FORMULATION DEVELOPMENT AND EVALUATION OF BIPHASIC DRUG DELIVERY SYSTEM OF ROPINIROLE HYDROCHLORIDE.

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ABSTRACT:

The present research work was carried out to develop a bilayer tablet of Ropinirole Hydrochloride. In this bilayer Ropinirole Hydrochloride IR layer and Ropinirole Hydrochloride SR layer was prepared and evaluated.

The final bilayer tablet was formulated using optimized batch of Ropinirole Hydrochloride IR layer and Ropinirole Hydrochloride SR layer i.e. I8 and S9 respectively. The final bilayer tablet formulation (I8-S9) complied with the internal specification for weight variation, thickness, hardness, friability, drug content and in vitro drug release. The optimized formulation was compared with market product and showed better result as that of marketed formulation. After the stability study observed optimized batch shows no significant change in physical appearance, drug content or invitro dissolution pattern after storage at 40±2°C / 75±5%RH for 3months.

Keywords: Bilayer Tablet, Ropinirole, thickness, hardness, friability, drug content.

1. INTRODUCTION:

Parkinson's Disease (PD) is a degenerative disorder of the central nervous system. It occurs due to the death of dopamine-generating cells in the substantia nigra, a region of the midbrain; the cause of this cell death is unknown. PD is characterized typically by motor features of tremor, rigidity, bradykinesia and postural instability and non-motor disorder symptoms such as Dementia, Depression, and falls or emerges with the progression of the disease. Ropinirole Hydrochloride (ROP) has been a recently introduced selective non-ergoline dopamine D2 receptor agonist, which stimulates striatal dopamine receptors to produce dopamine, for the treatment of PD. [1]

The biphasic delivery system is a new innovative drug delivery system utilized to provide immediate and sustained release doses within the same tablet, thus compliance problems associated with multiple dosing regimens can be overcome. Biphasic drug delivery system is an innovative drug delivery system for oral administration which is composed of one fast release layer and one control release layer. Layered tablet concept is utilized to develop sustained release formulations. This type of system is used primarily when maximum relief needs to be achieved quickly. [2,3]

It is tablet which is having two layers that may be either of the same drug or of two different drugs. Bilayer tablets allows for designing the dissolution and release characteristics and they have two layers in which one is immediate release layer of one drug and extended-release layer of another drug or both immediate and sustain release layer of same drug. [4-6]

ROP is a low molecular weight, highly water soluble drug. It is rapidly absorbed from the gastrointestinal tract and mean peak plasma concentrations have been achieved within 1.5 h after oral doses. The oral bioavailability of ROP is 50% due to extensive first pass metabolism by the liver. Its mean plasma half-life is 5–6 h [7,8]. The starting dose of ROP is 2 mg taken once daily for 1 to 2 weeks, followed by increases of 2 mg/d for one week and so on. For that, the patient has to take a conventional IR tablet 3-4 times a day. The drawback of conventional dosages can be overcome by formulating sustained release Solid Lipid Nanoparticles (SLNs) of ROP. Sustained drug release reduces the dosing frequency, minimizing the side effect, enhanced therapeutic efficacy and prevention of hepatic first pass metabolism of the drug and improves the bioavailability of drugs [9]

2. MATERIALS AND METHODS:

2.1. Material:

2.1.1. Chemicals

Ropinirole Hydrochloride, Croscarmellose sodium, Polyvinyl Pyrrolidone K 30, D-Mannitol, Sodium saccharin, Magnesium Stearate, HPMC, Talc, Microcrystalline cellulose, Acetone, Hydrochloric Acid, Methanol, Ethanol.

2.1.2. Instruments:

UV-Visible Spectrophotometer, FTIR Spectrophotometer with ATR, Electronic Analytical Balance, Ultrasonic Bath (Sonicator), Autoclave, Water distillation unit, Tablet compression machine 10 station, Tablet Dissolution Test Apparatus 08L, Digital Vernier caliper.

3. METHODS:

The sample of Ropinirole Hydrochloride was evaluated for color, odour, and taste. Melting point of Ropinirole Hydrochloride was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The solubility of Ropinirole Hydrochloride was checked

in solvents like water, 0.1 N Hydrochloric acids, and Phosphate buffer pH 6.8 etc. The infrared absorption spectrum of Ropinirole Hydrochloride was recorded with the wave number 4000 to 400 cm^{-1} by using Fourier transform infrared spectrophotometer (FTIR) (Shimadzu 8400s).

3.1. Optimization Evaluation of, Formulation and Ropinirole Hydrochloride IR layer tablet by 3^2 - Factorial Design

The application of mathematical optimization in the pharmaceutical field was first reported by Fonner et al (1970), using the Lagrangian method as a constrained optimization technique. A factorial design is used to evaluate two or more factors

simultaneously.

3.2. Formulation of Ropinirole Hydrochloride IR layer tablet:

From all the above formulations, Solid dispersion of Ropinirole Hydrochloride - PEG 4000 (1:3) showing Maximum aqueous solubility. Hence this dispersion showing maximum dissolution rate was converted to cost effective tablet formulations. SD's of drug with various ratios in optimum concentration (1:3) which showed the best increase in solubility were further subjected to formulation development and invitro assessment.

Pre-compression parameters and post compression parameters was studied. Formulation of optimize bi-layer tablet of Ropinirole Hydrochloride IR Layer (I8) and Ropinirole Hydrochloride SR Layer (S9).

Table. No. 01. Formulation of Tablets

Sr. No.	Ingredients	Formulation
	Formulation of Ropinirole Hydrochloride IR Layer (I8)	
1	Drug (RopiniroleHydrochlorde)	04
2	Cross-carmellose sodium	2.5
3	Polyvinyl pyrrolidone	0.5
4	D-mannitol	83.4
5	Sodium Saccharin	3
6	Magnesium stearate	2
7	Magnesium stearate	0.1
	Total	**100**
Sr. No.	**Formulation of Ropinirole Hydrochloride SR Layer (S9)**	
1	Drug (Ropinirole Hydrochloride)	20
2	HPMC	60
3	Magnesium Stearate	15
4	Talc	2
5	Microcrystalline cellulose	53

	Total	**150**
	Total tablet weight	**250**

3.3. Method of Formulation of optimized bilayer tablet

Method of preparation of optimized bilayer tablet by double compression:

1. The 150 mg powder of the sustain release layer (S9) was half compressed with lower compression force using 8 mm circular shape concave punch on Rotary tablet minipress-I (Rimek, Karnavati Engineering Ltd., Mehsana, Gujarat).
2. Over this compressed layer, 100 mg powder of immediate release layer was placed and compressed to form a bilayer tablet of sustained release of Ropinirole Hydrochloride and immediate release of Ropinirole Hydrochloride.

3.4. Evaluation of optimized bilayer tablet, Stability studies was done.

Stability study of optimized bilayer tablet formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions.

4. RESULT & DISCUSSION:

4.1. Preformulation Study of Ropinirole Hydrochloride

Organoleptic Property:
Ropinirole Hydrochloride it is a white or almost white crystalline odourless powder.

Melting Point:
The melting point of the drug matches with the values found in literature. Melting point of Ropinirole Hydrochloride

Solubility:

The solubility of Ropinirole Hydrochloride was Soluble in solvents like water, 0.1 N Hydrochloric Acid (HCl), Phosphate buffer pH 6.8 etc.

4.2. Fourier Transform Infra-Red Spectroscopy:

Table. No. 02. FTIR data

Sr. No.	Functional group	Standard frequency (cm-1)	Observed frequency (cm-1)
1.	N-H amine	3300-3500	3194.12
2.	C=C Aromatic ring	1475-1600	1519.95
3.	C-H Bending	690-900	856.40

4.	C-H Stretching	2800-3000	2949.16

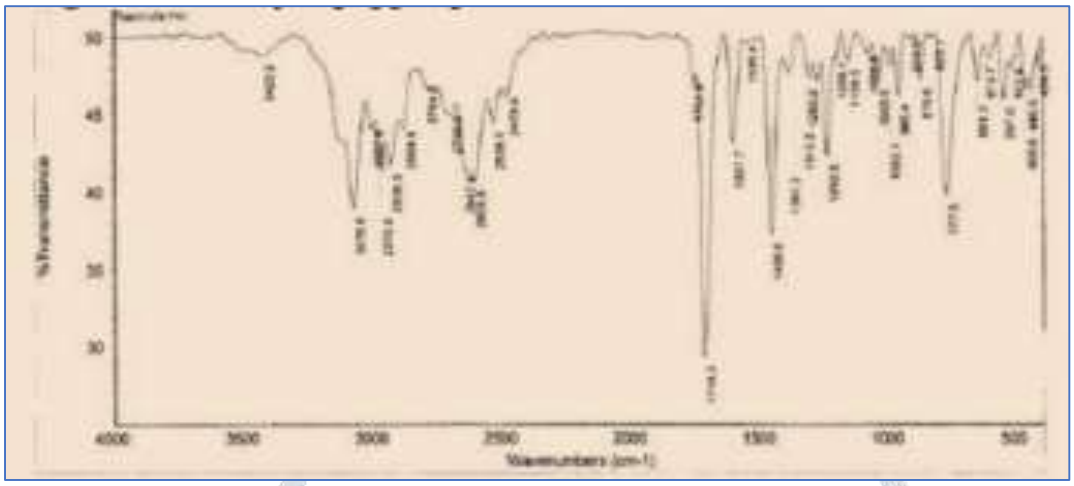

Fig.no.01. FTIR Spectra

4.3. Optimization, Formulation and Evaluation of Ropinirole Hydrochloride IR layer tablet by 3^2 -Factorial Design

Table No.03 Precompression evaluation of formulation mixture (Ropinirole Hydrochloride IR)

Batch No.	Bulk density (gm/cm^3) ±SD	Tapped density (gm/cm^3) ±SD	Compressibility index (%) ±SD	Hausner's ratio±SD	Angle of repose(ɵ) ±SD
I1	049.±0.02	0.51±0.01	3.97±0.117	1.02±0.173	25.61±0.41
I2	0.52±0.02	0.53±0.2	2.44±0.4084	1.02±0.070	25.85±0.70
I3	0.52±0.001	0.52±0.01	1.84±1.8391	1.0±0.029	26.11±0.31
I4	0.52±0.011	0.52±0.007	1.88±0.025	1.±0.02	25.72±0.01
I5	0.51±0.05	0.52±0.05	1.90±0.017	1.01±0.0	26.61±0.26
I6	0.51±0.01	0.52±0.01	2.54±0.710	1.01±0.01	26.51±0.04

I7	0.53±0.0	0.55±0.02	4.68±1.942	1.04±0.029	26.29±0.23
I8	0.48±0.014	0.50±0.07	5.25±0.7675	1.05±0.089	24.18±0.25
I9	0.53±0.022	0.55±0.01	2.46±0.7984	1.01±0.01	24.21±0.10

4.4. Evaluation of post compression parameters of IR Tablet

Table.no.04 Post compression evaluation of Ropinirole Hydrochloride IR tablet

Batch No.	**Thickness (mm) ±SD**	**Hardness (kg/cm^2) ±SD**	**Weight variation (%) ±SD**
I1	3.52±0.0180	3.1±0.070	0.102±0.49
I2	3.52±0.0112	3.2±0.070	0.098 ±0.279
I3	3.53±0.0212	3.1±0.070	0.0982±0.570
I4	3.68±0.194	3.1±0.70	0.100±0.39
I5	3.53±0.0295	3.1±0.118	0.101±0.57
I6	3.53±0.0234	3.1±0.70	0.100±0.29
I7	3.56±0.0122	3.1±0.187	0.100±0.34
I8	3.51±0.0122	3.2±0.141	0.101±0.16

I9	3.54±0.0187	3.2±0.223	0.098±0.19

4.5. Post compression evaluation of Ropinirole Hydrochloride IR Tablet

Table.no.05 Post compression evaluation of Ropinirole Hydrochloride IR Tablet

Batch No.	Disintegration Time (Min)	Drug content (%)
I1	5.44±0.33	87.20±0.001
I2	6.13±0.089	85.16±0.0001
I3	5.92±0.467	86.78 ±0.001
I4	6.22±0.069	90.21±0.001
I5	5.34±0.095	90.03±0.002
I6	5.90±0.622	93.48±0.002
I7	6.2±0.413	92.64±0.002
I8	5.36±0.159	94.96±0.002
I9	6.49±0.249	91.71±0.001

4.6. In-Vitro drug release of Ropinirole Hydrochloride IR Tablet

Table.no.06. In-Vitro drug release of Ropinirole Hydrochloride IR Tablet

Time (min)	Formulation Batches (% CDR)								
	I1	***I2***	***I3***	***I4***	***I5***	***I6***	***I7***	***I8***	***I9***
5	12.78	11.37	11.99	8.92	9.99	9.52	9.18	10.82	11.40
10	21.71	19.60	19.48	17.78	15.32	17.36	20.83	21.93	19.57
20	28.14	25.36	28.39	25.89	25.52	32.42	31.40	38.18	37.42
30	35.47	34.38	36.98	39.54	41.52	40.74	42.33	51.19	50.12
40	48.94	42.15	47.73	49.12	51.25	50.03	59.96	69.42	62.49
50	56.22	52.60	53.80	63.97	62.40	55.66	69.33	80.69	70.50
60	65.70	64.20	65.24	72.39	69.48	62.68	82.82	94.27	81.25

4.7 Evaluation of pre-compression parameters of SR Tablet

Table.no.07. Pre-compression evaluation of formulation mixture (Ropinirole Hydrochloride SR)

Batch No.	Bulk density (gm/cm^3) ±SD	Tapped density (gm/cm^3) ±SD	Compressibility index (%)±SD	Hausner's ratio±SD	Angle of repose (ɵ)±SD
S1	0.625±0.0620	0.679±0.061	7.83±1.111	21.10±0.032	25.30±0.01
S2	0.624±0.0131	0.706±0.05	12.06±0.475	1.03±0.0259	25.80±0.523
S3	0.648±0.0229	0.699±0.095	10.37±0.986	1.07±0.033	26.89±0.878
S4	0.624±0.0229	0.685±0.09	8.76±1.44	0.96±0.0225	24.71±0.72
S5	0.615±0.05	0.715±0.010	14.18±0.068	1.16±0.039	26.01±1.032
S6	0.637±0.210	0.671±0.025	9.94±0.0223	1..05±0.0239	26.87±0.313
S7	0.691±0.0141	0.668±0.017	10.85±0.4671	0.960±0.0026	2523±0.590
S8	0.6410.0252	0.709±0.210	13.00±0.1.429	1.13±0.0403	24.12±1.29
S9	0.689±0. ±0122	0.674±0.0273	14.12±0.735	1.84±0.005	24.33±1.612

4.8. Post compression evaluation of Ropinirole Hydrochloride SR Tablet

Table.no.08. Post compression evaluation of Ropinirole Hydrochloride SR Tablet

Batch No.	Thickness (mm) ±SD	Hardness (kg/cm^2) ±SD	Friability (%)	Weight variation (%) ±SD	Drug content (%)
S1	3.43±0.0187	4.2±0.141	0.62±0.120	0.21±0.593	92.62±0.0002
S2	3.45±0.015	4.6±0.111	0.68±0.195	0.242±0.409	89.12±0.0001
S3	3.40±0.01	4.3±0.111	0.71±0.62	0.25±0.474	91.95±0.001
S4	3.47±0.07	4.1±0.111	0.52±0.658	0..25±0.579	95.33±0.001
S5	3.44±0.015	4.5±0.05	0.594±0.632	0.247±0.498	90.08±0.001
S6	3.41±0.011	4.4±0.05	0.81±0.44	0.25±0.484	86.53±0.0001
S7	3.49±0.070	4.5±0.122	0.59±0.54	0.251±0.577	92.76±0.001

S8	3.44±0.0254	4.5±0.122	0.69±0.012	0.253±0.418	90.63±0.002
S9	3.49±0.007	4.2±0.1414	0.74±0.259	0.251±0.593	92.28±0.0001

4.9. In-Vitro drug release of Ropinirole Hydrochloride SR Tablet

Table.no.09. In-Vitro drug release of Ropinirole Hydrochloride SR Tablet

Time (min)	Formulation Batches (% CDR)								
	S1	***S2***	***S3***	***S4***	***S5***	***S6***	***S7***	***S8***	***S9***
1	**6.45**	**6.74**	**2.89**	**6.55**	**3.47**	**9.44**	**4.46**	**8.54**	**12.40**
2	17.20	13.32	10.59	19.43	9.93	16.84	8.91	12.86	18.07
3	21.63	18.88	18.51	25.17	13.68	19.02	13.99	17.50	23.75
4	27.83	21.24	23.86	29.28	18.13	21.26	19.08	20.34	30.43
5	34.35	24.53	27.13	35.55	26.55	26.97	27.67	24.62	36.53
6	36.06	30.74	33.10	39.56	32.90	34.74	30.53	30.99	41.57
7	43.95	34.23	40.02	44.18	39.25	42.81	33.87	36.90	52.51
8	51.50	41.45	45.22	58.87	45.60	55.55	38.17	43.33	63.73
9	54.93	52.45	51.76	66.76	68.30	76.96	55.33	49.72	72.90
10	60.76	61.85	58.92	72.73	75.81	86.92	58.81	59.58	83.89
11	65.91	68.09	68.51	77.16	79.86	90.27	65.04	71.01	89.15
12	68.01	74.15	76.20	80.05	81.78	94.16	82.15	82.75	96.29

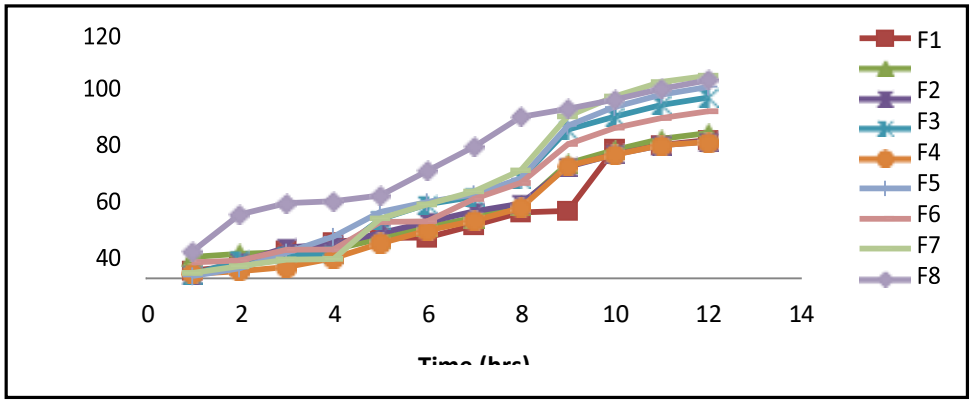

Figure no. 02. In-Vitro drug release of Ropinirole Hydrochloride SR Tablet

4.10. Evaluation of optimized bilayer tablet of Ropinirole Hydrochloride IR layer and Ropinirole Hydrochloride SR layer:

Table.no.10. Formulation of optimize bi-layer tablet of Ropinirole Hydrochloride IR Layer (I8) and Ropinirole Hydrochloride SR Layer (S9)

Sr. No.	Ingredients	Formulation
	Formulation of Ropinirole Hydrochloride IR Layer (I8)	
1	**Drug (Ropinirole Hydrochloride)**	4
2	**CCS**	2.5
3	**PVP**	5
4	**D-Mannitol**	83.4
5	**Sod.Saccharin**	3
6	**Mag.Steareate**	2
7	**Tartrazine**	0.1
	Total	**100**
Sr. No.	**Formulation of Ropinirole Hydrochloride SRLayer (S9)**	
1	**Drug (Ropinirole Hydrochloride)**	4
2	**HPMC**	2.5
3	**Magnesium stearate**	5
4	**Talc**	83.4
5	**MCC**	3
	Total	**150**

4.11. Evaluation of Pre-Compression Parameters of Bilayer Tablet

Table.no.11. Evaluation of Pre-Compression Parameters of Bilayer Tablet

Sr.No.	Precompression parameters	Ropinirole Hydrochloride Bilayer Tablets (I8S9)
1	Bulk density (gm/ml)	0.5444±0.012
2	Tapped density(gm/ml)	0.7472±0.025
3	Compressibility index %	14.18±0.010
4	Hausner's ratio	0.729±0.158
5	Angle of repose	28.81±0.186

4.12. Post compression Evaluation of optimized batch of Bilayer Tablet

Table No.12. Post compression Evaluation of optimized batch of Bilayer Tablet

Sr. No.	Parameter	Limits	Observation
1	Weight variation	600.5-724.5mg (±5%)	Complies
2	Thickness	6.5±0.5mm	6.05±0.23
3	Hardness	NLT 4 Kg/cm^2	5-6
4	Friability	NMT 1%	0.290
5	Disintegration Time of Nate IR tablet	NMT 15 Minutes	06.30

Table No.13. In-Vitro drug release of optimized bilayer tablet (I8-S9)

Time (Hrs.)	Limit	% Release
1	-	40.65±0.001
2	-	51.83±0.001
3	-	63.16±0.0002
4	-	81.58±0.015
5	-	84.41±0.002
6	-	87.25±0.002
7	-	94.33±0.001
8	-	96.22±0.003
9	-	97.17±0.0001
10	-	98.11±0.002
11	-	98.59±0.002
12	NLT 60%	98.82±0.002

4.13. Stability study of optimized formulation

Table No.14. Stability study of optimized formulation

Stability parameter at 40±2 ^{0}C/ 75±5% RH	Time (Days)			
	0	30	60	90
Ropinirole Hydrochloride Bilayer Formulation				
1)Disintegration (Min.)	6.31	6.18	6.13	06.05
2) Drug content %	97.91	97.89	97.84	97.70
3) In vitro dissolution	98.82	98.80	98.21	98.10

5. CONCLUSION:

Above studies successfully demonstrated the combination of hydrophilic (HPMC, Magnesium stearate) polymer were effectively sustain the release of Ropinirole Hydrochloride up to 12 hours and show the drug release as per specification given in USP. From the FT-IR can be concluded that the Ropinirole Hydrochloride was compatible with the polymers used in formulation of bilayer tablet.

The final bilayer tablet was formulated using optimized batch of Ropinirole Hydrochloride IR layer and Ropinirole Hydrochloride SR layer i.e. I8 and S9 respectively which shows better drug release when compared with market product. No significant change was observed in physical appearance, drug content and in vitro drug release before and after stability studies for 3 months. Hence, it is finally concluded that, the bilayer tablet technology can be successfully applied for sustained release and immediate release of Ropinirole Hydrochloride.

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