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DISSOLUTION METHOD DEVELOPMENT AND VALIDATION FOR PRAMIPEXOLE DIHYDROCHLORIDE EXTENDED RELEASE TABLETS IN MULTIMEDIA BY RP-HPLC

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ABSTRACT

The present research study describes the development and validation of an *in-vitro* dissolution method for Pramipexole dihydrochloride ER tablets by using reverse phase high performance liquid chromatography technique in different media. The method was developed and validated according to ICH guidelines. Dissolution method was developed in different media of pH 6.8 Phosphate buffer, pH 4.5 buffer and 0.1 NHCl and dissolution profiles up to 24 hrs. In respective dissolution medium were estimated. A simple isocratic analytical method was developed and was found to be accurate, precise, specific and linear. Thus, the proposed dissolution method and analytical method can be applied successfully for the quality control of Pramipexole dihydrochloride in marketed tablets.

KEYWORDS

Pramipexole dihydrochloride and ICH guidelines.

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INTRODUCTON

Pramipexole Dihydrochloride ER tablets contain Pramipexole as active ingredient. Pramipexole dihydrochloride monohydrate is a white or almost white crystalline powder. It is freely soluble in water, soluble in methanol, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride. Its pKa is 7.2 and pH is 2.8 to 3.4. The molecule has one chiral center and exhibits isomerism. Chemically Pramipexole Dihydrochloride is known as (*S*)-2-amino-4, 5, 6, 7-tetrahydro-6-(propylamino) benzothiazoledihydrochloride monohydrate[1]. Its

molecular formula isC_{10} H_{17} N_3 S·2HCl·H_2O, and its molecular weight is 302.27 gm^2. Pramipexole dihydrochloride is used in the treatment of Parkinson's disease and Restless Leg Syndrome (RLS)[3]. Typical structure of Pramipexole Dihydrochloride monohydrate structure is shown in Figure No.1.

Aim of research study is to develop a simple novel technique which can be opted easily for quantification of drug from dosage form by *in-vitro* dissolution test. Literature survey revealed that drug release from Pramipexole dihydrochloride ER tablets was determined by UV spectroscopy in pH 6.8 phosphate buffer as dissolution medium[4-6]. Various strengths of tablet are 0.375mg, 0.75mg, 1.5mg, 3.0mg and 4.5 mg. As per US FDA dissolution database for Pramipexole dihydrochloride tablets OGD media is pH 6.8 phosphate buffer.[7]

MATERIAL AND METHODS

REAGENTS AND CHEMICALS

Reference standard of Pramipexole dihydrochloride monohydrate have been used from Sigma Aldrich. Pramipexole dihydrochloride ER tablets (0.375 mg strength which contains 0.26 mg of Pramipexole) of Pramipexole have been used from licensed Neuheit Pharma technologies, India. RLD tablets (MIRAPEX, tablets 0.375 mg strength which contains 0.26 mg of Pramipexole) were used for dissolution testing.

Methanol (HPLC grade), ammonium formate (Sisco grade), Orthophosphoric acid (AR grade) Potassium dihydrogen phosphate (AR grade), Sodium hydroxide (AR grade), disodium hydrogen phosphate (AR grade), citric acid anhydrous (AR grade) and concentrated hydrochloric acid (AR grade) have been used for analysis.

METHODOLOGY

PREPARATION OF PH 5.0 AMMONIUM FORMATE BUFFER

Dissolved 31.53 g of ammonium formate in 2000mL of Milli-Q water.pH was adjusted to 5.0 ± 0.05 with 10% V/V Orthophosphoric acid solution. Buffer was filtered through a 0.45 µm mdi-HNN membrane filter.

PREPARATION OF MOBILE PHASE

Methanol and pH 5.0 ammonium formate buffer was mixed in the ratio of in the ratio of 10:90 % V/V respectively degassed.

PREPARATION OF DISSOLUTION MEDIA

Preparation of dissolution media (OGD Media)-pH 6.8 phosphate buffer

Transferred 1500mL of 0.2 M KH_2PO_4 buffer and 600mL of 0.2 M NaOH into a 10000mL of beaker. To these contents 3500mL of distilled water was added. Adjust to a pH was adjusted to 6.80±0.05 with 0.2 M NaOH. Then it was diluted to 6000mL with distilled water[8].

Preparation of dissolution media-pH 4.5 buffer (Mcllvaine citrate phosphate buffer)

Measured and transferred 2205mL of 0.2 M disodium hydrogen phosphate and 2795mL of 0.1M citric acid solution to a 5000mL beaker and mixed well.

Preparation of dissolution media-0.1 N HCl

Diluted 86mL of concentrated hydrochloric acid to 10000mL with distilled water.

DISSOLUTION PARAMETERS

Medium : Dissolution media
Quantity : 500mL

Type : USP apparatus I (Basket) #40mesh size
Bowl Temperature : 37 ± 0.5°C
Bath Temperature : 37.5°C
RPM : 100 rpm
Time Points : 1, 2, 4, 6, 9, 12, 16, 20 and 24hours.

TEST PREPARATION

Transferred 500mL of dissolution medium, preheated to 37°C into each dissolution vessel. Weighed and transferred one tablet into each of the dissolution vessel. After specified time intervals 10mL of sample was withdrawn from each dissolution vessel. Aliquots were replaced with

equal volumes of dissolution medium. Samples were filtered through a 0.45 µm nylon syringe filter.

PREPARATION OF STANDARD SOLUTIONS

Preparation of Standard Solutions -Dissolution media was used as diluent.

Preparation of Pramipexole standard stock solution: (about 349 ppm)

Weighed and transferred 50 mg of Pramipexole Dihydrochloride monohydrate standard in a 100mL volumetric flask. 70mL of dissolution medium was added and sonicated for 10 min to dissolve the contents and volume was make up with dissolution medium.

Preparation of Pramipexole standard stock solution-I: (about 17.4 ppm)

5mL was pipette out from Pramipexole standard stock solution and transferred to a 100mL volumetric flask and volume was make up with dissolution medium.

Preparation of Pramipexole standard solution for strength-0.375 mg (about 0.52 ppm)

3mL was pipette out from Pramipexole standard stock solution-I and transferred to a 100mL volumetric flask, and volume was make up with dissolution medium. This solution was filtered through a 0.45 µm nylon syringe filter and filtrate collected for analysis.

VALIDATION PARAMETERS–OGD MEDIA

Specificity

Specificity was evaluated by analyzing that in blank and placebo there is no interference at Rt of Pramipexole .Peak purity was also checked.

System Suitability

System suitability was checked by injecting a single blank and five replicates of Pramipexole standard. From obtained values % RSD, Plate count and peak tailing were evaluated.

Linearity

Standards of Pramipexole were prepared from standard stock solutions by appropriate dilutions using dissolution media. Linearity was plotted from about 0.045ppm to 8ppm for pH 6.8 phosphate buffer from obtained values correlation coefficients and regression coefficients were calculated.

Recovery

Recovery is to validate the closeness of test results obtained by the analytical procedure to the true value. The accuracy should be established across the specified range of the analyte concentration.

Recovery was done by selecting 10% of target concentration of lower strength (0.375 mg), 100 % of target concentration of middle strength (1.5 mg) and 120% of target concentration of higher strength (4.5 mg).

Precision

Precision was evaluated by using 6 tablets of Pramipexole Dihydrochloride monohydrate of lower strength i.e., 0.375 mg tablet (which contains 0.26 mg of Pramipexole). Dissolution samples were collected at different time intervals and % drug release at different time intervals (upto 24 hr.) were reported for in-house tablets and RLD tablets (MIRAPEX tablet).

MULTIMEDIA-DISSOLUTION PROFILE

With the concern of bioavailablility and bioequivalence.% Drug release from Pramipexole dihydrochloride ER tablets were estimated in pH 4.5 buffer and in 0.1 N HCl as dissolution media.

RESULTS AND DISCUSSION

A simple isocratic method was finalized for estimation of drug release from Pramipexole Dihydrochloride ER tablets by RP-HPLC method.

Finalized method was validated as per USP dissolution guidelines chapter 1092 and ICH guidelines and suitable results were reported.

Validation results-OGD media

Specificity

In blank and placebo no interference was observed at retention time(Rt) of Pramipexole, as shown in Figure No.2,3 and 4.Peak purity of Pramipexole was found to be passed as purity angle was found to be less than purity threshold, as figured in Figure No.5.

System Suitability

System suitability was found to be passed as % RSD, plate count and tailing factor were found to be acceptable as per ICH guidelines, as mentioned in Table No.1.

Linearity

Linearity was found to be passed and acceptable as per ICH guidelines. Result is tabulated in Table No.2 and linearity is plotted as figured in Figure No.6.

Recovery/Accuracy

Recovery was found to be passed and acceptable as per the acceptance criteria of USP dissolution guidelines chapter 1092.Observtions and results are tabulated in Table No.3

Precision

% Drug released from in-house tablets were compared with RLD(MIRAPEX) tablets and it was found that drug released from in-house tablets were close to that of the RLD tablets.% Drug release from in-house tablets is tabulated in Table No.4 and for RLD tablets tabulated in Table No.5. % Drug release profile of in-house versus RLD is figured in Figure No.7.

F2 value i.e., similarity factor between % drug release of RLD and In-house tablets was found to be passed.

Multimedia -Dissolution Profile

% Drug released from in-house tablets were found to closer to that of the RLD tablets. Dissolution profile of % drug release in pH 4.5 as dissolution medium is shown in Figure No.8. and % drug release tabulated in Table no.6 Dissolution profile of % drug release in 0.1 N HCl as dissolution medium is shown in Figure No.9. % drug release tabulated in Table No.7 F2 value i.e., similarity factor between % drug release of RLD and In-house tablets was found to be passed.

CHROMATOGRAPHIC CONDITIONS

S.No	Column	Inertsil ODS 3V (150 x 4.6 mm), 5µm
1	Wavelength	262 nm
2	Flow Rate	0.8mL / min
3	Column oven Temperature	25°C
4	Sample temperature	25°C
5	Injection Volume	400µL
6	Run Time	15 minutes
7	Elution	Isocratic (100 %Mobile phase)

Table No.1: System suitability of Pramipexole

Media	Standard Concentration (ppm)	Average area	Plate count	Tailing factor	% RSD
pH 6.8 phosphate buffer	0.52	509471	8676	1.1	0.4
	2	2177011	7700	1.2	0.1
	4	4352063	7733	1.3	0.1
	6	6488549	7655	1.3	0.0

Table No.2: Linearity

S.No	Concentration (ppm)	Area
01	0.045	35390.227
02	0.45	332561.373
03	2.26	1741677.484
04	6.78	5229647.533
05	8.14	6271300.217
Correlation coefficient (r)		**1.000**

Table No.3: Recovery/Accuracy

S.No	Recovery level	Sample	"mg/mL" added	"mg/mL" found	Average % recovery
1	10%	Sample-1	0.000054	0.00005	99.2 %
		Sample-2	0.000054	0.00005	
2	100%	Sample-1	0.002237	0.00224	101.3 %
		Sample-2	0.002237	0.00229	
3	125%	Sample-1	0.008053	0.00800	101.4 %
		Sample-2	0.008053	0.00834	

Table No.4: % Drug release at different time intervals –pH 6.8 phosphate buffer as dissolution medium – In-House tablets

Time interval, hr.	% Drug Release- RLD tablet						
	Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	Average
1	14.2	14.1	14.5	16.3	15.3	13.3	14.6
2	22.6	22.3	19.8	20.4	24.2	24.5	22.3
4	36.0	34.6	29.6	29.8	34.0	29.3	32.2
6	43.0	42.7	37.8	38.3	42.2	36.1	40.0
9	52.7	51.6	46.9	48.0	51.9	47.3	49.7
12	61.0	59.8	54.5	56.5	59.0	54.9	57.6
16	71.4	70.3	64.1	67.2	69.1	65.4	67.9
20	78.7	75.9	71.0	74.6	75.1	74.1	74.9
24	83.5	83.0	76.4	84.7	81.2	79.0	81.3

Table No.5: % Drug release at different time intervals –pH 6.8 phosphate buffer as dissolution medium RLD tablets

Time interval, hr.	% Drug Release- In-house tablet						
	Unit-1	Unit-2	Unit-3	Unit-4	Unit-5	Unit-6	Average
1	12.6	14.7	14.4	14.1	15.4	13.1	14.1
2	18.8	20.7	21.1	20.5	23.1	19.2	20.6
4	29.5	31.0	31.0	30.7	34.2	29.4	31.0
6	37.0	39.1	39.1	38.5	42.0	37.8	38.9
9	45.7	48.4	48.1	48.5	51.0	48.0	48.3
12	52.5	56.1	56.1	56.4	59.7	56.2	56.2
16	62.7	66.4	67.2	67.0	67.8	66.8	66.3
20	67.9	73.2	74.5	75.3	74.6	72.6	73.0
24	71.6	80.2	80.8	81.6	81.0	79.0	79.0

Table No.6: Average % Drug release–pH 4.5 buffer as dissolution medium –In-House and RLD tablets

Time interval, hr.	Average % Drug Release	
	In-house tablets	RLD tablets
1	16.1	15.2
2	21.9	22.3
4	35.0	34.1
6	43.7	41.4
9	55.1	53.8
12	60.8	61.3
16	69.3	70.6
20	73.6	76.6
24	80.9	80.4

Table No.7: Average % Drug release–0.1 N HCl as dissolution medium –In-House and RLD tablets

Time interval, hr.	Average % Drug Release	
	In-house tablets	RLD tablets
1	31.7	31.9
2	41.0	38.4
4	57.2	54.8
6	68.6	66.2
9	79.9	76.8
12	88.3	86.0
16	92.4	90.5
20	96.5	97.5
24	94.6	95.8

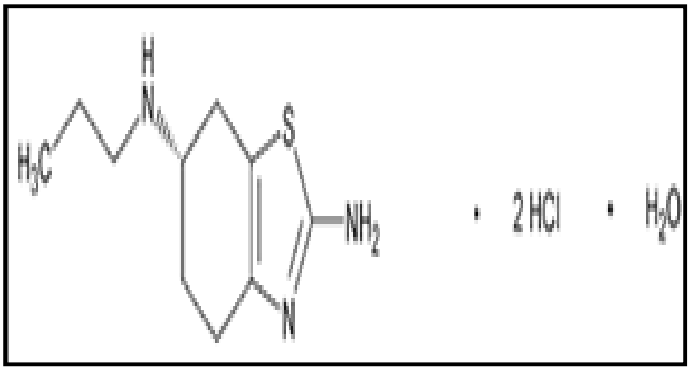

Figure No.1: Pramipexole dihydrochloride monohydrate –Structure

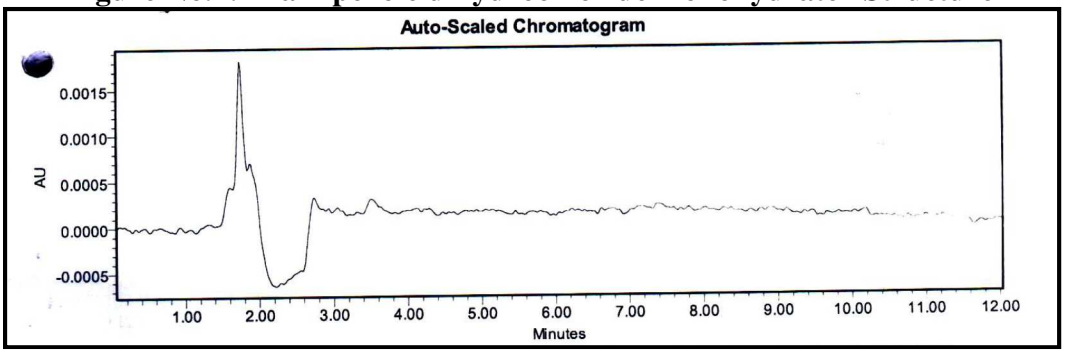

Figure No.2: Blank chromatogram (pH 6.8 phosphate buffer)

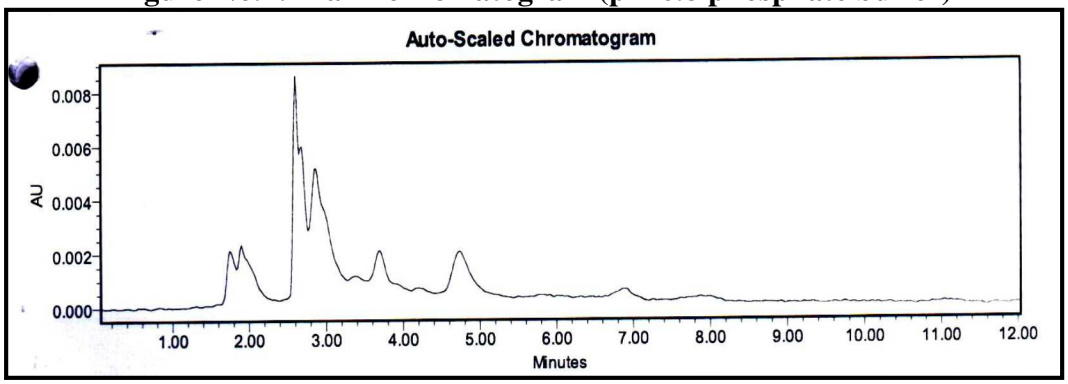

Figure No.3: Placebo chromatogram (pH 6.8 phosphate buffer)

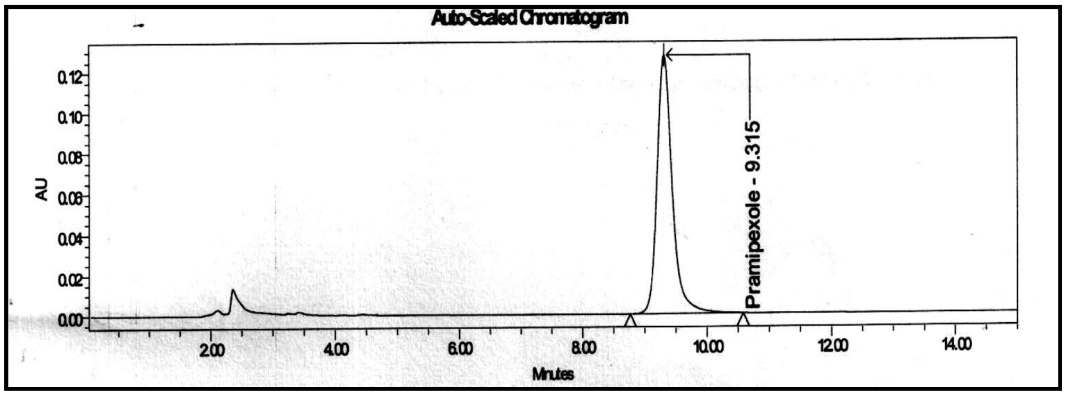

Figure No.4: Standard chromatogram (pH 6.8 phosphate buffer)

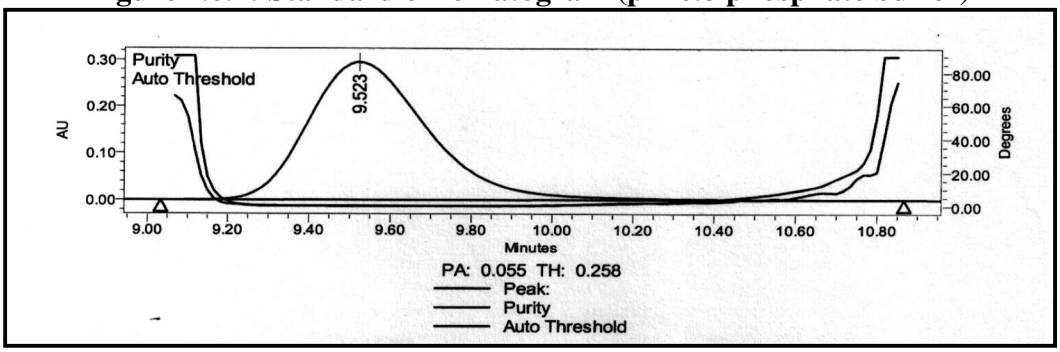

Figure No.5: Peak Purity of Pramipexole

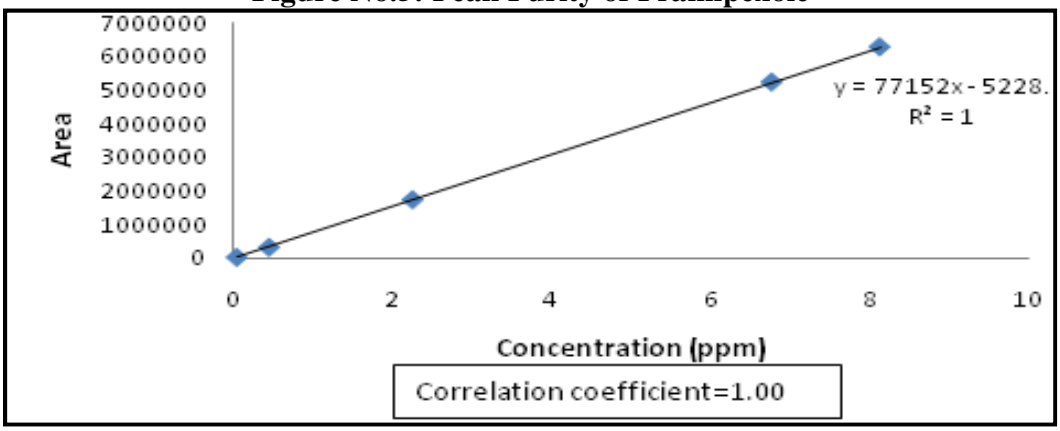

Figure No.6: Linearity –pH 6.8 phosphate buffer as dissolution media

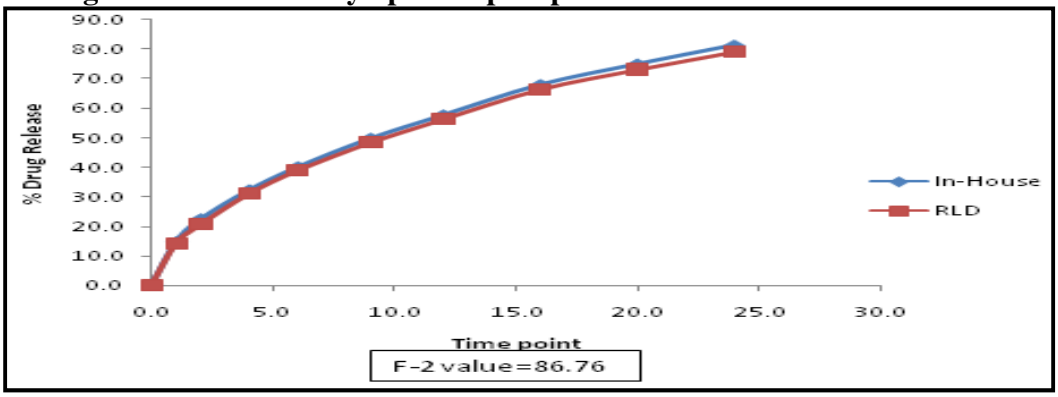

Figure No.7: % Drug Release In-house vs. RLD tablets -pH 6.8 phosphate buffer as dissolution media

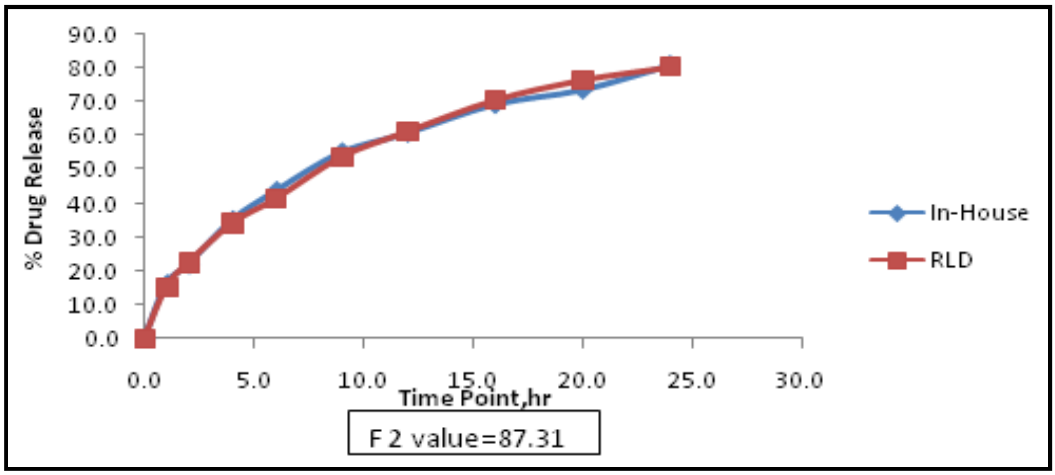

Figure No.8: % Drug Release In-house vs. RLD tablets -pH 4.5 buffer as dissolution media

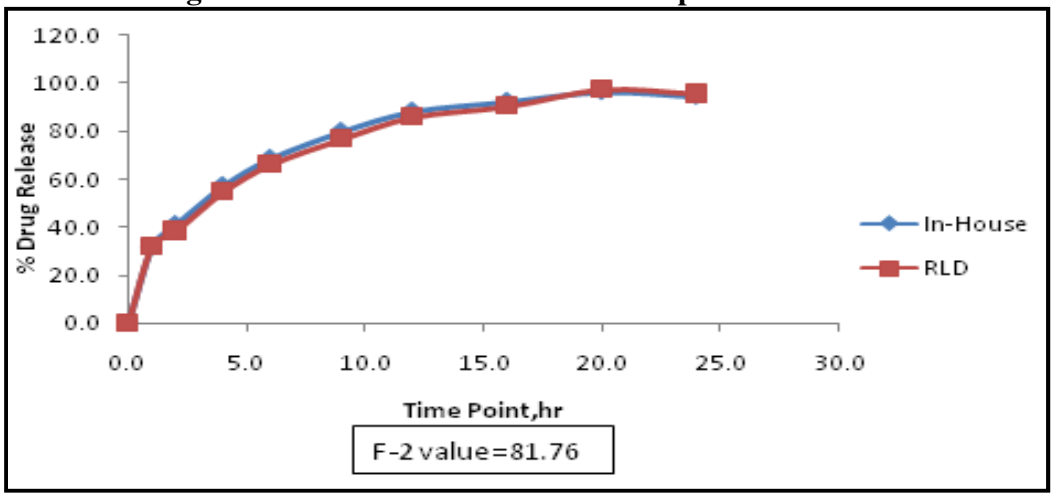

Figure No.9: % Drug Release In-house vs. RLD tablets -0.1 N HCl as dissolution media

CONCLUSION

A simple isocratic RP-HPLC method was finalized for estimation of drug release from Pramipexole Dihydrochloride ER tablets. This method is simple, specific and accurate .This method can be applied for quantification of Pramipexole form Pramipexole Dihydrochloride ER tablets of different strengths in different media. Based on results it was found that the method is appreciable as the results obtained from RLD tablets matches with the data provided by innovator drug(RLD tablet) This method can be applied in routine analysis in pharmaceutical industries and laboratories for estimation of drug release from Pramipexole Dihydrochloride monohydrate ER tablets.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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