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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF ROPINIROLE HYDROCHLORIDE

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Abstract: The purpose of present work was the development of sustained release tablets of Ropinirole HCl. It is used in the treatment of Parkinson's disease and also use for the treatment of restless legs syndrome. To enhance the duration of action and make a stable plasma drug concentration by preparing sustain release tablet. Formulation was optimized by using 3^2 full factorial design using HPMC K15M (20%) in combination with directly compressible filler microcrystalline Cellulose. The compatibility between drug and excipients were determined by FT-IR. Formulation were evaluated for weight variation, thickness, content uniformity, friability and *in vitro* release studies in 0.1N HCl for 2 hours and 6.8 phosphate buffer for remaining hours as dissolution medium using USP Type II (Paddle) apparatus at 50 rpm were performed. Dissolution studies revealed that all formulations could sustain drug release upto 12 hours. Statistical analysis of drug release data at 1, 5 and 9 hours indicated that the drug release is significantly affected by the concentration of the polymer and type of filler. The similarity factor was calculated for all formulation batches with theoretical release profile and F6 batch showed good similarity factor compared to other batches. The drug release of optimized formulation follows the zero-order kinetic model (R^2 = 0.998) and the mechanism found to be non-fickian diffusion according to korsmeyer-peppas equation. The optimized formulation was found stable under stability study as per ICH guidelines.

Keywords: Ropinirole Hydrochloride, Sustained Release Tablet, Directly Compression Method, HPMC K15M, MCC

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INTRODUCTION

Ropinirole hydrochloride is an anti-parkinsonian agent, selective dopamine D2-receptor agonist, widely used in the treatment of Parkinson's disease and restless legs syndrome. It is water soluble drug (solubility, 133mg/ml in water) getting rapidly absorbed from the gastrointestinal tract after oral administration, reaching peak plasma concentration in 1 hour. However, its elimination half-life in humans is short ($t_{1/2}$=5-6 hrs) and therapeutic dose needs to be administered three times a day. To reduce the dosing frequency and improve patient compliance, sustained-release (SR) formulations of Ropinirole hydrochloride is desirable, which will release Ropinirole hydrochloride for 12 hours.

Sustained Release Preparation provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action.[1-4]

Advantages

- Decrease incidence and/or intensity of adverse effects and toxicity.
- Predictable and reproducible release rates for extended duration.
- Improved patient compliance.
- Elimination of frequent dosing and wastage of drug, inconvenience of nighttime administration of drug.
- A greater selectivity of pharmacological activity.
- Reduction in GI irritation and other dose- related side effects.
- Reduction of the incidences and degree of toxic and side effects and irritation of gastro intestinal tract caused by some orally administrated drugs.
- Greater effectiveness in treatment of chronic conditions.
- Enhanced duration of activity for short half-life drugs.[2-3]

MATERIAL AND METHOD:

Ropinirole hydrochloride was obtained from (Cadila Pharmaceuticals Limited, Gujarat, India),

Various grade of Hydroxypropylmethylcellulose (Yarrow Chem.Products,Mumbai, India),

Guar gum, Xanthan gum and Chitosan were supplied by (Yarrow Chem.Products,Mumbai, India), Micro crystalline cellulose, Lactose and Dibasic Calcium Phosphate were supplied by (Chemdye Corporation, Ahmedabad, India), Talc and Magnesium stearate were supplied by (Chemdye Corporation, Ahmedabad, India).

Determination of UV λmax of Ropinirole HCl in 0.1 N HCl

Accurately weighed 10 mg Ropinirole HCl was transferred to 100 ml volumetric flask and was dissolved in 50 ml 0.1 N HCl. The volume was made up to the mark with 0.1 N HCl to prepare a stock solution of 100 µg/ml concentrations. This stock solution was suitably diluted with 0.1 N HCl to give a solution of 25µg/ml. This solution was scanned on UV spectrophotometer from 200-800 nm to find out λmax.

Determination of UV λmax of Ropinirole HCl in phosphate buffer pH 6.8

Accurately weighed 10 mg Ropinirole HCl was transferred to 100 ml volumetric flask and was dissolved in 50 ml phosphate buffer pH 6.8. The volume was made up to the mark with phosphate buffer pH 6.8 to prepare a stock solution of 100 µg/ml concentrations. This stock solution was suitably diluted with phosphate buffer pH 6.8 to give a solution of 25µg/ml. This solution was scanned on UV spectrophotometer from 200-800nm to find out λmax.

Differential Scanning Calorimeter

The thermogram of Ropinirole HCl was obtained by differential scanning calorimeter (DSC), on Shimadzu TA-60 model. **Specifications:** Sample holder: DSC aluminum cell, Amount of sample taken: 2 mg**,** Temp. range studied: 50°C to 300°C**,** Nitrogen flow rate: 100 ml /min**,** Reference sample: Blank DSC aluminum cell

Infra-Red Spectroscopy

The infrared spectrum of the native drug Ropinirole HCl was recorded on a Fourier Transformer Infra-Red Spectrophotometer in the range of 4000-400 cm^{-1}.

Calculation of Theoretical Release Profile of Ropinirole HCl from Sustained Release Tablets

Elimination half life of Ropinirole Hydrochloride $t_{1/2}$ = 5 hr

Time to reach peak plasma concentration (Tp) = 1 hr

Initial dose (DI) = 4 mg

Elimination rate constant (Kel):

Kel = $0.693/t_{1/2}$

= 0.693/5

= 0.1386 hr

Zero order release constant K0:

K0 = DI*Kel

= 4*0.1386

= 0.5544 mg/hr

Loading dose (Corrected DI) = DI - (K0*Tp)

= 4 – (0.5544*1) = 4 – 0.5544

= 3.4456 mg.

So, Maintenance dose = Total dose – Loading dose

= 10 mg –3.4456 mg = 6.5544 mg.

Table 1: Theoretical drug release profile

Time (hr.)	Total amt. Release from tablet containing 10 mg drug(mg)	% CPR
1	3.44	34.4
2	4.04	40.4
3	4.63	46.3
4	5.23	52.3
5	5.83	58.3
6	6.42	64.2
7	7.02	70.2
8	7.62	76.2
9	8.21	82.1
10	8.80	88.0

11	9.41	94.1
12	10	100

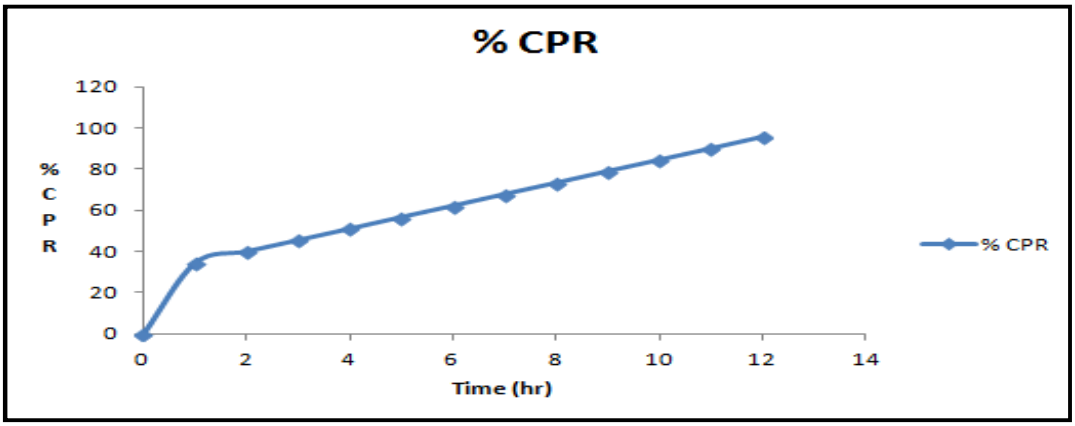

Figure 1: Theoretical Ropinirole hydrochloride release profile (T.P.)

Evaluation of Powder Mixture

Various flow property parameters like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Tapped density was measured using tapped density apparatus and angle of repose was measured using fixed funnel method.[7,9]

Preliminary Screening

Preliminary trial for selection of polymer for SR

Review of literature reveals that the Hydroxy Propyl Methyl Cellulose (HPMC) of K4M, K15M and K100M grade and Guar gum, Xanthan gum, Chitosan is required as a sustained release polymer. For screening of the polymer for formulation of sustained release tablet, Batches B1 to B6 were prepared using polymers.

Preliminary trial for selection of polymer

Table 2: Theoretical drug release profile

Ingredients	Quantity in mg/tablet					
	B1	B2	B3	B4	B5	B6
Ropinirole HCl (mg)	10	10	10	10	10	10
HPMC K4M (30 %)	60	-	-	-	-	-
HPMC K15M (30 %)	-	60	-	-	-	-
HPMC K100M (30 %)	-	-	60	-	-	-
Guar gum (30 %)	-	-	-	60	-	-
Xanthan gum (30 %)	-	-	-	-	60	-
Chitosan (30 %)	-	-	-	-	-	60
MCC	124	124	124	124	124	124
Talc	4	4	4	4	4	4
Mg. stearate	2	2	2	2	2	2
Total	200	200	200	200	200	200

*HPMC indicates hydroxypropyl methylcellulose

*****Average weight of each tablet is 200 mg.

Preparation of Ropinirole HCl Sustained Release Tablet by Direct Compression Method

Tablets of Ropinirole HCl with other excipients were prepared by direct compression. The weight of Ropinirole HCl was kept constant in all the prepared tablets at 10 mg/tablet. Different viscosity grades of HPMC namely HPMC K4M, HPMC K15M, HPMC K100M and Guar gum, Xanthan gum, Chitosan were chosen as polymeric matrix materials. MCC was selected as tablet diluent and magnesium stearate and talc were used as a lubricant. To make powder mixtures, the drug, polymer and filler were thoroughly mixed for 30 min in mortar. This powder mixture was then lubricated with magnesium stearate and talc then compressed into tablets in 7.2 mm tablet punching machine. The force of compression was adjusted so that hardness of all the prepared tablets ranges from 3-5 kg/cm^2.

Evaluation of Tablets

The prepared tablets were evaluated for various parameters. The hardness was determined by using Pfizer type hardness tester, where the force required to break the tablet was noted. The weight variation was conducted by weighing 20 tablets individually and calculating the average weight and comparing the individual tablet weight to the average value. The friability was determined using Roche friabilator. Weighed tablets were placed in the friabilator and operated for 4 min at 25 rpm. Tablets were then made free from dust and reweighed. The percentage weight loss was recorded and friability was calculated. For determination of drug content, five tablets were weighed individually and crushed in a mortar. Quantity of powder equivalent to 10 mg of Ropinirole HCl was accurately weighed and transferred in a 100 ml volumetric flask, add 25 ml N,N-dimethyl formamide and shake well for 5 min. Adjust the final volume with phosphate buffer pH 6.8 up to 100 ml. the drug content was determined by UV spectroscopy after a suitable dilution with reference to the calibration curve.[8,10]

***In Vitro* dissolution study**

The release rate of Ropinirole HCl from sustained matrix tablets were determined using USP dissolution testing apparatus II (paddle type) at 50 rpm. The dissolution test was performed using 750 ml of 0.1 N HCl (pH 1.2) for 2 h at 37 ± 0.5 ℃ and then 250 ml of 0.2 M tri sodium phosphate (Na3PO4.12H2O) was added and pH is adjusted to 6.8 as described in the USP 26/NF monograph. Dissolution test was carried out for a period of 12 hr using 0.1N HCl (pH 1.2) for first 2 hr and then the pH is adjusted to 6.8 for the rest of the period. The temperature of the dissolution medium is maintained at 37±0.5°C. 5 ml of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed with fresh dissolution medium. After filtration, the amount of Ropinirole hydrochloride release was determined from the standard calibration curve of pure Ropinirole hydrochloride.

Optimization of Sustained Release Tablet of Ropinirole HCl Using 3^2 Full Factorial Design

A statistical model incorporating interactive and polynomial term was used to evaluate the response:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_{11}X1^2 + B_{22}X2^2$$

The concentration of polymer (HPMC K15M) and type of filler (DCP, LACTOSE, MCC) were chosen as independent variables in 3^2 full factorial design, while Q1, Q5 and Q9 (% drug release after 1, 5 and 9 hours) Dependent variables.The composition of factorial design batches (F1-F9) is shown in Table 3

Table 3: Formulations of 3^2 full factorial design batches

Ingredients (mg/tablet)	Batches Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ropinirole HCl	10	10	10	10	10	10	10	10	10
HPMC K15M	30	30	30	40	40	40	50	50	50
DCP	154	-	-	144	-	-	134	-	-
Lactose	-	154	-	-	144	-	-	134	-
MCC	-	-	154	-	-	144	-	-	134
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total Weight (mg)	200	200	200	200	200	200	200	200	200

Check Point Analysis Study

The validity of the generated mathematical model was tested by two extra –design check point formulations (C1 and C2) and determine the *in vitro* release at Q1, Q5 and Q9 hr.

Table 4: Formulation of check point batch

Ingredients (mg/tablet)	Quantity taken (mg)	
	C1	C2
Ropinirole HCl	10	10
HPMC K15M	18.45	21.32
MCC	165.55	162.68
Talc	4	4
Mg. stearate	2	2
Total (mg)	200	200

Kinetic Modeling of Drug Release

To analyze the mechanism of drug release from the tablet, the dissolution data were fitted to the following equations. Kinetic modeling was performed using Microsoft excel 2007.

Stability Studies of the Optimized Formulation

Optimized formulation was subjected to stability study at temperature 40 ºC/75 % relative humidity (RH) for a period of 1 month. The optimized formulation sealed in aluminum foil was kept at above mentioned temperature and humidity condition. At the end of studies, samples were analyzed for the in vitro drug release and % drug content and other parameters such as hardness and friability.

RESULTS AND DISCUSSION:

Determination UV λmax of Ropinirole HCl

The ultraviolet spectrum of 25 µg/ml solution of Ropinirole HCl was determined in 0.1 N HCl and phosphate buffer pH 6.8.

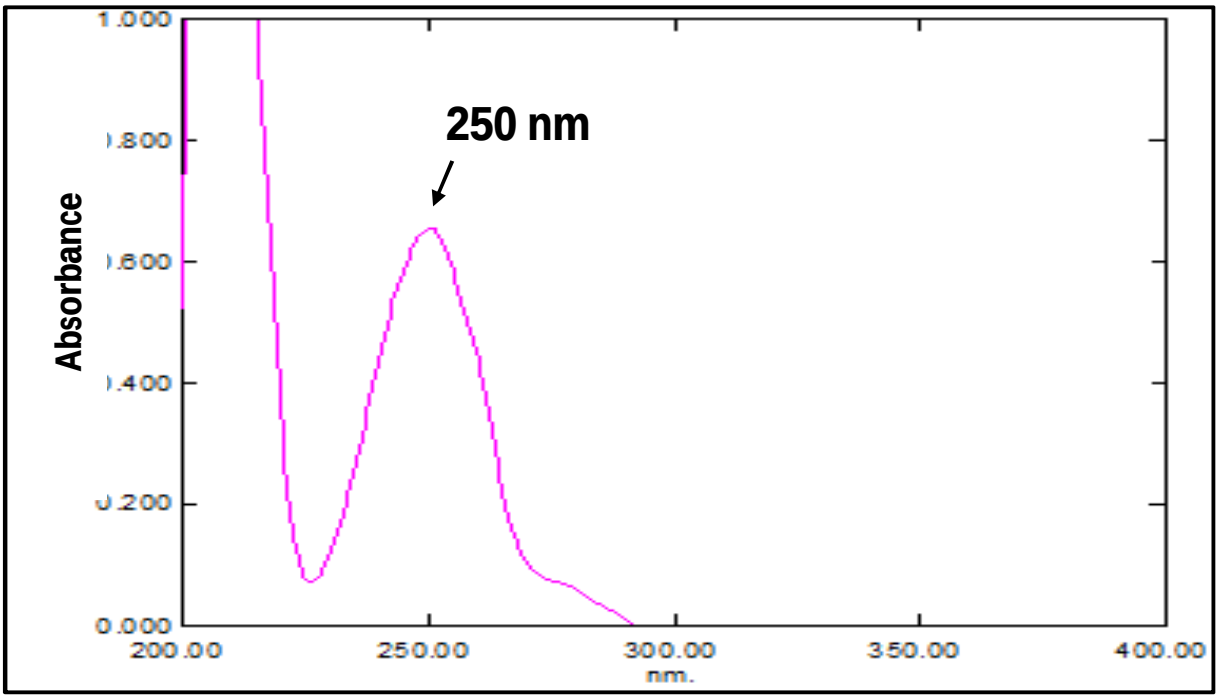

Figure 2 : UV λmax of Ropinirole HCl 0.1 N HCl and phosphate buffer pH 6.8

Drug Excipient Compatibility Study

1) Differential Scanning Calorimetry of Ropinirole HCl

The thermogram of drug was characterized by melting endotherm at 253.87°C as shown in Figure 3. Thus the DSC thermogram of the drug was found to be in agreement to the specifications. DSC thermograms of physical mixture of drug and excipients showed the melting peak of the drug at 248.19°C. It indicated that drug is compatible with all excipients and there was no major interaction of drug with excipients.

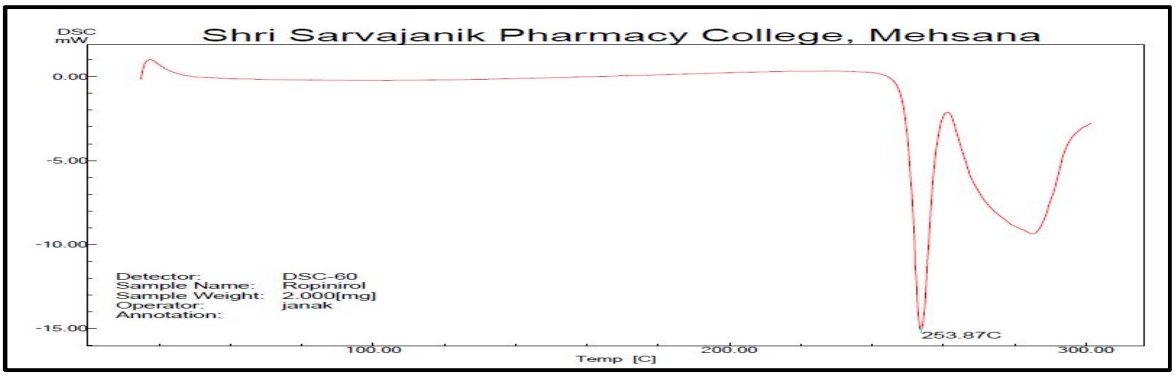

Figure 3: DSC spectra of Ropinirole HCl

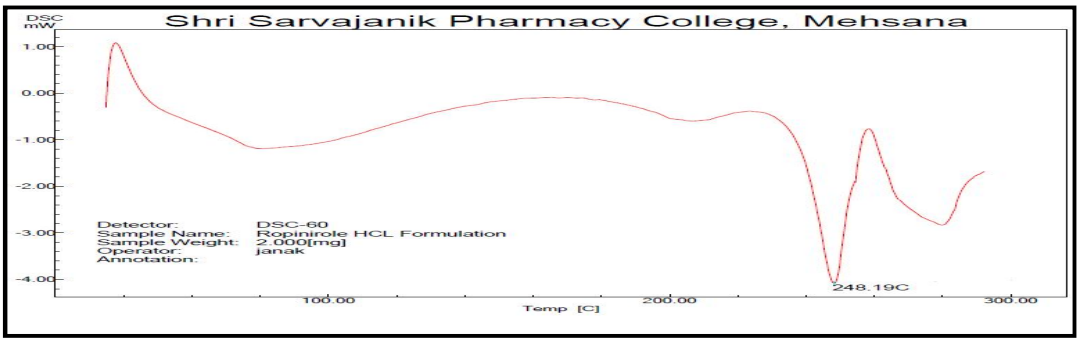

Figure 4: DSC of drug and excipients

2) FTIR Spectra of Ropinirole HCl

The peaks obtained at 1710 and 1725cm-1 for ketone group(C=O), 3413cm-1 for secondary amine group, 1596cm-1 for tertiary amine group, 2851 and 2968cm-1 for alkyl group confirm thepresence of the functional groups in Ropinirole HCl. It was concluded that no physical or chemical interactions of Ropinirole HCl with HPMC K15M, MCC, Lactose,DCP, Talc and Magnesium stearate.

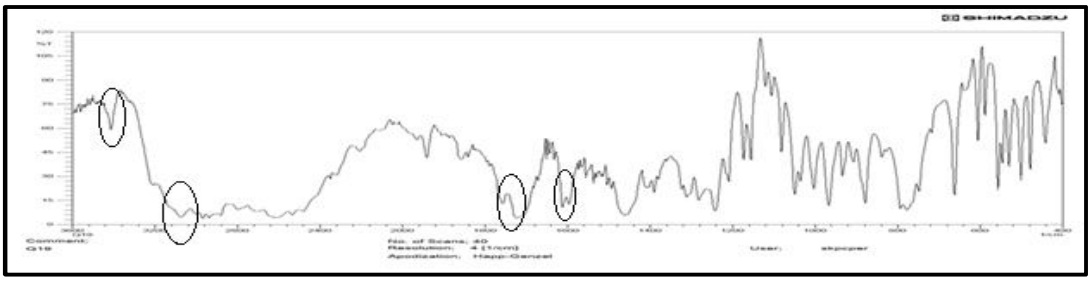

Figure 5: FTIR spectra of Ropinirole HCl

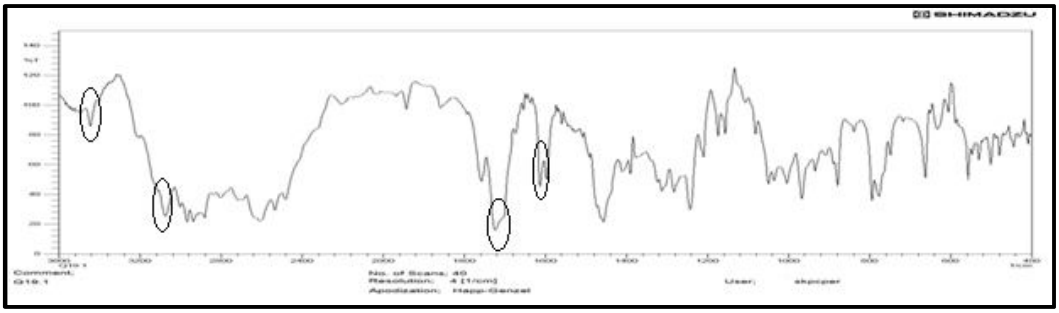

Figure 6: FT-IR spectra of drug+excipients

Preliminary Trial for Selection of Polymer for SR Tablets.

From the in vitro dissolution study it was found that HPMC K15M (30%) have more sustaining effect on release of drug than HPMC K4M, HPMC K100M, Guar gum, Xanthan gum and Chitosan. Hence, HPMC K15M is suitable for sustain release of Ropinirole HCl in low concentration. From the above studies, it was concluded that low concentration (15%, 20% and 25%) is optimized for further studies with full factorial experimental design.

Result of Sustain Release Tablets of Ropinirole HCl Using 3^2 Full Factorial Design

Table 5: Result of preformulation study of factorial design powder mixture

Parameter	Angle of repose(ɵ)	Loose bulk density (g/ml)	Tap density (g/ml)	Hausner's ratio	Carr's Index (%)
F1	27.22	0.500	0.556	1.11	10.00
F2	22.15	0.455	0.526	1.16	13.64
F3	25.45	0.476	0.588	1.24	19.05
F4	23.57	0.435	0.526	1.21	17.39
F5	24.15	0.417	0.476	1.14	12.50
F6	25.03	0.455	0.556	1.22	18.18

F7	28.55	0.417	0.500	1.20	16.67
F8	24.44	0.476	0.556	1.17	14.29
F9	26.32	0.455	0.526	1.16	13.64

Physicochemical Characterization

Table 6: Evaluation parameters of physicochemical characterization

Batch Code	Average Weight* (mg)	Friability* (%)	Thickness* (mm)	Hardness* (kg/cm^2)	Drug Content* (%)
F1	199.10±2.20	0.46	4.00 ± 0.15	4.3± 1.20	98.5 ± 1.20
F2	200.06±3.62	0.41	4.15 ± 0.26	4.5± 0.62	100.1 ± 2.12
F3	197.40±1.08	0.45	4.02 ± 0.12	4.8± 1.08	98.4 ± 1.48
F4	198.40±2.78	0.45	4.12 ± 0.17	4.6± 0.81	98.1 ±0.80
F5	199.20±1.68	0.45	4.18 ± 0.25	4.9± 0.78	99.7 ± 1.20
F6	200.05±2.41	0.38	4.08 ± 0.15	4.4± 1.41	100.1 ± 2.12
F7	199.30±2.30	0.31	4.13 ± 0.21	4.4± 0.30	98.8 ± 1.48
F8	198.40±1.05	0.44	4.14 ± 0.10	4.2± 1.05	97.7 ±0.80
F9	199.08±2.15	0.36	4.21 ± 0.10	4.8± 1.15	99.2 ± 1.70

***Values are expressed as mean ± S.D, n = 3**

***In-Vitro* Dissolution Study**

All the factorial batches showed drug release up to 12 hrs depending on concentration of HPMC K15M and type of filler (Figure 7). The results showed that there was a significant effect of DCP as compared to Lactose and MCC on the release of Ropinirole HCl. DCP extremely retarded the release of Ropinirole HCl hence F1, F4 and F7 batches failed to achieve release up to 12 hours. Formulations F5 and F6 shows drug release in a controlled manner for 12 hrs. The percentage drug release after 12 hour was 100.05% for formulations F6 which shows good release profile. Among all the factorial batches, the Formulation F6 containing 40 mg of HPMC K15M and MCC as filler was considered as the optimum formulation based on comparison of dissolution profiles.

Table 7: *In-Vitro* drug release studies of factorial batches (F1 to F5)

Time (hr)	%CPR*				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	15.06±0.32	22.44±0.49	28.19±3.50	13.23±1.03	18.38±0.57
2	25.93±0.33	32.96±0.25	38.74±3.21	23.05±1.27	24.23±0.49
3	28.72±0.25	45.62±0.33	49.95±3.62	26.93±1.18	32.75±0.17
4	30.61±0.41	54.76±0.58	58.43±2.64	29.92±0.89	38.83±0.57
5	34.76±0.42	65.89±0.15	66.45±2.71	32.58±0.73	42.48±0.49
6	36.89±0.90	69.56±0.91	71.89±2.53	35.91±0.69	50.75±0.50
7	39.40±0.42	73.65±0.37	74.54±1.92	37.06±0.93	55.93±0.83
8	41.69±0.75	77.02±0.05	78.88±2.62	40.97±0.26	61.67±0.12
9	44.89±0.52	85.64±0.18	86.19±1.99	42.14±0.11	67.90±0.20
10	47.35±0.93	88.86±0.99	89.75±1.69	45.10±0.06	75.59±0.45
11	50.36±0.52	94.59±0.29	93.98±1.49	47.43±0.09	82.89±0.88
12	52.73±0.42	97.21±0.45	97.64±2.30	49.31±0.10	90.58±0.76

*Values are expressed as mean ± S.D, n = 3

Table 8: *In-Vitro* drug release studies of factorial batches (F6 to F9 and TP)

Time (hr)	%CPR*				
	F6	F7	F8	F9	TP
0	0	0	0	0	0
1	25.93±2.93	11.11±0.70	14.09.±0.80	20.34±1.25	34.4
2	34.77±2.39	21.14±1.47	23.75±2.50	28.24±1.99	40.4

3	41.76±2.27	24.58±1.66	30.16±1.71	33.18±2.43	46.3
4	47.46±1.56	27.24±1.36	37.69±1.01	38.99±1.99	52.3
5	53.62±1.72	30.88±1.31	44.87±1.31	42.95±1.53	58.3
6	60.21±2.32	33.28±1.18	48.40±1.53	48.06±1.39	64.2
7	67.67±0.68	36.46±0.98	53.98±1.39	53.18±1.48	70.2
8	73.94±1.57	38.14±1.00	59.65±1.22	57.90±0.31	76.2
9	80.04±0.11	40.50±0.79	64.67±1.13	62.01±0.39	82.1
10	86.42±1.64	43.35±1.15	70.78±1.67	68.39±0.16	88.0
11	92.26±1.88	46.46±0.25	74.99±0.89	74.09±0.47	94.1
12	100.05±0.45	48.83±0.44	80.17±0.82	78.11±1.34	100

***Values are expressed as mean ± S.D, n = 3**

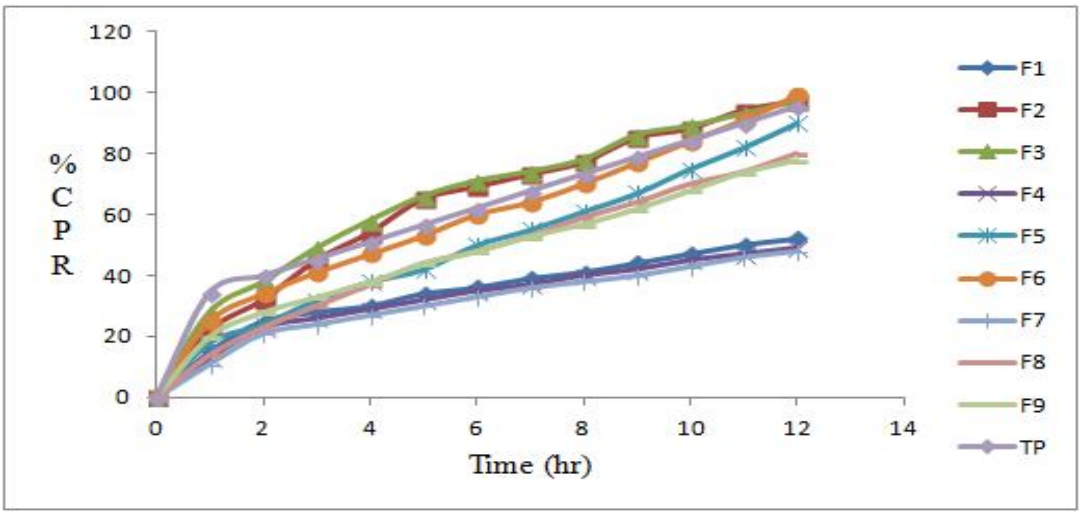

Figure 7: CPR profile of tablets of F1 to F9 batches and TP

Factorial Design Data (Using Design Expert 9.0.2.0 version)

Response Q_1: *In-Vitro* Drug Release at 1 hr.

Table 9: Summary output of regression analysis for effect of X_1 and X_2 on Q_1

	DF	SS	MS	F	P-Value Prob> F
Regression	5	264.44	52.89	89.25	0.0018
Residual	3	1.78	0.59		
Total	8	266.22			**Significant**
Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	18.22	-3.33	5.67	-1.00	-0.33	0.67
P-value	0.0018	0.0018	0.0004	0.0805	0.5836	0.3081
Full Model						
$Q_1 = 18.22 - 3.33\ X_1 + 5.67\ X_2 - 1.00 X_1^2 - 0.33 X_2^2 + 0.67\ X_1 X_2$						
Reduced Model						
$Q_1 = 18.22 - 3.33\ X_1 + 5.67\ X_2$						

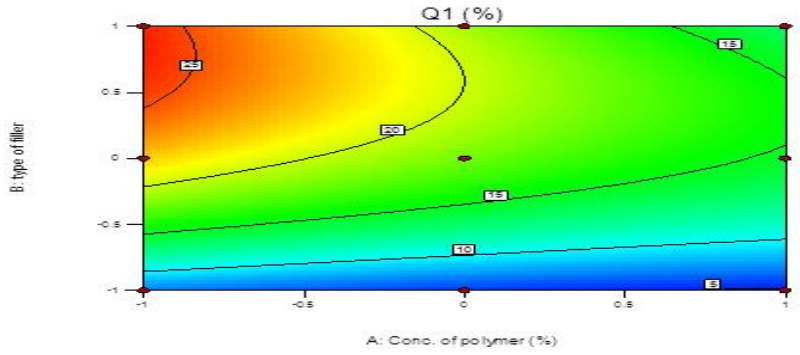

Figure 8: Counter plot of response 1(*In-Vitro* drug release at 1 hr)

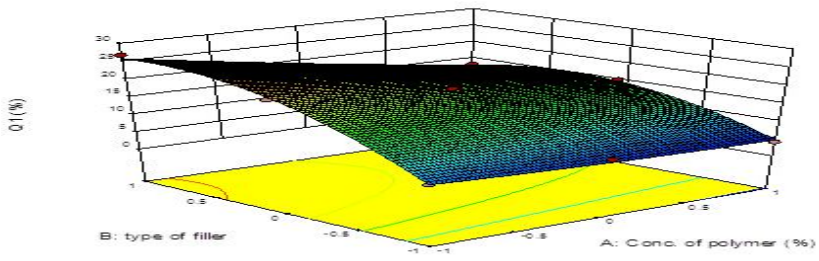

Figure 9: 3D surface plot of response 1(*In-Vitro* drug release at 1 hr)

Response Q_5: *In-Vitro* Drug Release at 5 hr.

Table 10: Summary output of regression analysis for effect of X_1 and X_2 on Q_5

	DF	SS	MS	F	P-Value Prob> F
Regression	5	1357.33	271.47	10.10	0.0429
Residual	3	80.67	26.89		
Total	8	1438.00			**Significant**
Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	47.33	-8.17	10.83	-5.00	4.50	-7.50
P-value	0.0429	0.0308	0.0144	0.1494	0.3072	0.1333
Full Model						
$Q_5 = 47.33 - 8.17\ X_1 + 10.83\ X_2 - 5.00\ X_1^2 + 4.50\ X_2^2 - 7.50\ X_1X_2$						
Reduced Model						
$Q_5 = 47.33 - 8.17\ X_1 + 10.83\ X_2$						

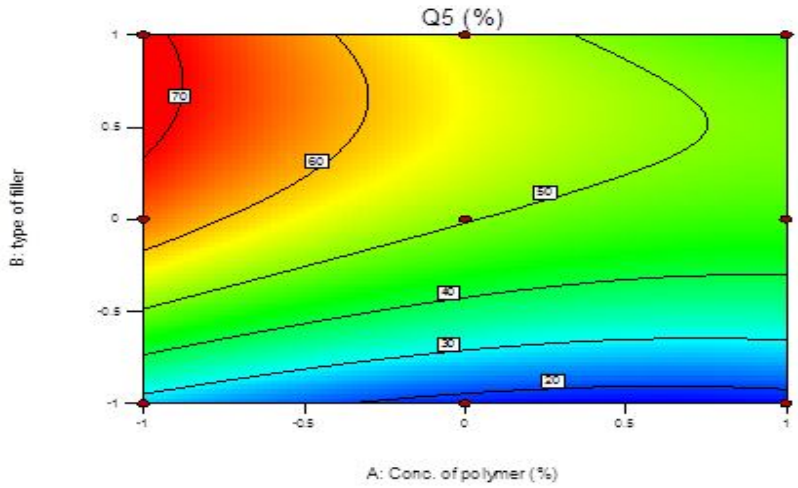

Figure 10: Counter plot of response 2(*In-Vitro* drug release at 5 hr)

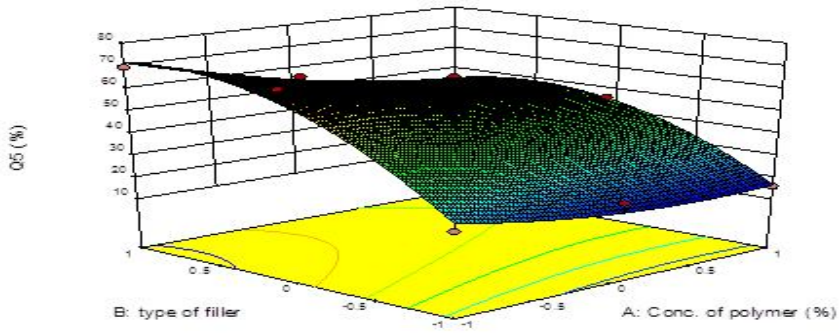

Figure 11: 3D surface plot of response 2(*In-Vitro* drug release at 5 hr)

Response Q9: *In-Vitro* Drug Release at 9 hr

Table 11: Summary output of regression analysis for effect of X_1 and X_2 on Q_9

	DF	SS	MS	F	P-Value Prob> F
Regression	5	2502.67	500.53	27.14	0.0106
Residual	3	55.33	18.44		
Total	8	2558.00			**Significant**

Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	71.00	-8.17	16.50	-13.50	1.56	-5.00
P-value	0.0106	0.0187	0.0025	0.0212	0.6553	0.1023

Full Model

$Q_9 = 71 - 8.17 X_1 + 16.50 X_2 - 13.50 X_1^2 + 1.56 X_2^2 - 5.00 X_1 X_2$

Reduced Model

$Q_9 = 71 - 8.17 X_1 + 16.50 X_2 - 13.50 X1^2$

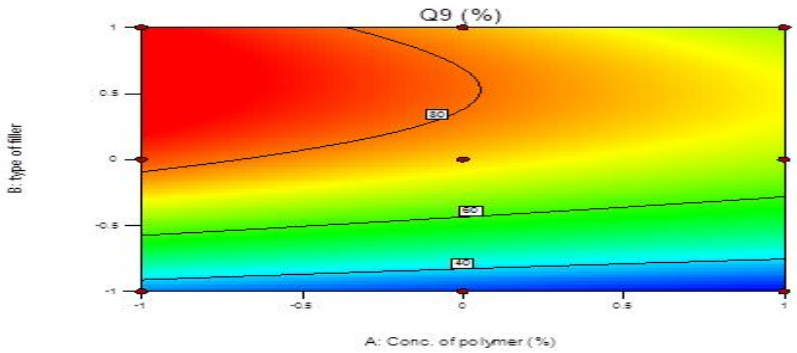

Figure 12: Counter plot of response 3 (*In-Vitro* drug release at 9 hr)

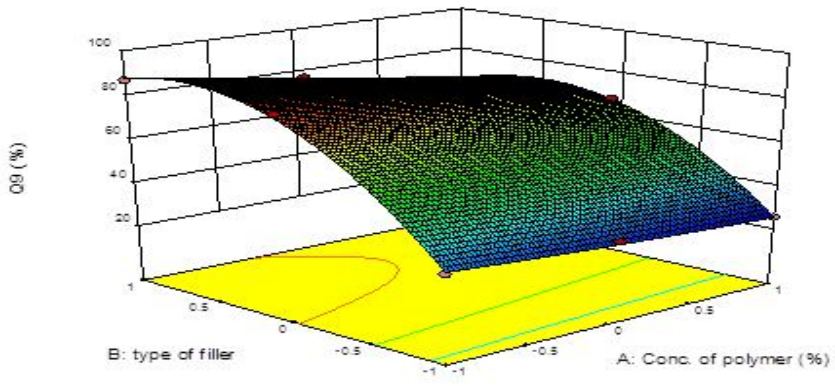

Figure 13: 3D surface plot of response 3 (*In-Vitro* drug release at 9 hr)

The plots demonstrate that X1 and X2 affect the Q1, Q5 and Q9. Based on the resultsobtained for Q1, Q5 and Q9, batch F6 was selected as best batch. The final selection is done after considering some aspects such as drug release profile and f_2 statastics.

Verification of Model by Check Point Batch

The different desired value of the three responses were entered and overlay plot of response variable Q_1 (*in-vitro* drug release at 1 hr), Q_5 (*in-vitro* drug release at 5 hr) and Q_9 (*in-vitro* drug release at 9 hr) were generated by using design expert version 9.0.2.0

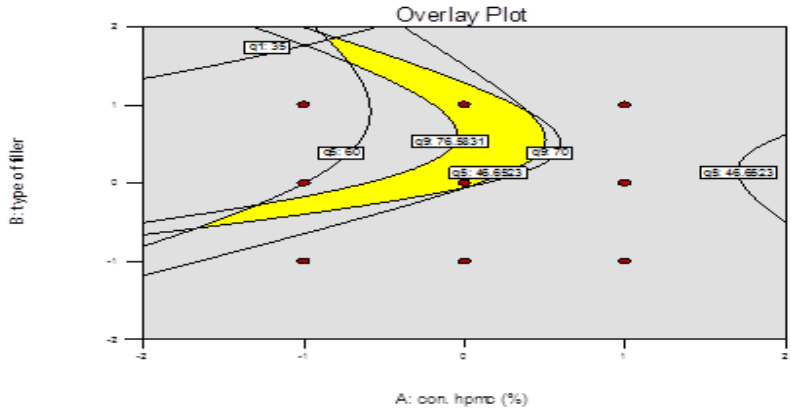

Figure 14: Overlay plot

Verification of model by comparing predicted response to actual response

Table 12: Predicted response and actual response of checkpoint batch

Batches	Predicted response			Actual Response		
	Q1 (%)	Q5 (%)	Q9 (%)	Q1 (%)	Q5 (%)	Q9 (%)
C1	22.78	50.21	73.32	23.56	52.10	75.15
C2	24.14	52.76	74.67	25.05	55.45	78.39

Actual response of C1 and C2 batch was measured and compare with the predicted response of check point batch. All the values of responses were within the upper and lower predicted interval. Hence, this model is valid and optimized batch can be selected from the overlay plot of this model.

Kinetic Modeling of Dissolution Data

Table 13: Results of model fitting

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order									
R^2	0.9847	0.9889	0.9809	0.9952	0.9876	0.9985	0.9822	0.9963	0.9958
B	3.0034	6.5699	5.9895	2.9230	6.3706	6.4090	2.9965	5.7692	5.1293
A	17.227	24.045	29.984	15.833	11.424	20.424	13.606	12.166	16.742
Firstorder									
R^2	0.9334	0.9218	0.9350	0.9182	0.9778	0.9777	0.9138	0.9467	0.9759
B	0.0396	0.0509	0.0431	0.0416	0.0588	0.0491	0.0457	0.0597	0.0489
A	1.2857	1.4579	1.5322	1.2467	1.2954	1.4414	1.1933	1.2614	1.3498
Higuchi									
R^2	0.9940	0.9767	0.9977	0.9806	0.9838	0.9880	0.9956	0.9968	0.9900
B	13.998	30.884	28.126	13.709	28.978	29.280	14.024	26.650	23.474
A	2.6299	-8.529	0.3611	1.4183	-17.79	-9.284	-1.099	-15.29	-7.134
Hixon Crowell									
R^2	-0.984	-0.978	-0.980	-0.980	-0.998	-0.998	-0.982	-0.996	-0.998
B	-1.001	-2.189	-1.996	-0.974	-2.123	-2.136	-0.998	-1.923	-1.709
A	27.590	25.318	23.338	28.055	29.525	26.525	28.797	29.277	27.752
Korsemeyer and Peppas									
R^2	0.9910	0.9956	0.9979	0.9906	0.9917	0.9924	0.9890	0.9996	0.9931
N	0.4621	0.6043	0.5057	0.4938	0.6558	0.5483	0.5434	0.6928	0.5472
A	-0.790	-0.648	-0.553	-0.839	-0.796	-0.635	-0.902	-0.851	-0.727

B= Slope, A= Intercept, R^2= Correlation coefficient, N=Diffusion exponent

Batches F1 to F9 showed sufficient correlation with Higuchi kinetic and zero order kinetic. The correlation coefficient of the optimized formulation F6 is follows the all kinetic models and shows the higher correlation (0.9985) with zero order kinetic. In the entire batches exponent 'N' was in between 0.46 and 0.69, so predominant drug release mechanism is anamolous.

Comparision of Dissolution Profiles for Selection of Optimum Batch

Table 14: Comparision of dissolution profile of F6 and theoretical profile

Time(hr.)	%CPR of theoretical profile	% CPR of F6 batch
0	0	0
1	34.4	25.93
2	40.4	34.77
3	46.3	41.76
4	52.3	47.46
5	58.3	53.62
6	64.2	60.21
7	70.2	67.67
8	76.2	73.94
9	82.1	80.04
10	88.0	86.42
11	94.1	92.26
12	100	100.05

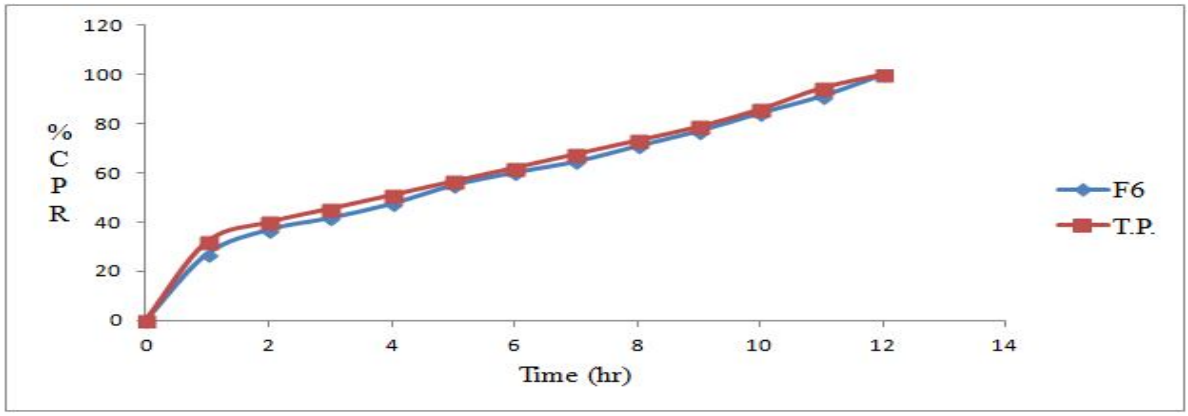

Figure 15: Comparision of dissolution profile of F6 and theoretical profile

Stability Studies

Table 15: Comparison of *in-vitro* drug release study after stability study

Time (hours)	% CPR (Initial)	% CPR (After one month storage at 40 ± 2 °C / 75 ± 5 %)
0	0	0
1	25.93	24.43
2	34.77	33.56
3	41.76	39.68
4	47.46	46.01
5	53.62	52.12
6	60.21	58.20
7	67.67	65.10
8	73.94	71.93
9	80.04	78.92
10	86.42	84.39
11	92.26	90.28
12	100.05	98.25

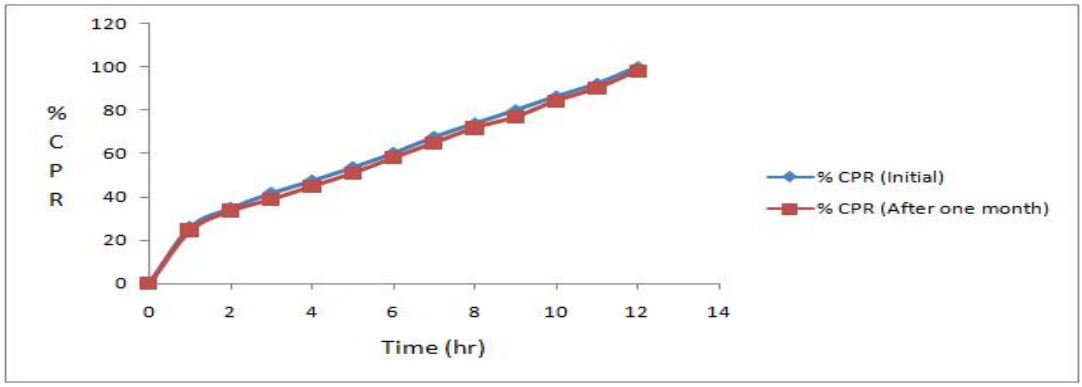

Figure 16: Comparison of *in-vitro* drug release after stability study

Table 16 : Evaluation of stability study of formulation F6

	In-Vitro Drug Release	% Drug Content*	Hardness* (kg/cm2)	Friability (%)	Similarity Factor (f_2)
Initial	100.05 % up to 12 hours	100.10 ±0.91	4.4 ± 1.41	0.38	80.26
After storage at 40 ± 2 0C and 75 ± 5% RH	98.25 % up to 12 hours	98.20 ±0.35	4.3 ± 1.56	0.36	78.43

***Values are expressed as mean ± S.D, n = 3**

REFERENCES:

1. Ratnaparkhi MP and Gupta JP: Sustained release oral drug delivery system - an overview. International Journal of Pharma Research and Review 2013; 2: 11-21.

2. Dixit N, Dutt M and Sagar BP: Sustained release drug delivery system. Indian Journal of Research in Pharmacy and Biotechnology 2013; 1: 305-310.

3. Singh A, Sharma R and Jamil F: Sustained release oral drug delivery system - an review. International Research Jornal of Pharmacy 2012; 3: 21-24.

4. Pundir S, Baloda A and Sharma D: Sustained release matrix technology and recent advance in matrix drug delivery system – a review. International Journal of Drug Research and Technology 2013; 3: 12-20.

5. Pippalla M, Sundaram M and Thirupathi T: Formulation and evaluation of extended release tablets of Metformin hydrochloride. International Journal of Pharmaceutical and Bio Science 2012; 2: 318-324.

6. Mishra U, Tripathy N, Pradhan K, Choudhury H and Tripathy S: Formulation development and evaluation of sustained release tablets of Zidovudine by model dependent approaches. International Journal of Pharmaceutical Research and development 2011; 3: 57-64.

7. Salger SV, Danki LS, Hiremath S and Sayeed A: Preparation and evaluation of sustained release matrix tablets of Propranolol hydrochloride. International Journal of Pharmaceutical and Bio Science 2010; 1: 227-241.

8. Deshkar S, Pawar M, Shirsat A and Shirolkar S: Development of sustained release tablet of Mebeverine hydrochloride. Journal of Pharmaceutical Education and Research 2013; 4: 64-69.

9. Rao R, Gandhi S and Patel T: Formulation and evaluation of sustained release matrix tablets of Tramadol hydrochloride. International Journal of Pharmaceutical and Science 2009; 1: 60-70.

10. Boddeda B, Kumari K, Chowdary KP: Formulation and Evaluation of Glipizide sustained release tablets. International Journal of Pharmaceutical and Biomedical Research 2012; 3: 44-48.

11. Sakore S and Chakraborty B: Formulation and evaluation of Enalaprile maleate sustained release matrix tablets. International Journal of Pharmaceutical and Biomedical Research 2013; 4: 21-26.