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FORMULATION AND EVALUATION OF BILAYER ENTERIC COATED TABLETS OF PANTOPRAZOLE AND LEVOSULPIRIDE (SR)

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ABSTRACT

The Experiment relates to formulation and development of oral pharmaceutical bilayer enteric-coated tablet of Pantoprazole and Levosulpiride(SR) for administration of therapeutically and prophylactically effective amount of Antipsychotic and proton pump inhibitor drug substance to resist the gastric fluids and obtained both a relatively fast or quick onset of therapeutic effect and maintenance of a therapeutically active plasma concentration for relatively long period of time up to 12hrs. Drug excipient compatibility study by FTIR analysis. Physical mixtures of drug and excipients kept for stability study at 40±2ºC & 75±5% relative humidity for 30 days in stability chamber. By Compare FTIR Peaks of Levosulpiride with peaks of Levosulpiride with excipient and Pantoprazole with peaks of Pantoprazole with excipient there was no significant change observed in the peaks and The FTIR analysis shows the characteristics peaks of API conclude that drug and excipient are compatible with each other.Second stage of formulation development is formulation of immediate release layer and sustained release layer for prepration of bilayer tablet. Formulate immediate release layer and sustained release layer individually by dry granulation and wet granulation method. Both Layers passes the Precompression tests and Formulation of Enteric-coating using Procoat ECM Aqua(Aw1001), HPMC (E-15), Titanium dioxide, PEG-6000 and solvent. It can be concluded from the obtained results that as the concentration of Methocel K100LV increases, The percentage drug release of Levosulpiride decreases.

KEYWORDS: Bilayer enteric-coating, Levosulpiride, Pantoprazole and Methocel K100LV.

INTRODUCTION

Levosulpiride is a substituted benzamide anti-psychotic, reported to be a selective antagonist of dopamine D_2 receptors activity on both central and peripheral levels. It is an atypical neuroleptic and a prokinetic agent. Levosulpiride is also claimed to have mood elevating properties. Levosulpiride is used in the treatment of psychoses, particularly negative symptoms of schizophrenia, anxiety disorders, dysthymia, vertigo, dyspepsia, irritable bowel syndrome and premature ejaculation.[1] Pantoprazole is a proton pump inhibitor which reduces acid secretion through inhibition of ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid.[2]

The pharmaceutical dosage forms containing combination drugs are very much Useful in therapies due to patient compliance.

- Pantoprazole is a proton pump inhibitor.
- Levosulpiride is substituted benzamide anti-psychotic drug.
- The formulation of both these drugs in combined dosage (Tablets) form is used for the treatment of psychosis and inhibits gastric acid secretion which are caused when the psychotic patient in stress condition. Levosulpiride is used for the treatment of psychosis and Pantoprazole to overcome inhibition of gastric acid secretion caused by stress condition of psychotic patient.

MATERIALS AND METHODS

Compatibility Studies

1 month compatibility study was done. Active pharmaceutical ingredients Pantoprazole sodium and Levosulpiride alone, along which each other, and each API with each of the excipient in 1:1 ratio was stored in amber colored, Type 1 Glass vial which is highly resistant glass & at a temperature of 40±2ºC & 75±5% relative humidity. After 1 month they were observed physically to see any changes if occurred and their FTIR (Cary630FTIR) were performed to check their compatibility & stability.[3]

By IR spectrum

The FTIR spectrum of Pantoprazole sodium and Levosulpiride should be compare with FTIR spectrum of mixture of drugs and excipients & both the drugs mixtures used in the formulation and there should be no interference in the peak of drug and excipients.

Table.1: Formula For 6 Formulations F_1, F_2, F_3, F_4, F_5, And F_6

Ingredients	F1	F2	F3	F4	F5	F6
Immediate Release Layer						
Pantoprazole sod. Eq. to Pantoprazole	48	48	48	48	48	48
Starch	38	40	42	44	46	48
Sodium Starch Glycollate	6.25	6.25	6.25	6.25	6.25	6.25
Sodium Carbonate	10	10	10	10	8	6
Sodium lauryl sulphate	4.02	4.02	4.02	4.02	4.02	4.02
Color Red oxide of Iron	0.437	0.437	0.437	0.437	0.437	0.437
HPMC(E-5)	2	2	2	2	2	2
Polysorbate-80	2	2	2	2	2	2
Colloidal silicon dioxide	1.15	1.15	1.15	1.15	1.15	1.15
Talc	3	3	3	3	3	3
Magnesium Stearate	1.15	1.15	1.15	1.15	1.15	1.15
Crospovidone	14	12	10	8	8	8
Purified Water	qs	qs	qs	qs	qs	qs
Sustained Release Layer						
Levosulpiride	75	75	75	75	75	75
MCC (PH102)	146.1	141.1	136.1	131.1	126.1	121.1
Methocel K100LV	50	55	60	65	70	75
PVP K-30	4.5	4.5	4.5	4.5	4.5	4.5
Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Colloidal Silicon Dioxide	1.4	1.4	1.4	1.4	1.4	1.4
Mg.Stearate	3	3	3	3	3	3
Enteric-Coated Ingredients						
Procoat ECM Aqua(Aw1001)	40	40	40	40	40	40
HPMC (E-15)	9.76	9.76	9.76	9.76	9.76	9.76
Talcum	0.5	0.5	0.5	0.5	0.5	0.5
Titanium Dioxide	0.5	0.5	0.5	0.5	0.5	0.5
PEG (6000)	0.8	0.8	0.8	0.8	0.8	0.8
Col. Red oxide of iron	0.437	0.437	0.437	0.437	0.437	0.437
Isopropyl Alcohol	qs	qs	qs	qs	qs	qs
Methylene Chloride	qs	qs	qs	qs	qs	qs
Total	**462**	**462**	**462**	**462**	**462**	**462**

(All ingredients in mg)

Formulation of Bilayer Enteric-coated Tablet

The study involves formulation of a Sustained release Levosulpiride 75mg Bilayer tablet, which produces relatively uniform blood level of Levosulpiride over a given period of therapy with oral administration once daily.

The Sustained Release was achieved by means of a polymeric matrix for which the tablet is formed. Because of Pantoprazole composition the immediate release layer suddenly release the drug and Sustained release layer tends to swell and slowly erode rather than

disintegrating. Formulation and development of Pantoprazole and Levosulpiride Bilayer enteric-coated tablet involves Three steps.[4,5]

Step-1 formulation of immediate release layer

Immediate release layer formed by a super disintegrant, diluent, alkaline agent used as buffering agent and lubricant.

Step-2 formulation of Sustained release layer

Sustained release tablet comprises of hydrophilic polymers, binder, diluents, lubricant.

Step-3 formulation of Enteric-coating

Enteric-coating formed film former, plasticizer, opacifying agents and solvent.

Preparation of Bi-layer Tablet

Bilayer tablets were prepared by using immediate and sustained release layer. Various batches of bilayer tablets were prepared by method according to formula Table, and compression by using 10.6 mm round punch on Bilayer rotary tablet machine (Fluid pack). Compression force was kept constant for all formulations.[6,7]

Steps Involved in Bilayer Tablet Preparation

Step 1. Filling immediate release layer.

Filled Pantoprazole immediate release layer blend as per formula in first hopper of bilayer tablet compression machine.

Step 2.Filling of Sustained release layer.

Filled Levosulpiride sustained release layer blend as per formula in second hopper of bilayer tablet compression machine.

Step 3. Slightly compressed immediate release layer.

Compressed immediate release layer at slightly low hardness. Ejection of upper punch.

Step 4. Addition of sustained release blends.

Ejection of upper punch, casuses addition of sustained release blends over immediate release layer.

Step 5. Compression of both layers.

Vacuum pressure is applied to prevent mixing of both layers.Compresion of both layers at optimum hardness we required. After ejection of bilayer tablet occured.

Preparation of Enteric- coating

Seal coating: Disperse HPMC (E-15) in isopropyl alcohol; dissolve PEG-6000 in methylene chloride. Then take talc, titanium dioxide & mix with HPMC (E-15) solution. Mix the PEG-6000 solution in it & dispersion of titanium. Add remaining quantity of methylene chloride and stir well for 30min. to get uniform suspension. Then sieve this suspension using 200# muslin cloth. Label the suspension and use within 24hrs.

Enteric Coating: Disperse Procoat ECM Aqua (Aw1001) in purified water. And take color, sifted through #100 no. sieve & mix with Procoat ECM solution & stir well for 30min. to get uniform suspension then sieve this suspension using 200# muslin cloth. Label the suspension and use within 24hrs.

7.3.7.3. Enteric-coating Procedure

The tablets were taken in a coating pan. Enteric-coating solution was sprayed on the tablets and was allowed to rotate until the solvent was evaporated. Finaly the tablets were dried by means of a current of the air. Several coating were given until the desired coat thickness was obtained. The tablets were dried between each coat.[8]

RESULTS AND DISCUSSION

Drug-excipient compatibility: With the help of IR spectrum it was found that the peak of Pantoprazole & Levosulpiride has no interference with the peak of excipients. Hence there is no interaction between the drug sample and the excipients likely to be used in the formulation and hence can be used in the formulation.[9]

From the studies performed it was concluded that the bilayer enteric-coated tablets of Pantoprazole and Levosulpiride using Methocel K100LV, Crospovidone, Titanium dioxide, Starch, HPMC(E-5,15), sodium starch glycolate, PVP K-30 can be prepared optimistically.

Table.2: Showing the Precompression Parameters of Pantoprazole immediate release Layer

Formulation	Bulk Density (g/ml)	Tapped Density (g/mg)	Carr's Index (%)	Hausner's Ratio	Angle Of Repose (Θ)
F_1	0.490	0.512	12.01	1.12	24.56
F_2	0.486	0.560	11.13	1.08	24.24
F_3	0.493	0.548	12.10	1.03	24.30
F_4	0.495	0.553	11.18	1.14	24.16
F_5	0.487	0.580	10.98	1.10	24.20
F_6	0.489	0.582	11.20	1.18	24.38

Table.3: Showing the Precompression Parameters of Levosulpiride Sustained Release Layer

Formulation	Bulk Density (g/ml)	Tapped Density (g/mg)	Carr's Index (%)	Hausner's Ratio	Angle Of Repose (Θ)
F_1	0.460	0.502	11.01	1.22	26.16
F_2	0.451	0.530	10.13	1.18	25.14
F_3	0.463	0.528	11.10	1.23	26.40
F_4	0.475	0.543	10.18	1.21	25.56
F_5	0.457	0.550	11.98	1.14	26.40
F_6	0.469	0.522	12.20	1.17	25.38

Table.4: Showing the Postcompression Parameters:

	Thickness(mm.)	Diameter(mm.)	Hardness(Kg./cm2)	Friability (%)
F1	4.95	11.03	6.2	0.62
F2	4.90	11.05	6.0	0.53
F3	4.92	11.02	6.5	0.45
F4	4.89	11.02	5.5	0.38
F5	4.90	11.04	5.5	0.56
F6	4.93	11.07	5.5	0.56

	Weight variation test (%)	Uniformity of dispersion
F1	+1.36, -2.27	Complies
F2	+1.44, -2.16	Complies
F3	+1.51, -2.32	Complies
F4	+1.46, -2.20	Complies
F5	+1.38, -2.14	Complies
F6	+1.40, -2.18	Complies

In-vitro Dissolution Test of Bi-layer Enteric-coated Tablet

Results of dissolution test for bi-layer enteric-coated tablet was represented in **Table. 5 and Table 6** for Levosulpiride and Pantoprazole respectively.

Table.5: Cumulative % Drug Release of Levosulpiride from Bi-layer Tablet in Phosphate buffer pH 6.8.

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	4.95±1.2	4.27±1.0	5.38±1.7	6.16±1.1	5.83±1.0	7.93±1.2
2	28.7±1.5	28.9±1.2	28.0±1.3	27.9±1.1	29.3±1.4	29.35±1.5
4	56.29±1.9	48.77±1.3	55.8±1.0	58.9±1.0	62.15±2.0	63.41±1.3
8	82.23±2.0	83.1±1.3	83.2±1.1	84.9±1.1	84.10±1.6	84.82±1.4
12	100.2±2.0	101.8±1.4	102±1.1	102±1.0	103.5±1.7	104.4±1.1

All values are mean ± SD, (n = 6)

The Cumulative % Drug release of Levosulpiride was found to be 104.4% (F6), in 12 hrs. which was in the limit (95%-105%).

Table. 6: Cumulative % Drug Release of Pantoprazole from Bi-layer Tablet in Tris-acetate buffer pH 8.5.

Time(min)	F1	F2	F3	F4	F5	F6
5	5.95±1.2	5.27±1.0	5.38±1.7	6.26±1.1	5.83±1.0	6.93±1.2
10	18.1±2.0	18.3±2.0	17.9±1.1	18.4±1.1	17.81±1.3	18.4±1.3
20	28.9±1.5	28.3±1.2	28.7±1.3	28.9±1.1	29.7±1.4	29.62±1.5
30	55.29±1.9	48.41±1.3	55.1±1.0	58.7±1.0	62.52±2.0	63.34±1.3
40	81.21±2.0	82.9±1.3	83.1±1.1	83.9±1.1	84.2±1.6	84.21±1.4
50	101.2±2.0	101.5±1.4	102±1.1	102±1.0	103.5±1.7	103.4±1.1

All values are mean ± SD, (n = 6)

The Cumulative % Drug release of Pantoprazole was found to be 103.4% (F6), in 50min. which was in the limit (95%-105%).

Stability study

Accelerated stability study was performed for the formulation F6 in the final product packaging. 1 month Stability studies showed no major significant changes when compared with zero day of formulation (F6).

Table.7: Results of Stability Study For Formulation F6

S.NO.	EVALUATON PARAMETERS	EVALUATION DATA BEFORE STABILITY STUDY	EVALUATION DATA AFETR STABILITY STUDY
1.	Thickness	4.93mm	4.92mm
2.	Diameter	11.07mm	11.07mm
3.	Hardness	5.5 Kg./cm2	5.3 Kg./cm2
4.	Friability	0.56%	0.55%
5.	Weight variation	+1.40, -2.18	+1.42, -2.19
6.	Uniformity of	Complies	Complies

	dispersion		
7.	Assay of Levosulpiride	98.70%	98.68%
8.	Assay of Pantoprazole	101.8%	101.6
9.	Uniformity of content	95.7 to 103.3%	95.7 to 102.3%

CONCLUSION

The Experiment relates to formulation and development of oral pharmaceutical bilayer enteric-coated tablet of Pantoprazole and Levosulpiride(SR) for administration of therapeutically and prophylactically effective amount of Antipsychotic and proton pump inhibitor drug substance to resist the gastric fluids and obtained both a relatively fast or quick onset of therapeutic effect and maintenance of a therapeutically active plasma concentration for relatively long period of time up to 12hrs. Experiment conclude that Bi-layer Enteric-coated tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick inhibits gastric acid secretion and second drug as sustained release of drug which block the presynaptic dopaminergic D_2 receptors for sufficient long time up to 12hrs. and reduce frequency of dose. It can be concluded from the obtained results that as the concentration of Methocel K100LV increases, %drug release of Levosulpiride decreases.

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