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Research Article

Formulation and evaluation of Raloxifene hydrochloride tablets with improved dissolution profile

Nayak Smita*, Suryawanshi Sanidhya and Vaidhun Bhaskar

Department of Quality Assurance, Gahlot Institute of Pharmacy, Koparkhairane, Navi Mumbai-400709, Maharashtra, India

***Correspondence Info:**
Smita Nayak,
Department of Quality Assurance,
Gahlot Institute of Pharmacy,
Koparkhairane, Navi Mumbai-400709,
Maharashtra, India
E-mail: smitanayak125@yahoo.com

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Ac-di-sol®,
Dimethyl Sulfoxide

Abstract

The objective of this research activity was to formulate and evaluate Raloxifene Hydrochloride (RLX HCl) tablets (BCS class II drug) with enhanced aqueous solubility thereby achieving a formulation with improved dissolution characteristics. Tablets were prepared by incorporating excipients such as disintegrant, solubilizer, wetting agent and evaluated for various pre compression and post compression parameters. Also assay and *in-vitro* dissolution studies were performed. Formula RLX HCl 27 containing disintegrant Ac-di-sol® (15 mg-intragranular and 5 mg- extragranular) and solubilizer Dimethyl Sulfoxide (DMSO- 10 mg) was selected as the best optimised formula. Optimised formula was scaled up and stability studies were carried out according to the stability protocol. The results indicated that the formulation was stable and had improved dissolution profile as compared to marketed tablet.

1. Introduction

The oral route of drug administration is the most common and preferred route of drug delivery, however limited drug absorption resulting in poor bioavailability is paramount to the potential problems that can be encountered while delivering an active agent via oral route [1]. The drugs belonging to the biopharmaceutical classification system (BCS) class II and class IV dissolve slowly, poorly or irregularly, which results in the incomplete release of the drug from the dosage form. For these drugs, the dissolution process which is the rate-controlling step, determines the rate and degree of its absorption [2]. The challenge posed by such drugs can be addressed to a large extent by improving the solubility of the drug or the dissolution characteristics of the drug from dosage form.

Raloxifene Hydrochloride (RLX HCl) is an oral selective estrogen receptor modulator (SERM); it is a benzothiophene that appears to have oestrogen agonist effects on bone and antagonist effects in uterine and breast tissue. It is used for the prevention and treatment of postmenopausal osteoporosis and to reduce the risk of invasive breast cancer in postmenopausal women who have osteoporosis or at high risk of invasive breast cancer [3]. RLX HCl is official in United States Pharmacopoeia. Chemically it is, Methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy] phenyl]-, hydrochloride. The molecular formula of RLX HCl is $C_{28}H_{27}NO_4S$. HCl and its molecular weight is 510.04. RLX HCl is almost white to pale yellow powder. It is very slightly soluble in water, in isopropyl alcohol, and in octanol; slightly soluble in alcohol; sparingly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide; practically insoluble in ether and in ethyl acetate [4].

RLX HCl belongs to BCS class II as it possesses low water solubility and high membrane permeability [5]. It has an absolute bioavailability of approximately 2% in humans as it undergoes first-pass metabolism in the liver by glucuronidation and enterohepatic cycling. It has a half-life of approximately 27.7 hours. RLX HCl and its monoglucuronide conjugates are highly (95%) bound to plasma proteins [6]. The daily adult dose of the drug is 60 mg/day.

There is a need to improve the aqueous solubility or dissolution characteristics of RLX HCl to consequently increase its therapeutic effect. Hence in the present work RLX HCl tablets will be prepared using superdisintegrants, wetting agents, and surfactants etc. to enhance its dissolution rate and thus help improve bioavailability.

2. Materials and methods

2.1 Materials

Raloxifene Hydrochloride was obtained as a gift sample from Sanika Chemicals. Micro Crystalline Cellulose (MCC), Ac-di-sol® and Poly Vinyl Pyrollidone K_{30} ($PVPK_{30}$) were obtained as gift samples from Signet Chemical Corporation Pvt. Ltd. All other chemicals and reagents used were either of Analytical or Pharmaceutical grade.

2.2 Methodology

2.2.1Preformulation study to evaluate drug-excipient compatibility [7-12]

A preformulation study was carried out for 14 days for drug- excipient compatibility testing. The drug was mixed thoroughly with excipients in the ratio 1:1, 1:5 and 10:1 and kept in closed vials at 25°C and 40°C for 14 days, samples were also exposed to UV light for 24hrs (Table 1). The samples were observed visually for any physical changes. Samples were analyzed by spectrophotometry, DSC and FT-IR techniques.

Table 1: Ratios of drug and various excipients used in preformulation studies

Sr. no.	Excipients evaluated	Drug: excipient ratio
1	Drug+ Polysorbate 80	1:1
2	Drug+ Micro Crystalline Cellulose	1:5
3	Drug+ Cross caramellose sodium (Ac-di-sol®)	1:5
4	Drug+ Poly Vinyl Pyrollidone K_{30}	1:5
5	Drug+ Magnesium Stearate	10:1

2.2.1.1 FT-IR Studies

FT-IR spectroscopy was employed to ascertain the compatibility between RLX HCl and the selected excipients. The pure drug, drug-excipient combinations and formulations were subjected to FT-IR studies. The scanning range was 400--4000 cm^{-1} and the resolution was 4 cm^{-1}. The pure drug and the drug with excipients were scanned separately. FT-IR spectrum of drug-excipient mixtures was compared with that of the pure drug.

2.2.1.2 DSC Studies

Thermograms of pure drug and drug-excipient samples were recorded by differential scanning calorimeter (SII Nanotechnology, SEIKO, DSC 6220). Each sample was scanned in aluminum pan at a heating rate of 10 °C/min over the range of 50--300 °C with an empty aluminum pan used as reference. Samples were heated under nitrogen atmosphere (flow rate of N_2, 50--60 ml/min).

2.2.2 Analytical Method Development

2.2.2.1 For Assay

i. Preparation of RLX HCl standard stock solution (1000 µg/ml) in methanol

A standard stock solution of RLX HCl was prepared by dissolving accurately weighed 25 mg of RLX HCl in methanol in a 25 ml volumetric flask and the volume was made up to 25 ml by using methanol to obtain a stock solution of 1000 µg/ml.

ii. Calibration curve of RLX HClin methanol

From this stock solution, aliquots with suitable dilutions were made in order to get solutions with concentrations of2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml and 14 µg/ml. The absorbance was measured at 286 nm using UV visible spectrophotometer. The standard curve was obtained by plotting absorbance v/s concentration in µg/ml. The developed method was validated as per ICH guidelines [13, 14].

2.2.2. For Dissolution

i. Preparation of RLX HCl standard stock solution (1000 µg/ml) in 1% w/w Polysorbate 80

A standard stock solution of RLX HCl was prepared by dissolving accurately weighed 25 mg of RLX HCl in small amount of methanol in a 25 ml volumetric flask and the volume was made up to 25 ml by using 1% w/w Polysorbate 80 to obtain a stock solution of 1000 µg/ml.

ii. Calibration curve of RLX HCl in 1% w/w Polysorbate 80

From this stock solution, aliquots with suitable dilutions were made in order to get solutions with concentrations of 6µg/ml, 9µg/ml, 12µg/ml, 15µg/ml, 18µg/ml, 21 µg/ml, 24 µg/ml and 27µg/ml. The absorbance was measured at 297 nm using UV visible spectrophotometer. The standard curve was obtained by plotting absorbance v/s concentration in µg /ml. The method was validated as per ICH guidelines [13, 14].

2.2.3 Preparation of RLX HCl tablets

Nine batches of RLX HCl were formulated by varying concentrations of two of the excipients (DMSO and Ac-di-sol®) to get a 2^3factorial design (Table 2). The tablets were prepared by non-aqueous granulation technique.

Table 2: Formulation of Raloxifene Hydrochloride tablets-Factorial design study

Ingredients	mg/tablet								
	RLX HCl 20	RLX HCl 21	RLX HCl 22	RLX HCl 23	RLX HCl 24	RLX HCl 25	RLX HCl 26	RLX HCl 27	RLX HCl 28
Raloxifene hydrochloride	60	60	60	60	60	60	60	60	60
Ac-di-sol®	5	5	5	10	10	10	15	15	15
DMSO	5	10	15	5	10	15	5	10	15
MCC	222	222	222	222	222	222	222	222	222
PVP K_{30}	10	10	10	10	10	10	10	10	10
Ac-di-sol®	5	5	5	5	5	5	5	5	5
Mg Stearate	3	3	3	3	3	3	3	3	3
Tablet weight	310	310	310	310	310	310	310	310	310

2.2.4 Evaluation of tablets

A. Pre-Compression Tests [15]

The granules were evaluated for bulk density, tapped density, angle of repose, Hausner's ratio, Carr's compressibility index tests.

B. Post-Compression Tests [16-17]

Compressed tablets were subjectedto thickness, hardness, friability, drug content, disintegration and dissolution tests.

***In-vitro* dissolution studies**

In vitro dissolution studies for the prepared RLX HCl tablets were carried out using USP Type II dissolution apparatus at 37±1°C and 50 rpm using 900 ml 1% w/w Polysorbate 80 in water. Aliquots (5 ml) of the sample were withdrawn at 10, 20, 30, 45, 60, 90 and 120 minutes using a pipette and were replenished immediately with the same volume of fresh dissolution medium. Aliquots were filtered, suitably diluted and analyzed spectrophotometrically at 297 nm using a UV-3000 LABINDIA UV-Visible Spectrophotometer.

2.2.5 Evaluation of data

The dissolution data was fitted to various kinetic models to find the best fit model. Similarity factor and difference factor were determined in order to select the optimum formula for scale up and stability studies. 3D response plots were generated to find influence of various excipients on release pattern of drug from formulation.

2. 2.6 Stability studies

Preliminary trial batches and factorial batches for RLX HCl were formulated and *in vitro* dissolution studies for these batches were performed wherein the release pattern of each batch was found to be different. The batch exhibiting good dissolution profile with maximum drug release initially as well as at the end of 2 hours was selected for stability studies. Two stability batches batch nos. RLX HCl 29 and RLX HCl 30 were manufactured by scaling up the selected formula (Formula RLX HCl 27) and kept for stability studies according to the stability protocol made as per ICH guidelines. The effects of temperature, relative humidity and time on the physicochemical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The different parameters that were studied are appearance, weight variation, hardness, thickness, disintegration time, assay and dissolution. Also the stability samples were evaluated for any degradation by DSC, FT-IR and XRD techniques.

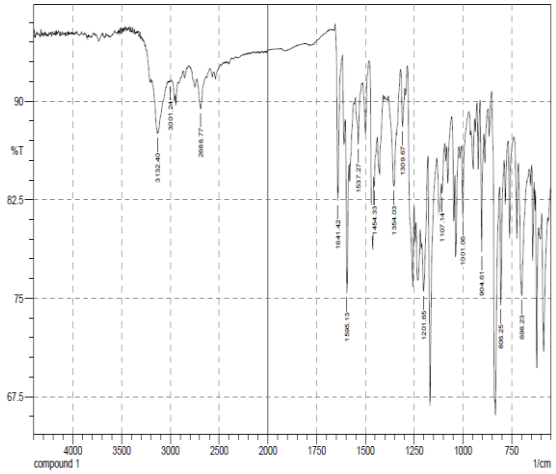
3. Results and discussion

3.1. Preformulation study to evaluate drug- excipient compatibility

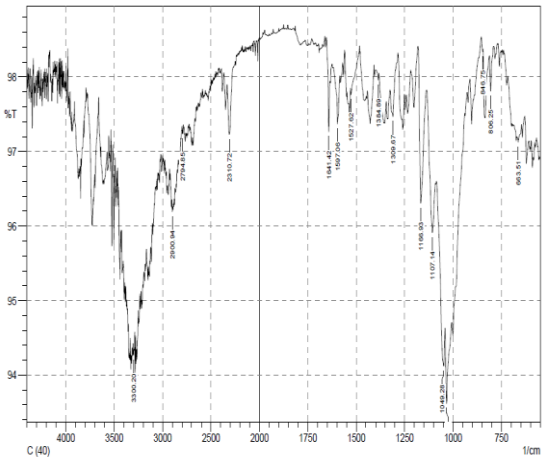
3.1.1 Analysis by FT-IR

C-O-C group represented by 1595.13 and C=O group represented by 1641.42 waves no. present in drug are also seen in mixtures of drug + excipients exposed to 40°C for two weeks indicating that there is no interaction between drug and excipients. (Fig. 1)

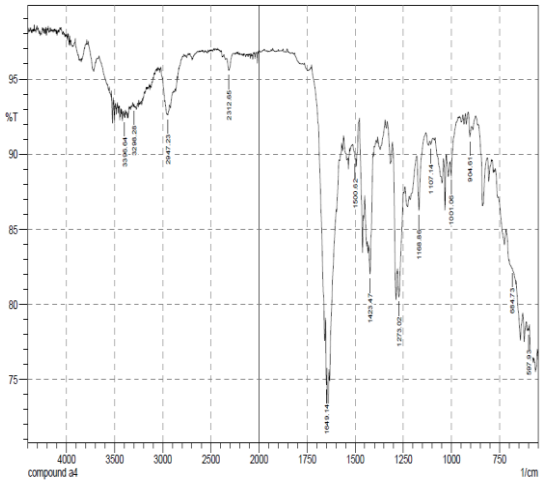
a) RLX HCl
C-O-C stretching-1595.13
C=O stretching-1641.42



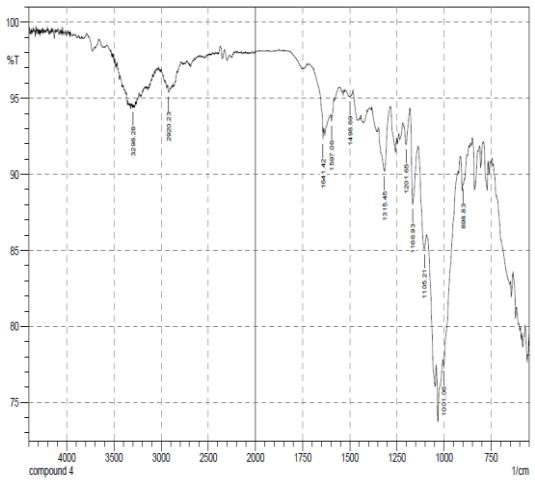
b) Drug + Micro crystalline cellulose
C-O-C stretching-1595.13
C=O stretching-1641.42



c) Drug + Ac-di-sol®
C-O-C stretching-1597.06
C=O stretching-1641.42



d) Drug+ PVP K_{30}
C-O-C stretching-1500.62
C=O stretching-1649.14



e) Drug + Magnesium stearate
C-O-C stretching-1595.13
C=O stretching-1641.42

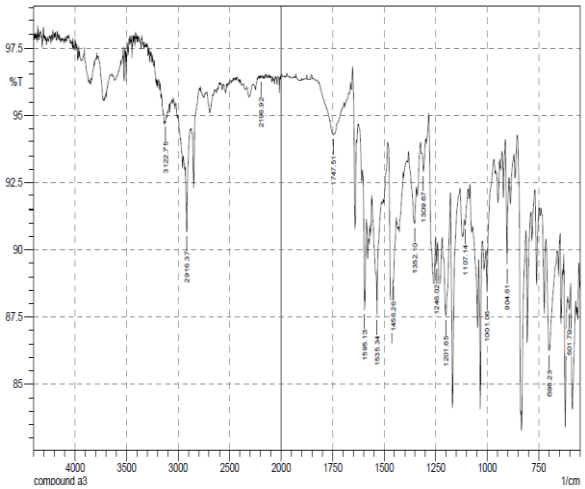


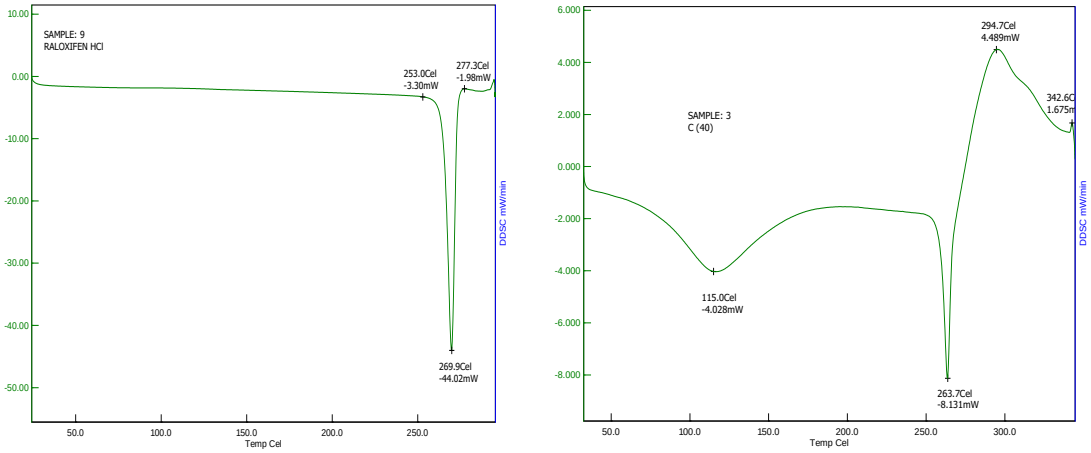
Figure 1: FT-IR scans of a)RLX HCl, b)RLX HCl + Micro crystalline cellulose, c) RLX HCl + Ac-di-sol®, d) RLX HCl + PVP K_{30}, e)RLX HCl + Magnesium stearate

3.1.2 Analysis by DSC

In figure 2, scan a) shows DSC thermograph of pure drug (RLX HCl) singly and other scans [b), c), d) and e)]show DSC thermographs of drug in combination with different excipients. Scans reveal that the melting point of RLX HCl is 269.9°C which is not altered to a great extent by the excipients used in the study. It may be concluded that all studied excipients are compatible with RLX HCl and can be used in formulation development.

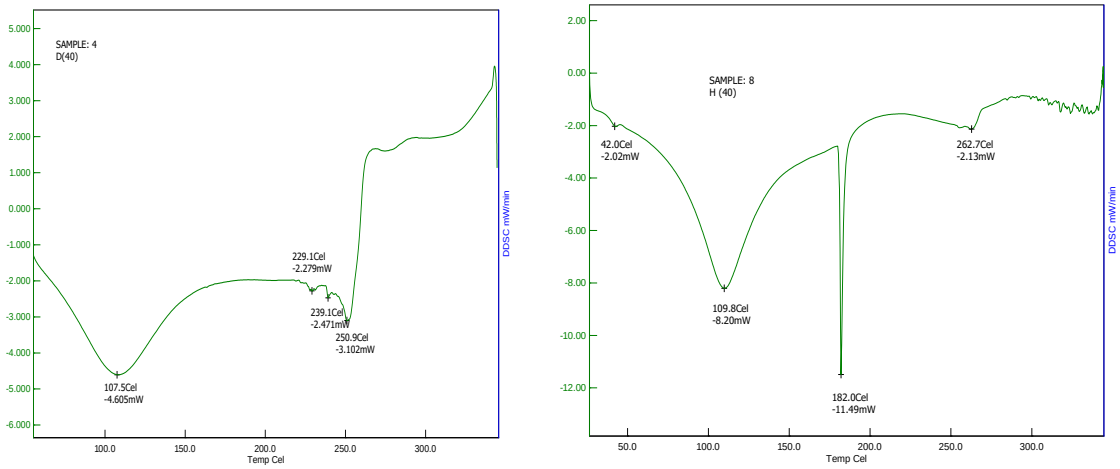
a) RLX HClb) Drug + Microcrystalline cellulose

Melting Point: 269.9°C Melting Point: 263.7°C



c) Drug + Ac-di-sol® **d) Drug + PVP K_{30}**

Melting Point: 250.9°C Melting Point: 262.7°C



e) Drug + Magnesium Stearate

Melting Point: 259.2°C

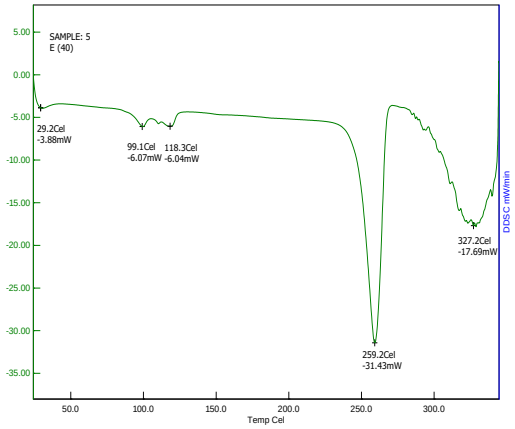


Figure 2:DSC scans of a)RLX HCl, b)RLX HCl + Micro crystalline cellulose, c) RLX HCl + Ac-di-sol®, d) RLX HCl + PVP K_{30}, e)RLX HCl + Magnesium stearate

3.1.3 Analysis by UV

UV scans of RLX HCl + Polysorbate 80 (1:1), RLX HCl + MCC (1:5), RLX HCl + Ac-di-sol® (1:5) & RLX HCl + PVP K_{30} (1:5) and RLX HCl + Magnesium stearate (10:1), initially and at room temperature, 40°C and UV/24 hours were found to elicit no change in wavelength maxima indicating the drug to be compatible with these excipients.

3.2 Analytical method development

3.2.1 For assay

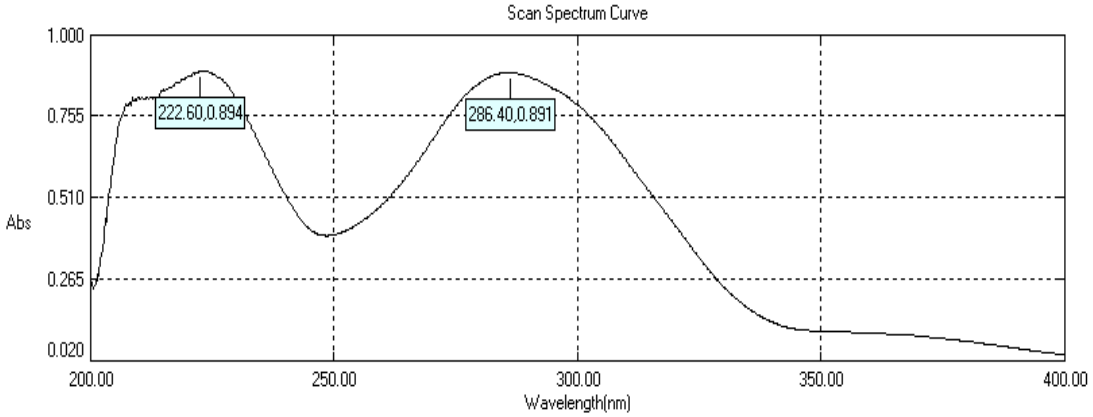


Figure 3: Spectra of Raloxifene Hydrochloride in methanol

RLX HCl shows absorption maxima at 286 nm in methanol (Fig. 3) and corresponds to value mentioned in literature [18].

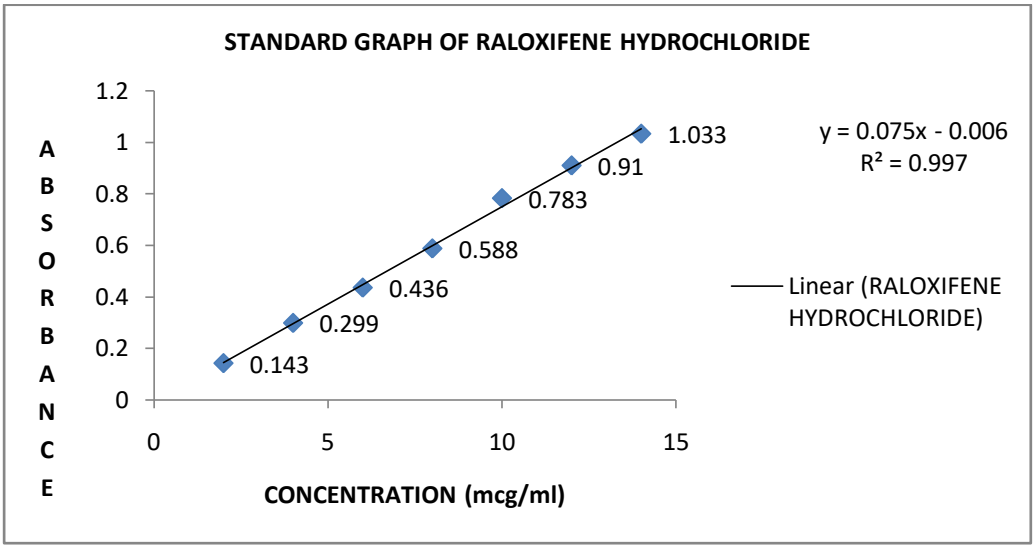


Figure 4: Calibration Curve of Raloxifene Hydrochloride in methanol

Using the values obtained, graph was plotted (Fig. 4) and standard equation was derived. The coefficient of correlation was found to be 0.9972 indicating that the drug follows Beer Lambert's law in the concentration range studied. The optical characteristics of the drug are recorded in Table 3.

Lambert's law in the concentration range studied. The optical characteristics of the drug are recorded in Table 3.

Table 3: Optical characteristics of Raloxifene hydrochloridein methanol

Parameters	Observed values
λmax (nm)	286 nm
Beer's range (µg/ml)	2-14 µg/ml
Correlation Coefficient (r^2)	0.997
Regression equation	Y=0.0757x+0.0067
Intercept (a)	0.0067
Slope (b)	0.0757
LOD	0.580 µg/ml
LOQ	1.763 µg/ml

3.2.2 For dissolution

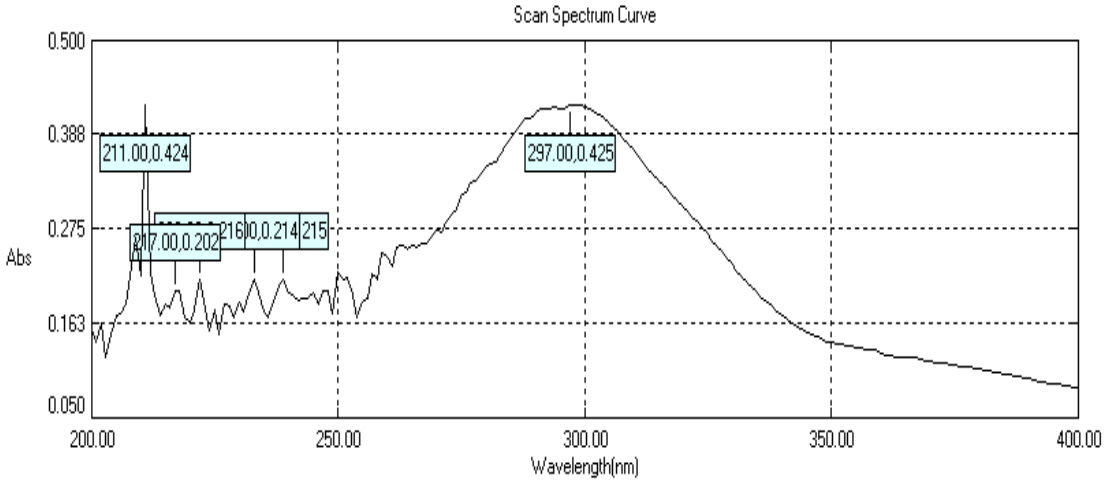


Figure 5: Spectra of Raloxifene Hydrochloride in 1% Polysorbate 80

RLX HCl shows absorption maxima at 297 nm in 1% Polysorbate 80 (Fig. 5) and corresponds to value mentioned in literature [11].

Using the values obtained, graph was plotted (Fig. 6) and standard equation was derived. The coefficient of correlation was found to be 0.9972 indicating that the drug follows Beer Lambert's law in the concentration range studied. The optical characteristics of the drug are recorded in Table 4.

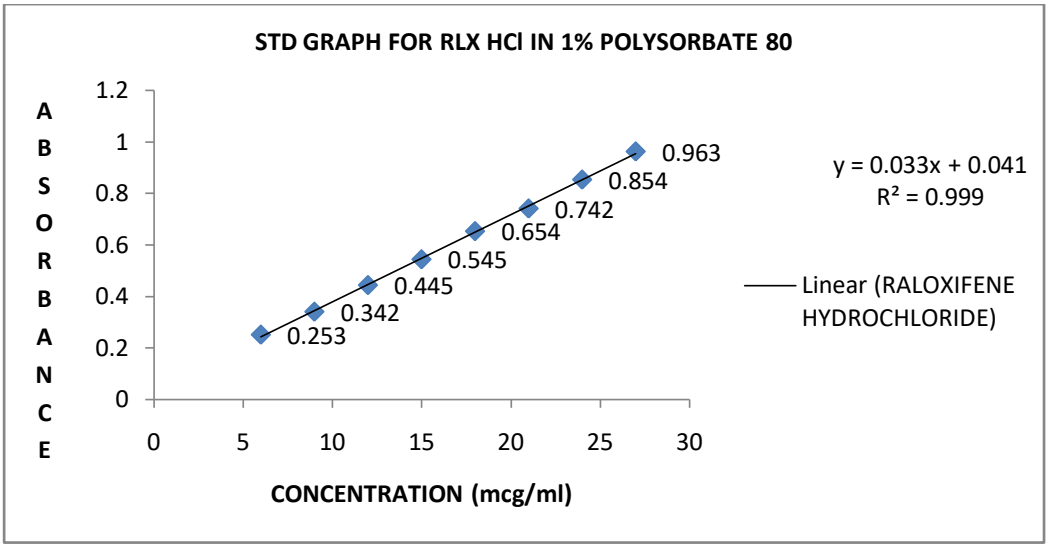


Figure 6: Calibration Curve of Raloxifene Hydrochloride in 1% Polysorbate 80

Table 4: Optical characteristics of Raloxifene hydrochloride in 1% Polysorbate 80

Parameters	Observed values
λmax (nm)	297 nm
Beer's range (µg/ml)	6-27 µg/ml
Correlation Coefficient (r^2)	0.999
Regression equation	Y=0.0338x+0.0412
Intercept (a)	0.0412
Slope (b)	0.0338
LOD	0.099
LOQ	0.3

3.3. Assay for factorial batches

Table 5: Results for assay of factorial batches

Batch	Percent drug content
RLX HCl 20	95.08
RLX HCl 21	98.68
RLX HCl 22	108.36
RLX HCl 23	107.06
RLX HCl 24	98.68
RLX HCl 25	99.97
RLX HCl 26	97.68
RLX HCl 27	106.16
RLX HCl 28	105.86

The drug content in all the batches were found to be within the prescribed limits of 90-110 % (Table 5) [4].

3.4 Dissolution profile for factorial batches

Based on the results obtained for the factorial batches (Table 6) it was observed that these batches exhibited a better *in vitro* release profile as compared to the marketed preparation wherein batch no. RLX HCl 27 showed the highest amount of drug release at all the time intervals (Fig. 7). Therefore batch no. RLX HCl 27 was considered to be the best optimized formula exhibiting best dissolution profile of the drug.

Table 6: Dissolution Profile for Trials Carried Out as Per Factorial Design

Time (in mins)	RLX HCl 20	RLX HCl 21	RLX HCl 22	RLX HCl 23	RLX HCl 24	RLX HCl 25	RLX HCl 26	RLX HCl 27	RLX HCl 28	Marketed Batch
10	29.28	31.36	30.09	36.17	32.74	31.94	35.78	39.08	26.11	28.9
20	46.92	54.07	47.23	50.51	54.43	53.88	51.5	53.67	47.06	44.73
30	62.8	61.56	63.51	61.81	67.6	66.05	70.4	68.33	60.19	57.55
45	67.25	75.02	71.59	67.39	76.46	71.21	75.13	76.15	73.65	60.91
60	70.71	81.62	74.78	72.06	79.37	76.49	78.39	79.46	76.75	65.59
75	72.34	80.57	77.49	73.2	81.41	78.45	80.16	81.94	77.42	72.53
90	73.78	79.26	77.76	74.79	82.55	81.37	82.15	83.93	80.09	69.44
120	76.63	77.1	75.85	75.85	85.34	82.91	84.54	85.24	81.97	69.21

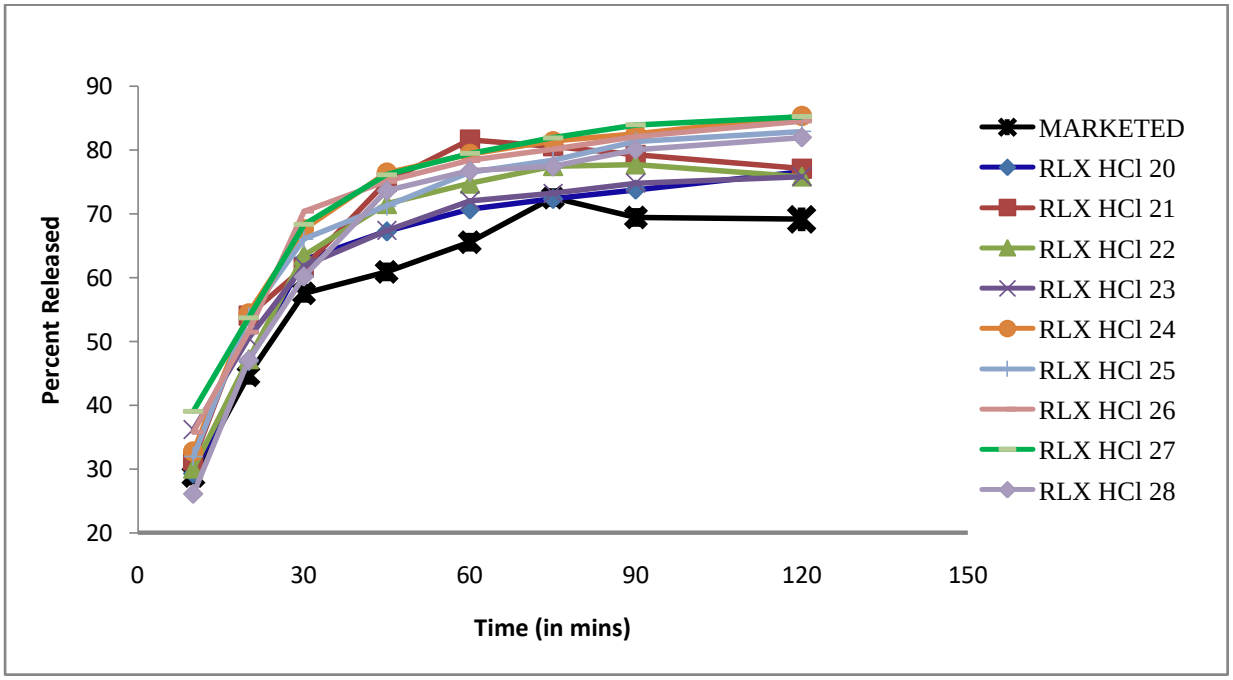


Figure 7: Dissolution Profile for Trials Carried Out as Per Factorial Design

3.5 Evaluation of data

3.5.1 Difference factor (f_1) and Similarity factor (f_2)

Of the nine batches, three batches had a far superior release profile and were compared with each other by determining the difference factor (f_1) [19] and the similarity factor (f_2)[19] to select the best formulation for stability studies

(Table 7). According to the results obtained for the difference and the similarity factor it can be concluded that there exists a similarity between these three batches as the value obtained for the similarity factor value lies between 50-100 i.e., these three batches do not vary significantly with respect to dissolution profile. However there exists a minor statistically non-significant difference between these three batches as the value obtained for the difference factor lies between 0-15. Batch nos. RLX HCl 24 and RLX HCL 27 contained minimum concentrations of Ac-di-sol® and DMSO as compared to batch no. RLX HCl 28. Hence batch no. RLX HCl 28 was not selected for scale up and stability studies. Batch no. RLX HCl 27 exhibited better drug release within initial 10 minutes as compared to batch no. RLX HCl 24. Hence the formulation was selected for scale up and stability studies.

Table 7: Results for the Similarity factor and the Difference Factor for Batch Nos. RLX HCl 24, RLX HCl 26 and RLX HCl 27

Batch no.	Difference factor (f1)	Similarity factor (f2)
RLXHCl 24 and RLX HCl 26	0.3 %	82.85 %
RLX HCl 24 and RLX HCl 27	1.391 %	79.75 %
RLX HCl 26 and RLX HCl 27	1.717 %	83.4 %

3.5.2Fitting of data to kinetic models

Based on r^2 values, the model that best fits drug release data was korsmeyer-peppas for batch nos. RLX HCL 21 to RLX HCl 28 (Table 8). In case of batch no. RLX HCl 20, the data fitted 1st order model.

Table 8: Fitting of data to kinetic models

Formulation Code	Zero order (r^2)	1st order (r^2)	Higuchi (r^2)	Korsmeyer-Peppas (r^2)
RLX HCl 20	0.683	0.892	0.815	0.871
RLX HCl 21	0.583	0.529	0.734	0.833
RLX HCl 22	0.629	0.564	0.775	0.859
RLX HCl 23	0.716	0.644	0.846	0.910
RLX HCl 24	0.685	0.592	0.820	0.873
RLX HCl 25	0.709	0.605	0.837	0.878
RLX HCl 26	0.687	0.613	0.818	0.884
RLX HCl 27	0.726	0.654	0.853	0.916
RLX HCl 28	0.701	0.598	0.834	0.880

3.5.3 Response plots to determine influence of excipients on drug release

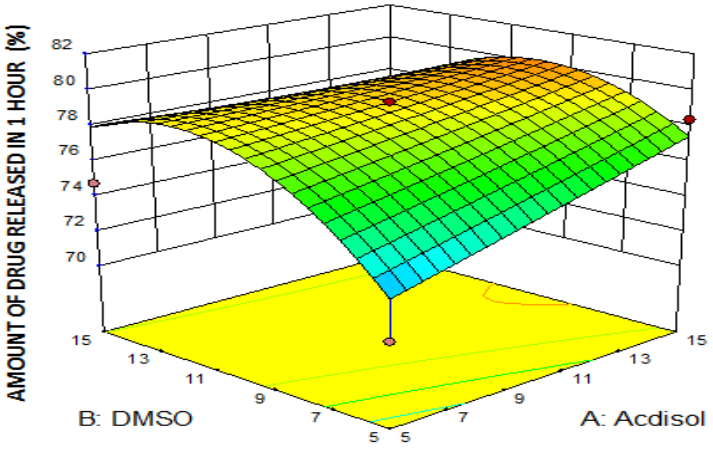


Figure 8: 3D response plot for Amount of Drug Released in 1 hour (%)

As the concentration of Ac-di-sol® and DMSO increased from 5 to 15 mg, the amount of drug released in 1 hour increased (Fig. 8). Thus increase in concentration of both lead to improved dissolution characteristics.

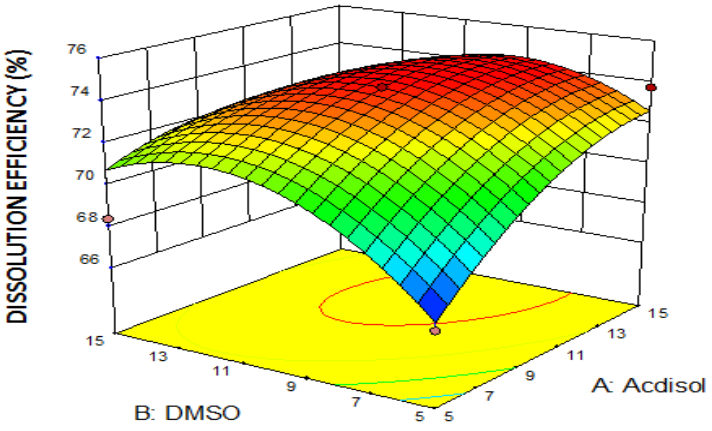


Figure 9: 3D response plot for Dissolution Efficiency (D.E %)

Dissolution Efficiency (%) was found to be highest at higher concentrations of Ac-di-sol® and DMSO i.e. 10 mg/tablet and 15mg/tablet respectively (Fig. 9). Thus, an optimum concentration of both provides highest dissolution profile.

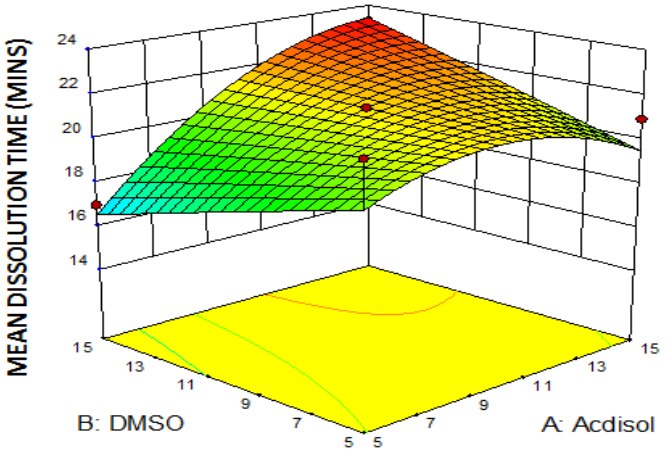


Figure 10: 3D response plot of Mean Dissolution Time

As the concentration of Ac-di-sol® and DMSO increased from 5 mg to 15 mg/tablet, an increase in the mean dissolution time was observed (Fig. 10).

3.6 Results of stability studies

The stability batches RLX HCl 29 and 30 were subjected to accelerated studies as per ICH guidelines. Three month data revealed that all physicochemical parameters remained within acceptable limits.

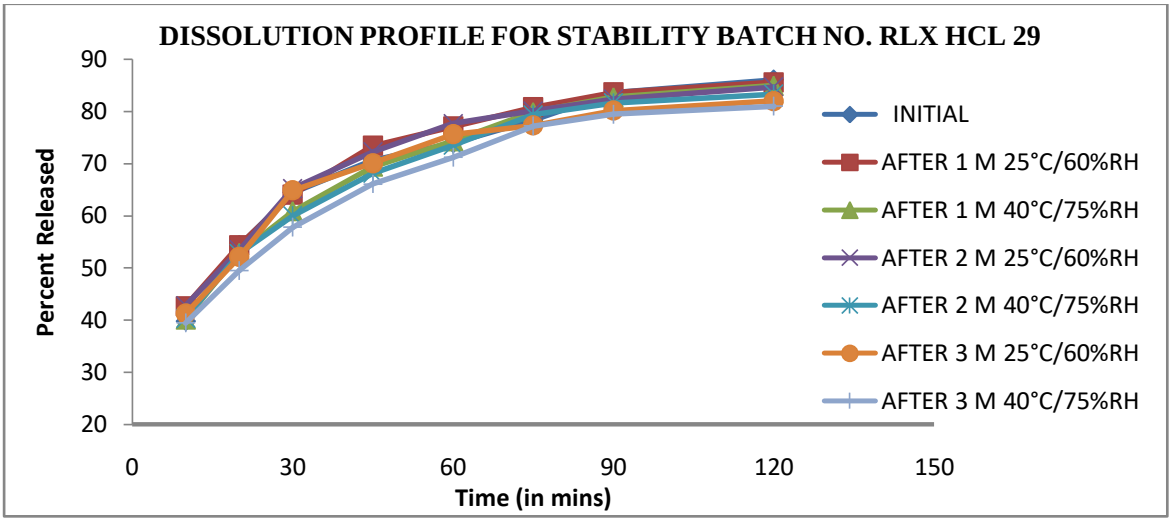


Figure 11: Dissolution profile for stability batch no. RLX HCl 29

Initial dissolution profiles and 3 months 40°C/75%RH dissolution profiles of RLX HCl 29 and RLX HCl 30 were compared by finding the difference factor (f_1) and the similarity factor (f_2). Results indicated that both batches behaved similarly. Hence the formula is reproducible.

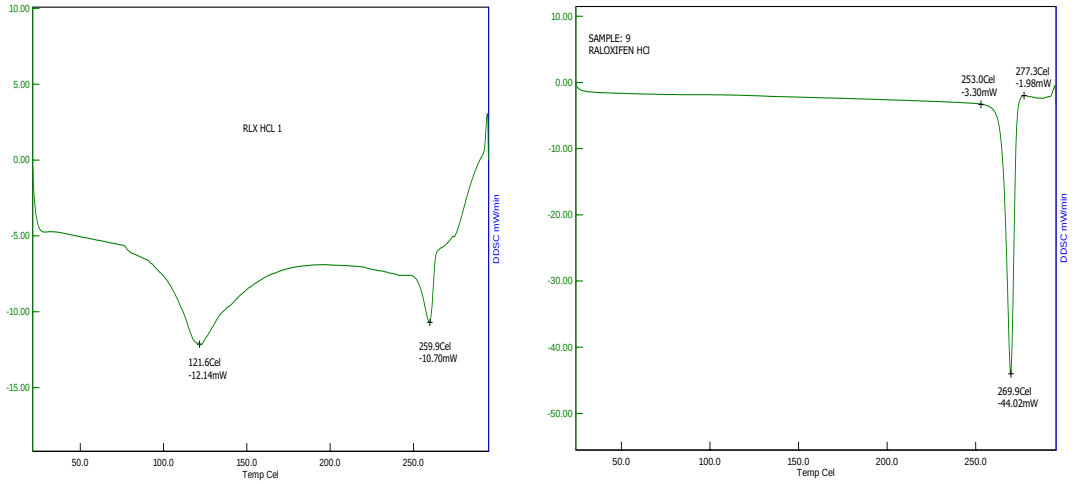
Table 9: Results for the Similarity factor and the Difference Factor for batch nos. RLX HCl 29 and RLX HCl 30

Batch No.	Difference factor (f1)		Similarity factor (f2)	
	Initial	3 months 40°C/75%RH	Initial	3 months 40°C/75%RH
RLX HCl 29	1.149 %	0.184 %	85.8 %	86.95 %
RLX HCl 30	1.163 %	0.325 %	85.8 %	86.95 %

3.6.1. Analysis of stability batch no. RLX HCl 29 by DSC

DSC thermograms obtained for stability batch no. RLX HCl 29 showed no significant change in the endothermic peak initially and at the end of 3 months. Hence it can be concluded that the batch was found to be stable (Fig. 12).

a) Initial **b) After 3 months at 25°C/60%RH**



Melting Point: 269.9°C Melting Point: 259.9°C

Figure 12: DSC scan of a) RLX HCl 29 at 0 months, b) RLX HCl 29 after 3 months storage at 25°C/60%RH

3.6.2. Analysis of stability batch no. RLX HCl 29 by FT-IR

C-O-C group represented by 159.25 and C=O group represented by 1639.55 waves no. present in the initial sample are also seen in the samples exposed to 25°C/60%RH and 40°C/75%RH for three months indicating that the batch to be stable (Fig. 13).

a) Initial
C-O-C stretching-1593.25
C=O stretching-1639.55

b) After 3 months at 25°C/60%RH
C-O-C stretching-1593.25
C=O stretching-1639.55

c) After 3 months at 40°C/75%RH
C-O-C stretching-1593.25
C=O stretching-1639.55

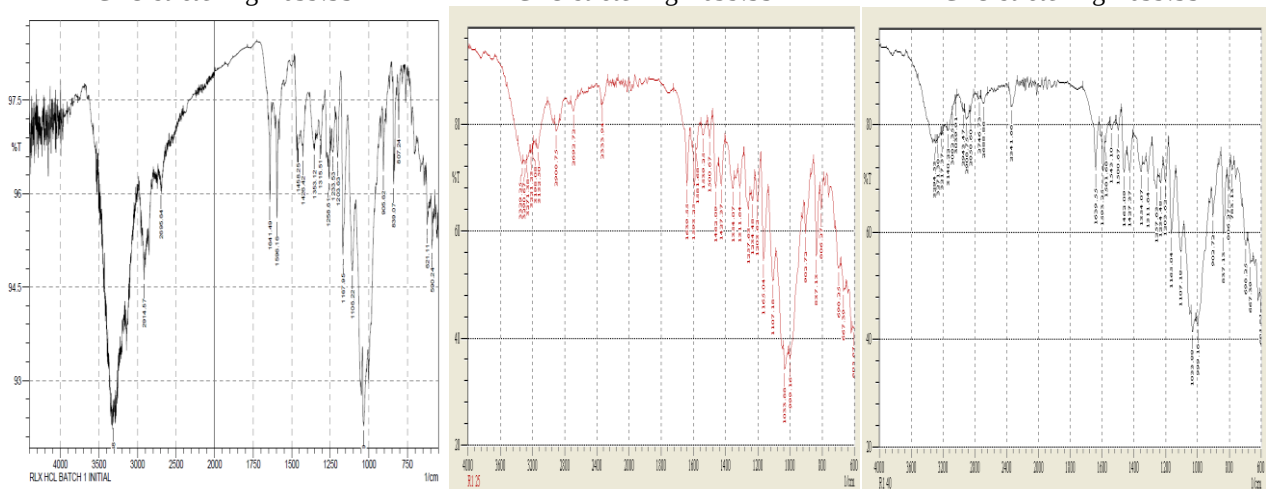


Figure 13: FT-IR scan of a) RLX HCl 29 at 0 months, b) RLX HCl 29 after 3 months storage at 25°C/60%RH, c)RLX HCl 29 after 3 months storage at 40°C/75%RH

3.6.3. Analysis of stability batch no. RLX HCl 29 by XRD

XRD scans for stability batch no. RLX HCL 29 showed that the sample was crystalline in nature, as demonstrated by numerous distinct peaks observed at 2θ initially. The prominent peaks from initial sample at 2θ of were clearly seen at the same position in the samples exposed to 25℃/60%RH and 40°C/75%RH for 3 months. In addition, there is slight increase in crystallinity as it is evident by more number of diffractions at 40°C/75% RH (Fig. 14). This may have implications on long term dissolution profile of the formulation.

a) Initial **b) After 3 months at 25°C/60%RH** **c) After 3 months at 40°C/75%RH**

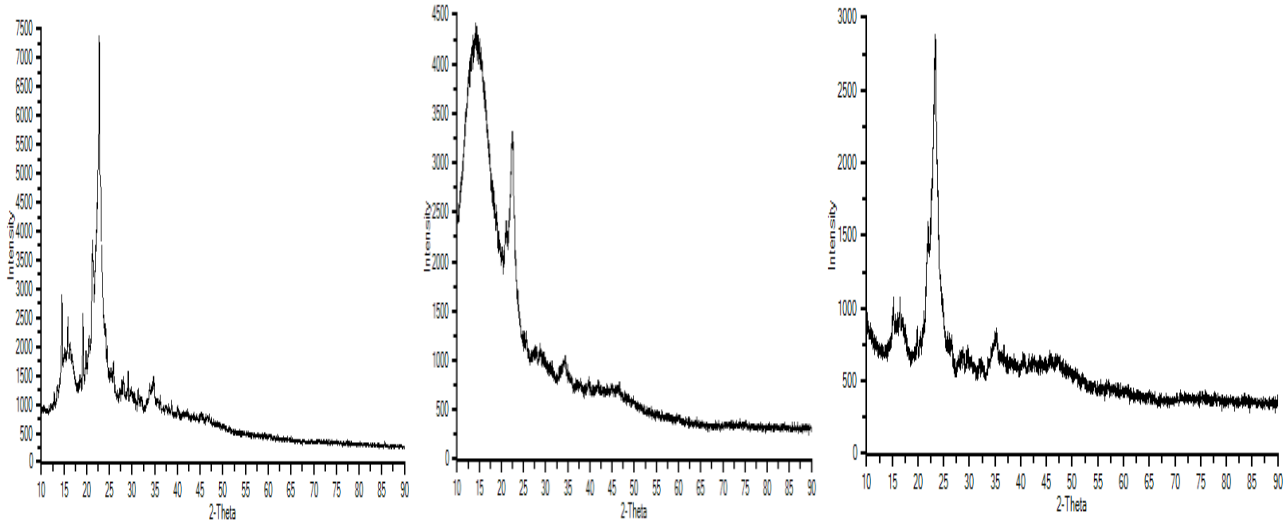


Figure 14: XRD scan of a) RLX HCl 29 at 0 months, b) RLX HCl 29 after 3 month's storage at 25°C/60%RH, c) RLX HCl 29 after 3 months storage at 40°C/75%RH

4. Conclusion

Analytical method development was done for both API and the formulation. Drug-excipient compatibility results exposed no incompatibility between drugs and various excipients. Following the preliminary trials for formulation of RLX HCl tablets, factorial batches were designed. The best optimized formula was finalized, scaled up into two batches and were put up on stability. Stability studies were carried out as per protocol. Results indicated that the stability batches complied with official as well as in house limits indicating that the drug is stable in the dosage form. The release profile indicates that around 85% of the drug is released at the end of 2 hours. Thus the developed formulation is a safe effective delivery system with increased aqueous solubility of RLX HCl thus improving in the dissolution characteristics and increasing the possibility of improved bioavailability.

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