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FORMULATION AND EVALUATION OF RALOXIFENE HYDROCHLORIDE TABLETS TO ENHANCE THE SOLUBILITY

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Abstract:

Poor aqueous solubility and dissolution limit the oral bioavailability of Biopharmaceutics Classification System (BCS) class II drugs. In this study, we aimed to improve the aqueous solubility and oral bioavailability of raloxifene hydrochloride (RLX), a BCS class II drug, using a Solid Dispersions. Solid dispersions were created utilizing the solvent evaporation method at a 1:1 ratio with various carriers, and they demonstrated improved solubility compared to API. Carriers with improved dissolving rates included polyplasdone, polyaxomer, and ß-cyclodextrin. Tablets were prepared by incorporating excipients and evaluated for various pre compression and post compression parameters. Also assay and in-vitro dissolution studies were performed. When the tablets were evaluated, they fell inside the predetermined range. It is determined that inclusion complex (ß-cyclodextrin), hydrophilic polymer (PVA), and surfactant (polaxomer) are used to increase the solubility of raloxifene hydrochloride.

Keywords: *Raloxifene Hydrochloride, Cyclodextrin, Polaxomer 407, Poly vinyl pyrrolidone, Solid Dispersions.*

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INTRODUCTION:

Osteoporosis poses a significant health problem worldwide; a 50-year-old postmenopausal woman has a 40–50% risk of having osteoporotic fracture in her lifetime [1]. Lifestyle changes, weight-bearing exercise, calcium and vitamin D supplementation, and pharmacologic therapy are the general measures for the prevention of postmenopausal osteoporosis [2]. Anti-resorptives are the major pharmacologic agents for osteoporosis which inhibit the development and/or action of osteoclasts. They include bisphosphonates [selective estrogen receptor modulator (SERM)], hormone replacement therapy, and calcitonin [3].

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 [4]. 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 [5]. 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 [6].

Raloxifene hydrochloride (R-HCl) is an FDA-approved SERM for the prevention and treatment of osteoporosis. It is a BCS class II drug, with slight aqueous solubility. Absolute bioavailability of R-HCl is 2% due to its poor water solubility and extensive first-pass metabolism. Also, it exhibits a high inter-subject variability [7,8]. Various strategies have been reported to improve the solubility and bioavailability of R-HCl, such Solid Dispersions [9], inclusion complexes, and co-grinding. There is a need to improve the aqueous solubility or dissolution characteristics of RLX HCl to consequently increase its therapeutic effect using Solid Dispersion technique [10]. 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.

MATERIALS AND METHODS:

Raloxifene Hydrochloride was obtained from Dr. Reddy's Laboratories. Cyclodextrin was obtained from A.R. Life Sciences. Crospovidone XL, Crospovidone 10, Polaxomer 407, Poly vinyl pyrrolidone (PVP) K17, K30 was obtained from Sigma Aldrich.

Methods

Preformulation Studies

Solubility Studies

Weighed and placed 500 mg of Raloxifene hydrochloride (RLX) into various conical flasks. Individual conical flasks were filled with 50 cc of various dissolution media and sealed properly [12]. They were sieved using a 0.45 PTFE filter after all the flasks had been sonicated for one hour. The clear solution is diluted with suitable dissolving media, and absorbance values at 280 nm were recorded.

Compatibility studies

FTIR, drug content was used to assess the interaction studies.

Formation of Solid Dispersions by Solvent Evaporation Technique

5 ml of methanol were used to dissolve 2 gramme of RLX in a china dish. 2 grammes of carrier were added to the methanol solution, and the combination was allowed to evaporate for 24 hours at room temperature [13]. The mixture was then gathered, put in amber-colored glass containers, hermetically sealed, and kept at room temperature.

Table 1: Preparation of Solid Dispersions of RLX

S.No.	Composition	Ratio
1.	RLX + PEG-6000	1 : 1
2.	RLX + PVA 4-88	
3.	RLX + ß-cyclodextrin	
4.	RLX + PVP K17	
5.	RLX + PVP K30	
6.	RLX + Polyplasone XL10	
7.	RLX + Polaxomer 407	
8.	RLX + Polaxomer 407	
9.	RLX + HPC L.S	
10.	RLX + HPMC K4MCR	
11.	RLX + Pharmatose 200M	
12.	RLX + Supertab 11SD	
13.	RLX + Supertab 21AN	
14.	RLX + Mannitol	

Evaluation of Solid Dispersions

Angle of repose:

Using the fixed funnel approach, the angle of repose was calculated. A funnel was placed on top of horizontally-arranged graph paper and fixed with the tip at a predetermined height (h). The base radius (r) of the conical pile was calculated [14].

Angle of repose(θ):

$\tan \theta = h/r$ Where; θ = Angle of repose

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

Compressibility index

The bulk capacity and tapped size of a powder are both measured to ascertain it.

Compressibility index = 100 × tapped density / bulk density

Particle Size Determination

Optical microscopy was used to examine the generated solid dispersions' average particle sizes [15].

Saturated Solubility studies

Additional 500 mg RLX dispersion samples were balanced. Each volumetric flask received 50 ml of purified water, which was then appropriately sealed [16]. The sonicator was filled with all the flasks, and it was run for one hour. The samples were then sieved using a 0.45 PTFE filter once the flasks had been removed. Filtered water was used as a blank to measure the absorbance values at 280 nm after the clear solution was appropriately diluted with diluents.

Preparation of Tablets

The direct compression procedure was used to create the tablets. While adjusting the diluents' concentration in accordance with the assay, the ratio of medication to disintegrant was kept constant.

Each component was weighed, put through a sieve #40, and then mixed for 15 minutes. Magnesium stearate was then added, and the powder blend was mixed for 5 minutes [17]. Using a 16-station micro press from Cadmach, blend was compacted into tablets.

Table 2: Preparation of RLX Solid Dispersion tablets

Component (mg/tablet)	Formulations						
	RLX_1	**RLX_2**	**RLX_3**	**RLX_4**	**RLX_5**	**RLX_6**	**RLX_7**
Solid dispersions	119	120	121	122	123	124	125
Supertab DCL 21 AN	86	85	84	83	82	81	80
Supertab DCL 11 SD	20	20	20	20	20	20	20
Polyplasdone XL	15	15	15	15	15	15	15
Magnesium stearate	2	2	2	2	2	2	2
Opadry white	8	8	8	8	8	8	8
weight of tablet (mg)	250	250	250	250	250	250	250

Evaluation of tablets

Following the calculation of the average weight, each tablet was balanced separately and the weights were recorded. The masses of each tablet were then measured and associated to the mean weight to see if there was any variation [18]. This test emphasises the requirement that the weights of all the pills in a given batch should be consistent.

Hardness

Using an Erweka hardness tester, the tablets' hardness was determined [19]. The tablet being tested is placed on the hardness tester's surface, and the display readout showing the amount of pressure needed to break the tablet in kP is noted.

Friability

Using a friabilator, a test for friability was conducted. Each batch of 6.5 mg tablets was weighed, added to a chamber, and permitted to rotate for 100 revolutions. These tablets drop six inches during each revolution, subjecting them to shock. Tablets were weighed once more after 100 revolutions, and the weight decrease suggested friability. Weight loss should not be accepted if it exceeds 1%.

Disintegration Time

Six tablets were put in 6 tubes of a basket, and 800 ml of water was consumed while keeping the temperature at 37 ± 2 °C. It took some time for all of the tablets to totally disintegrate [20].

Estimation of Drug Content

The weight equivalent of 180 mg of RLX from 20 crushed tablets was put into a 250 ml volumetric flask, diluents were placed, and the mixture was maintained in a sonicator for roughly 30 minutes with periodic shaking. Using centrifuge tubes with caps, a part of the aforementioned solution was centrifuged at 2500 rpm for 10 minutes. A 50 ml volumetric flask was filled with 5 ml of the aforementioned supernatant solution, which was then diluted with diluents and estimated by UV [21].

Dissolution Studies

The experiment was conducted with the paddles rotating at 50 rpm and the temperature held steady at 37 ºC ±1 ºC. 5 ml samples were taken at 10, 20, 30, and 45 min according to the FDA dissolution data source [22]. To keep the volume constant throughout the experiment, an equivalent capacity of dissolving medium was changed. Withdrawn samples were diluted, and the amount of medication dissolved was calculated using a UV spectrophotometer at 285 nm.

RESULTS AND DISCUSSION:

Solubility studies remained completed in varied range of pH, it is detected that RLX displays very poor solubility.

Table 3: Solubility Studies

Dissolution Media	Quantity of Drug Soluble (mg/ml)
Water	0.39
0.1 N HCl	0.19
0.1%Tween 20	0.62
pH 3.0 Glycine	0.14
pH 4.5 acetate buffer	0.21
pH 6.8 phosphate buffer	0.20
pH 7.2 phosphate medium	0.29

FTIR

The FTIR of RLX revealed its distinctive peaks at 3530, which are caused by the phenol -OH group, 1641, 1595, and 806, which are caused by the thiophene C-H, and 1158, which are caused by the C=O stretching. The absorption spectrum of RLX and its carriers did not significantly change, according to their FTIR spectra. This suggests that there was no incompatibility among the medicine and the carriers.

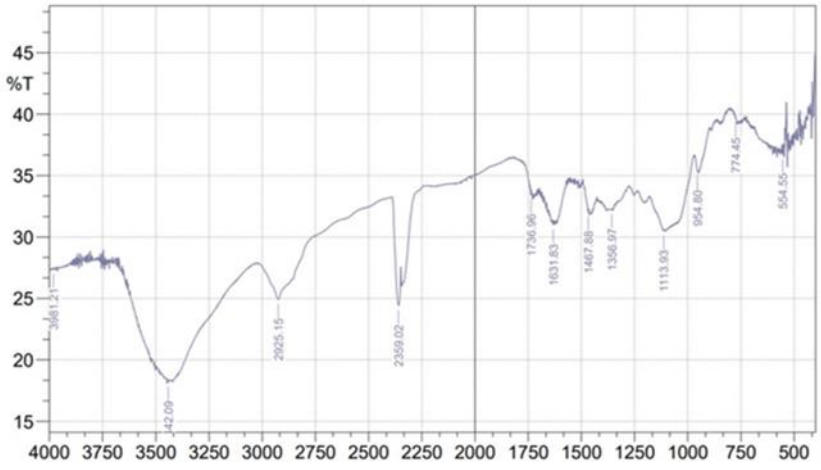

Figure1: FTIR spectrum of Pure Drug (Ranolazine)

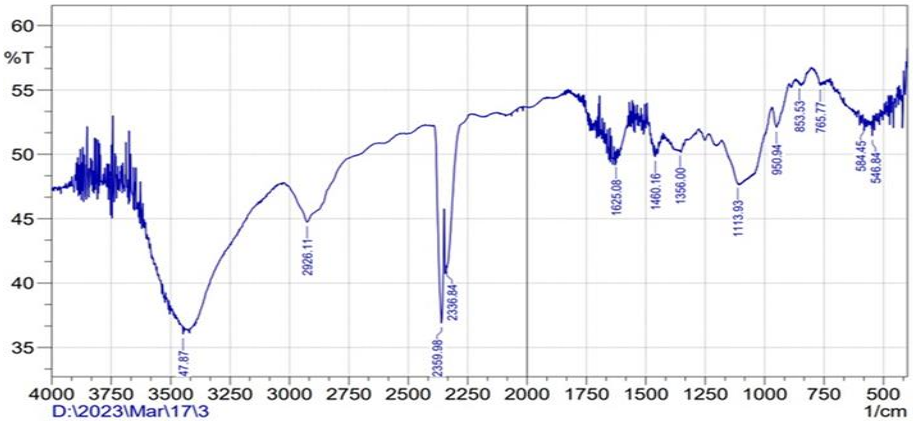

Figure 2: FTIR spectrum of optimized formulation

Studies revealed that polaxomer and ß-cyclodextrin have the highest solubilities; out of all the utilised carriers, seven were found to be suitable.

Due to its hydrophilic character, ß-cyclodextrin undergoes complexation with hydrophobic medications. Being a surfactant, polyaxomer may have quickly hydrated into the polymer solution when the dispersion came into contact with water, solubilizing the near drug elements and freeing the drug into the medium.

Table 4: Saturation solubility studies

S.NO	Formulation	Quantity of medication solvable (mg/ml)
1	RLX $_1$	0.59
2	RLX $_2$	0.88
3	RLX $_3$	2.20
4	RLX $_4$	2.0
5	RLX $_5$	1.52
6	RLX$_6$	1.22
7	RLX $_7$	1.10
8	RLX $_8$	0.39
9	RLX$_9$	0.50
10	RLX $_{10}$	0.52
11	RLX$_{11}$	0.52
12	RLX$_{12}$	0.50
13	RLX$_{13}$	0.48

Flow properties:
All of the dispersions were discovered to have good flow characteristics and a fair compressibility index. The range of the mean particle size was between 72.5 and 102.4 microns. All dispersions had drug contents that ranged from 93% to 105%. Therefore, any solid dispersions can be compressed into tablets with a rapid release.

Table 5: Pre-compression parameters

S.NO	Solid Dispersions	Angle of Repose	Carr's Index (%)	Particle Size (µm)	Medication Content(%)
1	RLX 1	19	13	80±3.9	92±0.18
2	RLX 2	28	19	99.8±6.8	96±0.32
3	RLX3	29	17	86±7.1	96±0.28
4	RLX4	22	15	69±5.9	98±0.19
5	RLX5	21	14	74±3.1	92±0.41
6	RLX6	23	15	96±5.9	98±0.30
7	RLX7	25	15	91±3.0	103±0.40

All standards are stated as mean ± SD, n=3

Utilizing the USP apparatus II (paddle), dissolution experiments were carried out on all solid dispersions. The order of ß-cyclodextrin, PVA 4-88, Polaxomer 407, PVP K 17, Polyplasone XL 10, PVP K 30, and PEG 6000 for drug release from solid dispersions.

Table 6: Medication Release Outline of RLX Solid Dispersions

Time (Min)	% Cumulative Drug Release						
	RLX_1	RLX_2	RLX_3	RLX_4	RLX_5	RLX_6	RLX_7
10	7.9±3.8	19±1.6	4.8±1.9	8.8±3.0	5.8±1.8	5.9±1.8	19±3.8
20	21±12.0	77±1.1	15±2.1	24±1.5	19±1.8	27±1.6	51±3.8
30	23±2.2	88±1.2	28±2.2	39±1.8	24±2.2	39±1.8.	53±3.6
45	30±1.8	94±3.8	69±1.8	42±1.2	31±1.4	52±1.8	61±3.8
Infinity	39.8±1.5	95±2.1	99.8±2.5	64±1.2	35±1.9	54±1.4	77±4.5

All values are stated as mean ± SD, n=3

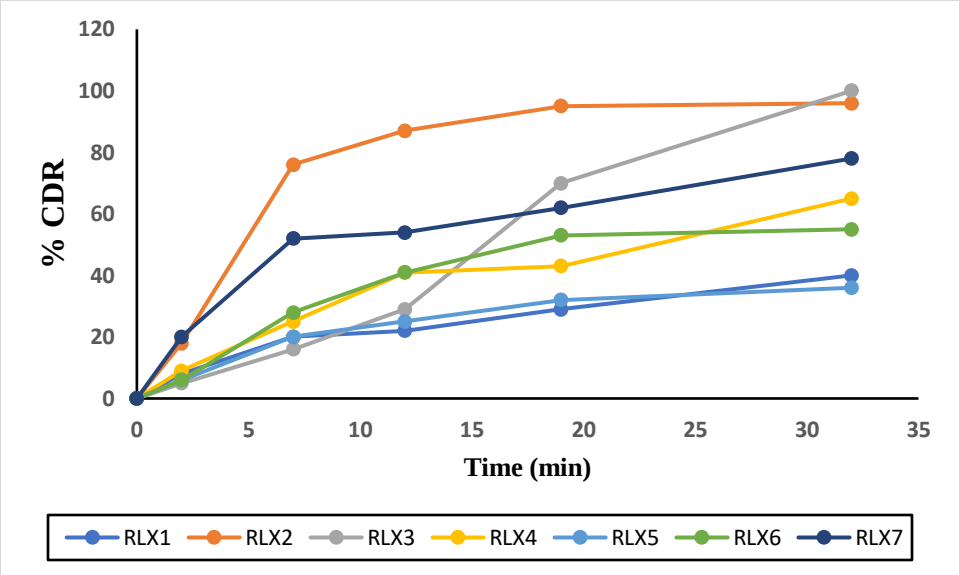

Figure 3: Dissolution Outlines of RLX Tablet Formulations

Tablets made from solid dispersions were tested for assay, hardness, friability, and disintegration time. The stipulated limitations were found to be met by all of the batches.

Table 7: Post-Compression parameters

Tablet	Weight uniformity (mg/tablet)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	D.T (min)	Drug content (%)
RLX_1	242±0.54	4.1±0.18	6.0±0.52	0.19	5-6	100.8
RLX_2	241±0.88	4.3±0.22	5.0±0.42	0.24	2-3	100.1
RLX_3	242±0.56	4.3±0.22	9.0±0.48	0.44	2-3	99.2
RLX_4	241±0.48	4.7±0.08	6.0±0.90	0.20	3-4	101.4
RLX_5	239±0.66	3.2±0.24	5.0±0.94	0.19	8-9	100.8
RLX_6	241±0.56	4.3±0.30	10.0±0.12	0.32	1-2	101.8
RLX_7	239±0.88	4.6±0.35	3.1±0.36	0.20	9-10	102.2

All values are expressed as mean ± SD, n=

For each of the tablet formulations, dissolution investigations were conducted. The order of the carriers that affected the drug release of the tablet formulations was Polaxomer > ß-cyclodextrin > PVP K-17 > PVA > Polyplasdone XL-10 > PVP K-30 > PEG-6000.

Table 8: Medication Release Profiles of RLX Tablet Formulations

Time (min)	Cumulative % drug release						
	RLX_1	RLX_2	RLX_3	RLX_4	RLX_5	RLX_6	RLX_7
10	4±1.4	11±1.5	13±0.1	6±0.5	10±1.2	13±1.5	11±0.8
20	17±1.8	24±0.6	35±0.9	27±1.6	17±2.5	25±1.6	44±1.8
30	22±1.8	33±0.9	62±1.8	35±0.8	29±1.4	33±1.6	63±0.8
45	34±0.5	45±1.5	73±1.4	48±0.9	41±1.4	47±1.2	90±0.8

All are articulated as mean ± SD, n=3

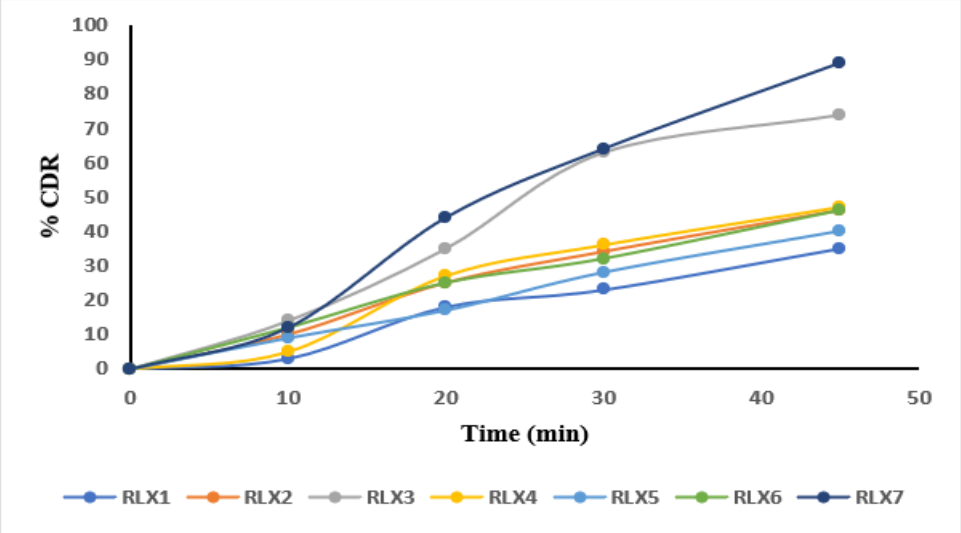

Figure 4: Dissolution Profiles of Tablet Formulations

CONCLUSION:

In order to increase its solubility and dissolution rate, RLX was chosen as a therapeutic candidate based on its biopharmaceutical properties. By utilizing different carriers and the solvent evaporation process, solid dispersions were created.

RLX and the carriers utilized in the formulations were subjected to preformulation experiments, and it was discovered that they were compatible. By using FTIR analysis to characterize them, it was determined that they were compatible and had no interactions. Solid dispersions were created utilizing the solvent evaporation method at a 1:1 ratio with various carriers, and they demonstrated improved solubility compared to API. Carriers with improved dissolving rates included polyplasdone, polyaxomer, and ß-cyclodextrin. Angle of repose and Carr's index, two flow qualities that were assessed, were determined to have good flow characteristics and an acceptable compressibility index. It was discovered that the direct compression method works well for compressing solid dispersions into tablets. When the tablets were evaluated, they fell inside the predetermined range. It is determined that inclusion complex (ß-cyclodextrin), hydrophilic polymer (PVA), and surfactant (polaxomer) are used to increase the solubility of raloxifene hydrochloride.

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