made up to 100 ml in volumetric flask using Phosphate buffer pH 6.8. From this stock solution 10 ml was withdrawn and was diluted to 100ml in volumetric flask which gives the concentration of 100 µg/ml. From this stock solution aliquots were withdrawn in volumetric flask to give concentrations 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml. Absorbance of each solution was measured at 355 nm using Shimadzu UV- 1700 UV-Vis double beam spectrophotometer with Phosphate buffer pH 6.8 as a reference standard.

Formulation of SR tablets:

The sustained release tablets were prepared by wet granulation method. The active ingredient (Nicardipine) was passed through the sieve#40 followed by the other ingredients through the same sieve. Nicardipine, MCC and natural polymers were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug. PVP K-30 was weighed accurately and was mixed with IPA to form a solution which is to be used as binder solution and was kept separately. The granulation, drying and sieving were followed by lubrication for final compression. Magnesium stearate and talc were

weighed and they were passed through sieve#20.Then they were mixed with the dried granules of Nicardipine in a polybag for 5minutes to get a uniform blend. Then the lubricated granules of Nicardipine were weighed accurately and fed into the die of single punch machinery and compressed. For this 9mm round punch was used for compression.

Formulation of Sustained release tablets:

Sustained release tablets were prepared using the concentration formulae below. The tablets were prepared on 16 station tablet compression machine by wet granulation. The tablets of different formulations were punched with 9mm round punch on compression machine. MCC was used as diluent, magnesium stearate and talc were used as lubricant and glidant respectively. The composition of formulations was shown in Table 1.

Determination of Pre-compressed parameters:

The bulk density was determined by transferring the accurately weighed sample of powder to the graduated measuring cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formula.

Density = Mass/Volume

The tapped density was determined by the following formula.

Density = Mass/Tapped Volume

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

The % compressibility was determined for flowability characteristics. Compressibility (%) = (Pt –Pb)/ Pt x 100. Pt is the tapped bulk density and Pb is the initial bulk density. The packing factor (Hausner's ratio) was calculated as the ratio of bulk density after tapping to bulk density before tapping. The obtained results are shown in Table 2.

Evaluation of Tablets: Physical parameters evaluation corresponding to thickness, diameter, tablet weight variation and friability test were carried out according to United States Pharmacopeia (USP). The obtained results are shown in Table 3.

Compatibility Studies: The spectrum obtained after the analysis is shown in Fig 3. The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of Nicardipine mentioned in Table 4 were also found in the spectrum formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and excipients.

Data obtained from *in vitro* analysis were fitted to various kinetic equations and the obtained results were shown in Table 6, respectively**.**

***In-vitro* Dissolution test:** *In vitro* drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 12 hr, at 50 rpm, pH 6.8 phosphate buffer for 12hrs for sustained release tablets. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug content in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer and cumulative percent drug release was calculated. The *in-vitro* dissolution test was carried out according to USP and the results are shown in Fig 4.

RESULTS AND DISCUSSION:

The tablets were formulated to evaluate the best composition for Nicardipine's sustained release. The formulations were designed by either exclusively using a single polymer only such as Guar gum (F1), HPMC (F2), Xanthum gum (F3); or by increasing the polymer concentration to 45 (F4, F5, F6). Formulations containing a mixture of the two or more natural polymers were also designed

(F7 to F13). Out of all the formulations containing a single polymer only (in concentrations of 30 mg.), F1 that contained guar gum exclusively displayed the highest amount of drug release.

Table 1. Formulation table for sustained release tablets

Formulation	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}
Nicardipine	20	20	20	20	20	20	20	20	20	20	20	20	20
Guar gum	30	-	-	45	-	-	30	30	-	45	45	-	30
HPMC	-	30	-	-	45	-	30	-	30	45	-	45	30
Xanthum gum	-	-	30	-	-	45	-	30	30		45	45	30
MCC	175	175	175	160	160	160	145	145	145	115	115	115	115
PVP K-30	15	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	8	8	8	8	8	8	8	8	8	8	8	8	8
Total weight	250	250	250	250	250	250	250	250	250	250	250	250	250

PVP- Polyvinyl pyrrolidone, IPA- Isopropyl alcohol. All the ingredients are in 'mg.'

Table 2. Pre compression parameters for SR tablets

Formulation	Angle of Repose(θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio	Result
F1	28.38±0.06	0.614±0.01	0.754±0.04	18.56±0.05	1.22±0.03	Excellent
F2	27.36±0.04	0.661±0.01	0.812±0.03	18.59±0.06	1.22±0.02	Excellent
F3	25.55±0.03	0.648±0.02	0.793±0.02	18.27±0.03	1.23±0.03	Excellent
F4	29.11±0.06	0.612±0.01	0.766±0.03	20.12±0.03	1.25±0.02	Excellent
F5	27.72±0.07	0.668±0.01	0.828±0.02	19.34±0.03	1.23±0.02	Excellent
F6	28.14±0.07	0.663±0.03	0.820±0.03	19.19±0.05	1.23±0.02	Excellent
F7	28.39±0.02	0.676±0.02	0.831±0.03	20.19±0.01	1.25±0.04	Excellent
F8	26.31±0.06	0.659±0.02	0.847±0.02	20.67±0.02	1.26±0.04	Excellent
F9	26.51±0.02	0.682±0.01	0.893±0.02	17.34±0.03	1.53±0.02	Excellent
F10	25.65±0.03	0.671±0.01	0.720±0.03	21.12±0.03	1.18±0.02	Excellent
F11	27.14±0.07	0.686±0.02	0.821±0.02	17.19±0.05	1.46±0.04	Excellent
F12	28.51±0.02	0.658±0.01	0.654±0.04	18.34±0.03	1.43±0.02	Excellent
F13	24.65±0.03	0.666±0.02	0.827±0.03	22.14±0.03	1.28±0.02	Excellent

From the above pre-compression parameters it was clear evidence that granules had excellent flow properties.

Table 3. ***Post compression parameters evaluation***

F. Code	Hardness (kg/cm^2) †	Thickness (mm) ‡	Weight (mg) ‡	Friability (%)
F1	7.25±0.02	3.40±0.03	300±0.01	0.58±0.05
F2	7.53±0.02	3.32±0.03	300±0.03	0.50±0.05
F3	7.46±0.01	3.40±002	300±0.03	0.52±0.05
F4	7.31±0.03	3.40±0.01	300±0.02	0.33±0.05
F5	7.59±0.03	3.41±0.01	300±0.03	0.31±0.03
F6	7.87±0.02	3.41±0.01	300±0.03	0.32±0.05
F7	7.94±0.06	3.11±0.02	300±0.05	0.45±0.01
F8	7.81±0.05	3.11±0.03	300±0.04	0.49±0.04
F9	7.15±0.02	3.20±0.03	300±0.06	0.58±0.04
F10	7.43±0.02	3.12±0.03	300±0.02	0.50±0.02
F11	7.56±0.01	3.50±002	300±0.04	0.52±0.04
F12	7.21±0.03	3.30±0.01	300±0.01	0.33±0.05
F13	7.29±0.03	3.51±0.01	300±0.05	0.31±0.03

Table 4. Concentration and absorbance's of Nicardipine in 6.8pH Phosphate buffer

S.No	Concentration	Absorbance
1	0	0
2	5	0.088
3	10	0.180
4	15	0.269
5	20	0.360
6	25	0.443

Table 5. *In-Vitro* Drug Release Studies for SR tablets cumulative percentage drug release from sustained release tablets

Time(hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1	12	11.5	10.2	7.5	11.3	12.5	9.5	9.3	7.5	11.3	12.5	9.3	9.5
2	20	16	13	12.3	15.2	20	15	13.9	12.3	15.2	20	15	13.9
3	34	28	27	25	36.4	35	33	34	25	36.4	35	34	33
4	45	37	35	34	45.2	46	43.4	46	34	45.2	46	42	45.8
5	61	55	52	42	42.4	59	57	60	42	42.4	59	57	60
6	70	71	67	53	50.2	68	70	71	53	50.2	68	70	74.5
8	82	80.5	74	65	65.3	77	78	78.6	65	65.3	77	79.6	78.3
10	--	--	80	78	83.2	90	83	79	78	83.2	86.3	80.9	79.4
12	--	--	--	84.7	--	--	94.7	89	79.8	89.4	90	83.4	80.8

Table 6. Release kinetics for F7 formulation for sustained release tablets

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.264938805	-0.100994807	31.0147686	1.421895774
Intercept	6.348812095	2.098533714	-14.41850882	0.639539655
Correlation	0.968384256	-0.978301696	0.967474051	0.895062581
R 2	0.937768067	0.957074209	0.936006039	0.801137024

Fig 1: FTIR spectra of Nicardipine pure drug

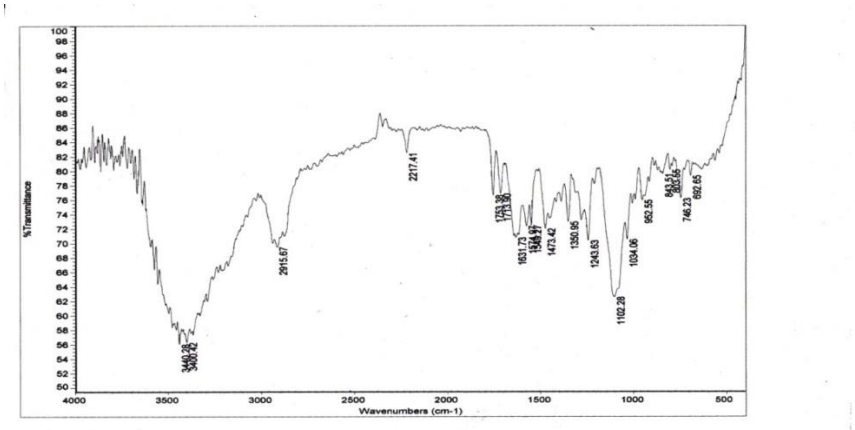


Fig 2: FTIR spectra of Nicardipine optimized formulation

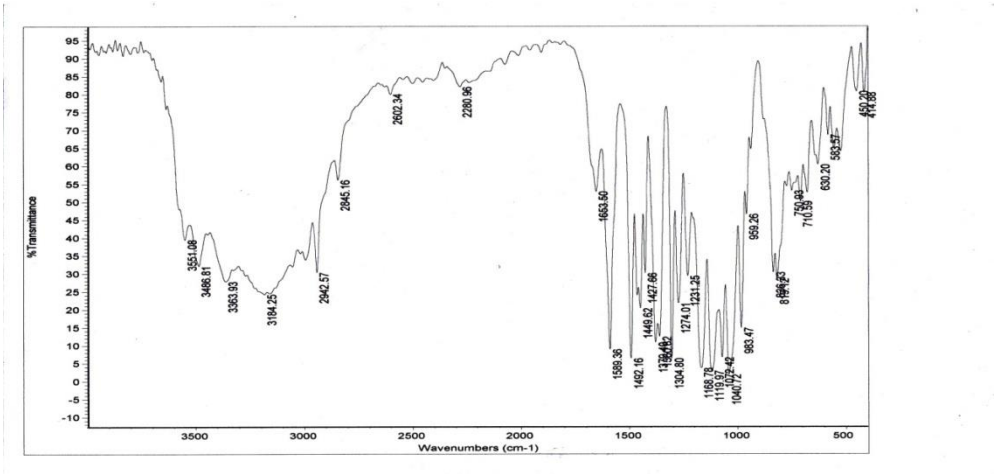


Fig 3: Calibration curve of Nicardipine in 6.8pH Phosphate buffer

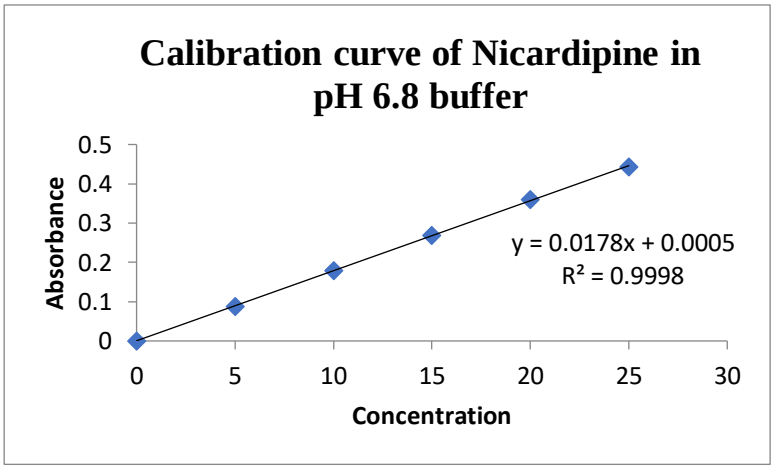
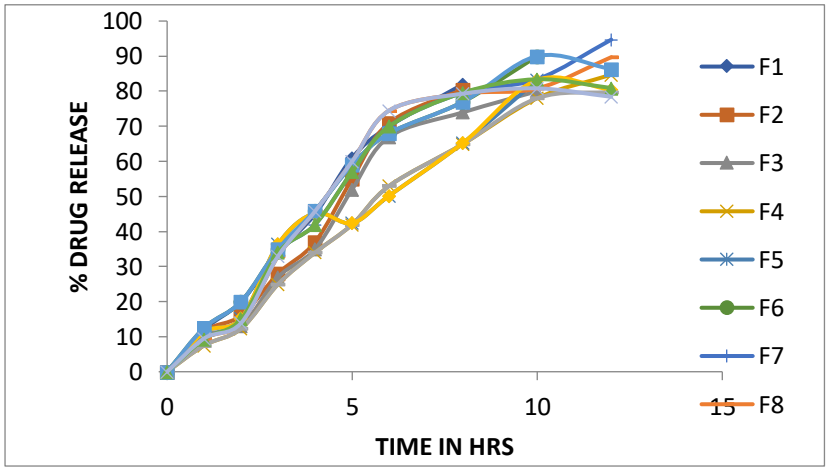


Fig 4 - Dissolution graph for sustained release formulations



If we consider the formulations containing the increased concentration of 45 mg. of single polymers only, then F6 displayed the highest drug release of 90% in 10 hours. F13 formulation which contained the combination of 30 mg. each of HPMC, guar and xanthum gum, showed drug release up to 12 hours duration but only 80.8% of the entire drug dose could be released. Rest of the formulations F7 to F12 contained a combination of either of the two polymers. From the table, it was confirmed that the F7 formulation SR tablets fulfilled all the parameters required for sustained release. In that, Guar gum was used along with HPMC as the retardant i.e. to impede the release of the drug in one go; instead the drug was released in a phased manner. In the first hour of dissolution, 9.5% of the total drug concentration was released and by 12 hours 94.7% was released. All the formulations are having angle of repose of 27±2º which shows excellent flow properties. The hardness of the tablets was between 7-8 kg/cm^2, friability value is less than 0.59%, the percentage compressibility is less than 22% for all the formulations and the thickness of tablets is on the average 3.30 mm.

CONCLUSION:

The present work has delivered a simple orally administrable tablet for the antihypertensive drug Nicardipine. In the F7 formulation, the hardness of the tablet was 7.94±0.06 kg/cm^2, thickness of 3.11±0.02 mm., weight of 300±0.05mg. and friability value of 0.45±0.01%. The formulation has excellent physico-chemical parameters and is capable of releasing the drug in a sustained manner over a period of 12 hours. Hence, further studies detailing the *in-vivo* data, *in-vivo- in- vitro* correlation and scaling up can be carried out in the future with this formulation.

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REFERENCES:

1. Brott TH, Thalinger KA, Hertzberg VI. Hypertension as a risk factor for spontaneous intracerebral hemorrhage. Stroke. 1986 Nov;17(6):1078-83.
2. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. New England Journal of Medicine. 2004 Feb 26;350(9):886-95.
3. Christlieb AR, Warram JH, Królewski AS, Busick EJ, Ganda OP, Asmal AC, Soeldner JS, Bradley RF. Hypertension: the major risk factor in juvenile-onset insulin-dependent diabetics. Diabetes. 1981 Nov 1;30(Supplement 2):90-6.
4. Forrest KY, Maser RE, Pambianco G, Becker DJ, Orchard TJ. Hypertension as a risk factor for diabetic neuropathy: a prospective study. Diabetes. 1997 Apr 1;46(4):665-70.
5. Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. Calcified Tissue International. 2009 Feb 1;84(2):103-11.
6. World Health Organization. A global brief on hypertension: silent killer, global public health crisis: World Health Day 2013. World Health Organization; 2013.
7. Chabria NB, Narayanan N. Formulation and in vitro evaluation of oral floating nicardipine hydrochloride tablets using polyethylene glycol 6000 and various HPMC grades. Pharmacophore. 2014;5:494-508.
8. Banker GS, Anderson NR. Tablets. The theory and practice of industrial pharmacy. 1987;3:293-345.
9. Bhowmik D, Srivastava S, Paswan S, Dutta AS. Sustained release drug delivery system potential. The pharma innovation. 2012 Apr 1;1(2, Part A):48.
10. Azarmi S, Farid J, Nokhodchi A, Bahari-Saravi SM, Valizadeh H. Thermal treating as a tool for sustained release of indomethacin from Eudragit RS and RL matrices. International journal of pharmaceutics. 2002 Oct 10;246(1-2):171-7.
11. Mutalik S, Naha A, Usha AN, Ranjith AK, Musmade P, Manoj K, Anju P, Prasanna S. Preparation, in vitro, preclinical and clinical evaluations of once daily sustained

release tablets of aceclofenac. Archives of pharmacal research. 2007 Feb 1;30(2):222-34.

12. Gopalakrishnan P. *Formulation and Evaluation of Aceclofenac and Famotidine Tablets for Floating Drug Delivery System* (Doctoral dissertation, Padmavathi College of Pharmacy, Dharmapuri).
13. Dwarakanadha Reddy. P, Swarnalatha. D,Design, Development and Characterization of Telmisartan Controlled Release Matrix Tablets by Using Natural Polymers, J. Pharm. Sci. & Res. Vol. 8(8), 2016, 710-714
14. Dhake A. S. Formulation and Evaluation of Sustained release of Ofloxacin tablet. Indian drugs. 2005, Vol.42, issue. 5, Pages. 317-318.
15. Basak SC, Rao YS, Manavalan R, Rao PR. Controlled release HPMC matrix tablets of propranolol hydrochloride. Indian journal of pharmaceutical sciences. 2004;66(6):827.
16. Llabot JM, Manzo RH. Double-layered mucoadhesive tablets containing nystatin. AAPS PharmSciTech. 2002 Sep 1;3(3):47-52.
17. Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AApS pharmSciTech. 2006 Jun 1;7(2):E23-9.
18. Girish S. Sonara, Devendra K. Jaina. Preparation and *in -vitro* evaluation of bilayer and floating-bioadhesive tablets of Rosiglitazone maleate. Asian Journal of Pharmaceutical Science. 2007, Vol. 2, issue 4, Pages.161-169.