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FORMULATION AND EVALUATION OF METOCLOPRAMIDE AND LANSOPRAZOLE BILAYER TABLETS

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ABSTRACT:

The main objective of the present research work was to develop a bilayer tablet of Lansoprazole and Metoclopramide hydrochloride and in separate layers to avoid incompatibility and thus to maximize the efficacy of both drugs in combination for the effective treatment to prevent and treat stomach ulcers. Lansoprazole and Metoclopramide hydrochloride were formulated as immediate and sustained release layers respectively. In vitro dissolution kinetic studies of an optimized in both layer and bilayer tablet forms show good linearity of regression coefficient Lansoprazole is used to treat certain stomach and esophagus problems (such as acid reflux, ulcers). It works by decreasing the amount of acid your stomach makes. It relieves symptoms such as heartburn, difficulty swallowing, and persistent cough.. In our present research, we have selected the Lansoprazole active ingredient for study because it has treat stomach ulcers. In the present investigation we combine Lansoprazole and Metoclopramide hydrochloride as a formulated bilayer tablet to more effeteness of Lansoprazole.

Keyword: Lansoprazole, Metoclopramide, Bilayer tablet, Stomach ulcers

1. INTRODUCTION

Bilayer tablet is a unit compressed tablet dosage form intended for oral administration. It comprises of two layers in which one layer is formulated as a conventional or immediate release part and another layer as modified release part or both of the former or later of the same or different drugs. Bilayer tablets enjoys the benefit of combining two drug with modified release pattern and scores over other formulations in terms of ease of manufacture, scale-up feasibility that caters the demands of industries. Unlike conventional formulations, there is a lack of saw tooth kinetics ensuring effective therapy with better plasma drug level.

1.1Advantages of bilayer tablet:

1. Incompatible substances can be separated by formulating them in separate layers as two layered tablets.
2. Bilayer tablets require fewer materials when compared to the compression coated tablets.
3. The weight of each layer can be accurately controlled in contrast to putting one drug of a combination product in sugar coating.
4. Bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles.
5. Different release profiles of the drugs can be achieved by combining layers of drugs with various release patterns or by combining slow release with immediate release layers.
6. The pharmacokinetic advantage relies on the fact that the drug release from the fast releasing granules leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granules.
7. Bilayer tablets help in reducing the fluctuations that arise in the plasma concentrations of the drugs.
8. These bilayer tablets improve patient compliance by reducing the frequency ofdosing.
9. Bilayer tablets help in maintaining the chemical and physical integrity of the drugs in the layers.

1.2 Disadvantages of bilayer tablets:

1. Bilayer tablets are mechanically complicated to design or manufacture.
2. It is harder to predict their long term mechanical properties due to poormechanical and compression characteristics of the constituent materials in the adjacent layers
3. There is a possibility of elastic mismatch of the layers.
4. Insufficient hardness.
5. Inaccurate individual mass control.
6. Reduced yield and tendency to delaminate at the interface between theadjacent layers.

1.3 Sustained Release Drug Delivery System:

Controlled release pharmaceutical dosage forms have received much attention lately. Such controlled release tablets are highly desirable for providing a constant level of pharmaceutical agent to a patient. Attempts at controlled release tablets have been made in the past, with mixed success.

1.4 Advantages of sustained release systems:

a. Sustained blood levels: Slower the rate of absorption, the less the blood concentrations fluctuate within a dosing interval. For drugs with relatively short half-lives, the use of extended release products may maintain therapeutic concentrations over prolonged periods.

b. Attenuation of adverse effects: With conventional dosage forms, high peak blood concentrations may be reached soon after administration with possible adverse effects related to transiently high concentration.

The use of extended release formulations avoids the high initial blood concentrations which cause the sudden reduction in the blood pressure.

c. Improved patient compliance: Drugs with short biological half lives need to be given at frequent intervals to maintain blood concentrations within the therapeutic range. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local and systemic effects.

d. Increased safety margin of high potency drugs due to better control of plasma levels.

e. Maximum utilization of drug enabling reduction in total amount of dose administered.

f. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personal time to dispense, administer and monitor the patient.

g. Opportunities for product differentiation, product life-cycle management, market expansion and patent expansion.

1.5 Disadvantages of sustained release forms:

a. The necessity to ensure that drug leakage, and other factors which would cause inadequate control and possibly lead to dangerous situations, do not occur.

b. Administration of sustained release medication does not permit the prompt termination of the therapy.

c. The necessity to ensure the adequate safety of the devices with respect to device components and their degradation products together with the biocompatibilities of the actual devices.

d. Sufficiently large dose to accommodate the longer dosing interval.

e. These dosage forms being bulkier than the immediate release analogs, larger proportion of release controlling excipients need to be incorporated.

f. Possibility of dose dumping due to food, physiological factors or formulation variables and thus increased risk of toxicity.

2. MATERIAL AND METHOD

2.1 Organoleptic Properties:

a. Colour:

A small quantity of powders were taken in butter paper and observed in well-illuminated place.

b. Taste and odour:

Very less quantity of powders is tasted and perceived to observe the odor as well.

c. Solubility:

The approximate solubility of substances are indicated by the descriptive terms. Solvents such as Methanol, alcohol and water and isopropyl alcohol are used for the solubility studies.

2.2 Drug excipient compatibility studies:

Drug Excipients compatibility studies are carried out by mixing the drug with various excipients in different proportions was placed in a vial, and rubber stopper was placed on the vial and sealed properly. Studies were carried out in glass vials at Accelerated conditions, 40º C ± 2° C / 75% RH ± 5 % RH for a storage period of 4 weeks. After storage, the sample was compared with control at 2-8° C and observed physically for liquefaction, caking and discoloration.

2.3 IR Studies:

The IR studies for drug excipient compatibility are mainly meant to confirm the integration of the drugs active moiety when combined with the excipients. The samples are previously grounded and mixed thoroughly with Potassium bromide and compressed through the hydraulic press to form pellets. The spectral smoothening and the baseline corrections procedures are done prior to sampling and the sample being scanned at 400cm^{-1} to 4000cm^{-1} ambient temperature.

2.4 Particle size distribution:

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieves were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed bysieves of decreasing pore size (larger sieve number) towards the bottom. using the following formula for determine particle size distribution

Average mean diameter= Σnd / Σx

Where n= weight of the powder retained in grams d= arithmetic mean size openings in µm

x= percentage weight of the powder retained. The same procedure is repeated for all the powders.

2.4.1 Analytical method development for Metoclopramide and Lansoprazole:

Accurately weighed 20 mg of Metoclopramide and Lansoprazole each and is dissolved in 100 ml of 6.8 pH phosphate buffer. This is regarded as the primary stock solution. From this primary stock solution, 1ml, 2ml, 3ml, 4ml, 5ml and 6ml is pipetted out and made up to 100ml with pH 6.8 phosphate buffer, to produce 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml and 12µg/ml respectively. The absorbance was measured at 295 nm by using a UV-Vis spectrophotometer.

2.5 Characterization of Tablets:

2.5.1 Pre compression properties:

a. Angle of Repose:

Angle of repose was calculated using the following equation:

$$\tan \theta = h/r$$

Where, h = height of the powder

r = radius of the powder heapθ = is the angle of repose.

b. Determination of Bulk Density and Tapped Density: The bulk density and the tapped density were calculated using the following formula.

$$\text{Bulk density} = W/V_0 \quad \text{Tapped density} = W/V_f$$

Where,

W = Weight of the powder

V_0 = Initial volume

V_f = final volume

c. **Carr's Compressibility Index**: Carr's index of each formulation was calculated according to equation given below:

$$\text{Carr's Compressibility Index (\%)} = [(TD-BD) \times 100] / TD$$

Where,

TD = Tapped densityBD = bulk density

d. Hausner's Ratio

Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. It is the ratio of tapped densityand bulk density. Hausner found that this ratio was related to interparticle friction and,as such, could be used to predict powder flow properties. Generally a value less than

$$\text{Hausner's Ratio} = \text{Tapped density/Bulk Density}$$

e. Loss on Drying (LOD)

Loss on drying is performed using the IR moisture analyzer. Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under

specified conditions.

2.6 Formulation Bilayer tablets

The composition of bilayer tablets prepared usingLansoprazole and Metoclopramide

Table No.1 Formulation Code of Lansoprazole Layer

S.No	Name of the Ingredient	F1	F2	F3	F4	F5	F6
Dry Mixing							
1	Lansoprazole	20	20	20	20	20	20
2	Mannitol	38	38	38	38	38	38
3	Na_2CO_3	27	27	27	27	27	27
4	Avicel PH102	16	16	16	16	16	16
5	Aerosil	0.6	0.6	0.6	0.6	0.6	0.6
Granulation							
6	Povidone	7	7	7	7	7	7
7	IPA	q.s	q.s	q.s	q.s	q.s	q.s
Sub coating							
8	HPMC	2.4	2.4	2.4	2.4	2.4	2.4
9	IPA	q.s	q.s	q.s	q.s	q.s	q.s
Enteric Coating							
10	HPMC P	16	12	_	_	_	_
11	Kollicoat MAE30DP	_	_	16	12	_	_
12	Eutragit NE30D	_	_	_	_	16	12
13	PEG	4	4	4	4	4	4
14	Talc	0.6	0.6	0.6	0.6	0.6	0.6
15	Water	q.s	q.s	q.s	q.s	q.s	q.s
Tabletting Excepients And Lubrication							
16	Avicel PH200	64	68	64	68	64	68
17	Iron Oxide Red	0.4	0.4	0.4	0.4	0.4	0.4
18	Magnesiumstearate	2	2	2	2	2	2
19	Talc	2	2	2	2	2	2
	Total Weight	200	200	200	200	200	200

Table No.2 Formulation Code of Metoclopramide Layer

S.No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
1	Metoclopramide	**50**	**50**	**50**	**50**	**50**	**50**	**50**
2	HPMCK4M	-	-	32	48	8	32	16
3	HPMCK15M	32	48			24	16	32
4	Lactose	82	66	82	66	82	66	66
5	Microcrystalline Cellulose	32	32	32	32	32	32	32
6	Magnesium Stearate	2	2	2	2	2	2	2
7	Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0
8	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total Weight	200.0	200.0	200.0	200.0	200.0	200.0	200.0

2.7 Evaluation of Lansoprazole and Metoclopramide Bilayer tablets

a. Appearance:

The tablet should be free from cracks, depressions, pinholes etc. The colour and the polish of the tablet should be uniform on whole surface. The surface of the tablets should be smooth.

b. Dimensions:

Thickness and diameter of a tablet were measured using vernier calipers. These values were checked and used to adjust the initial stages of compression.

c. Weight Variation test:

Take 20 tablets and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the U.S.P. test if not more that 2 tablets are outside the percentage limit and if no tablet differs by morethan 2 times the percentage limit.

% Maximum positive deviation = $(W_H - A / A) \times 100$

% Minimum negative deviation = $(W_L - A / A) \times 100$

Where,

W_H = Highest weight in mg. W_L = Lowest weight in mg.

A = Average weight of tablet in mg.

d. Hardness test:

Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets.

e. Friability test:

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It is being rotated at a rate of 25 rpm. The percentage friability was measured by using the following formula

$$\% F = \{1-(W / W_o)\} \times 100$$

Where,

%F = friability in percentage W_o = Initial weight of tablet

W = Weight of tablets after revolution.

f. Content uniformity:

A sample of 30 tablets are randomly seleced and 10 of them are individually assayed. 9 of the 10 tablets must contain >85% and <115 of drug content. The tenth tablet must contain <75% and >125% of the labeled content.If these conditions are not met,the remaining 20 tablets are assayed individually and none must fall outside the 85%-115% range.

2.8 Release kinetics:

The mechanism study of drug release via a swellable and dissoluble hydrophilic polymer matrix is not as extensive as for purely diffusion, swelling or polymer dissolution controlled drug release systems since all these processes are coupled, thus making the models more intricate and difficult to solve. The selection of particular model for release is based on regression coefficient of release profile obtained from its slope. The regression value (r^2) approaching towards 1 shows best fit for particular model. Hence the model for which release profile shows the regression coefficient value close to 1 was chosen for determination of release of drug from dosage form.

2.9 Stability study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity & light & enables recommended storage conditions, re-test periods and self half lives to be established. Lansoprazole and Metoclopramide Bilayer tablets were packed in HDPE containers and

evaluated for accelerated stability studies at 40ºC/75% RH conditions.

Storage conditions: 40±2°C/75±5%RH.

3. RESULTS AND DISCUSSION

3.1 Organoleptic Properties:

Table No3 Organoleptic Properties for Lansoprazole

Test	Specification / limits	Observations
Colour	White or almost white powder	White or almost white powder
Taste	Bitter	Bitter
Odour	Characteristic odour	Characteristic odour

Table No.4 Organoleptic Properties for Metoclopramide

Test	Specification / limits	Observations
Colour	White or almost white powder	White or almost white powder
Taste	Bitter	Bitter
Odour	Characteristic Odour	Characteristic Odour

3.2 Angle of Repose:

Table No.5 Angle of repose for Lansoprazole

S. No.	Material	Angle of repose	Average angle of repose
1.	Lansoprazole	38·62°	38·81°±0.57
2.		39·42°	
3.		38·39°	

Table No.6 Angle of repose for Metoclopramide

S. No.	Material	Angle of repose	Average angle of repose
1.	Metoclopramide	39·46°	38·85º±0.59
2.		38·53°	
3.		38.57°	

3.3 Determination of Bulk density and Tapped density:

Table No.7 Bulk Density and Tapped Density for Lansoprazole

S.No.	Material	Bulk Density (gm / ml)	Average Bulk Density (gm / ml)	Tapped Density (gm / ml)	Average Tapped Density (gm /cc)
1	Lansoprazole	0.367	0.362±0.01	0.534	0.537±0.01
2.		0.361		0.540	
3		0.359		0.536	

Table No.8 Bulk Density and Tapped Density for Metoclopramide

S.No.	Material	Bulk Density (gm / ml)	Average Bulk Density (gm / ml)	Tapped Density (gm / ml)	Average Tapped Density (gm / ml)
1	Metoclopramide	0.351	0.351± 0.01	0.531	0.526± 0.01
2.		0.349		0.521	
3.		0.353		0.528	

3.4 Powder Compressibility and Hausner ratio

Table No. 9 Compressibility Index and Hausner ratio

Materials	Compressibility index	Hausner ratio
Lansoprazole	32.71	1.55
Metoclopramide	33.64	1.57

3.5 Solubility:

Table No.10 Solubility of Lansoprazole

Quantity of Lansoprazole	Quantity of solvents	Inference
100 mg	100 ml of water	Slightly soluble
100 mg	100 ml of 95 % ethanol	Freely soluble
100 mg	100 ml methanol	Freely Soluble

Table No.11 Solubility of Metoclopramide

Quantity of Metoclopramide	Quantity of solvents	Inference
100 mg	100 ml of water	Very slightly soluble
100 mg	100 ml of 95 % ethanol	Sparingly soluble
100 mg	100 ml of methanol	Slightly Soluble
100 mg	100ml of dimethylformamide	Sprangly soluble

3.6 Analytical method development for Lansoprazole andMetoclopramide

Absorption Maxima Scan of Lansoprazole and Metoclopramide

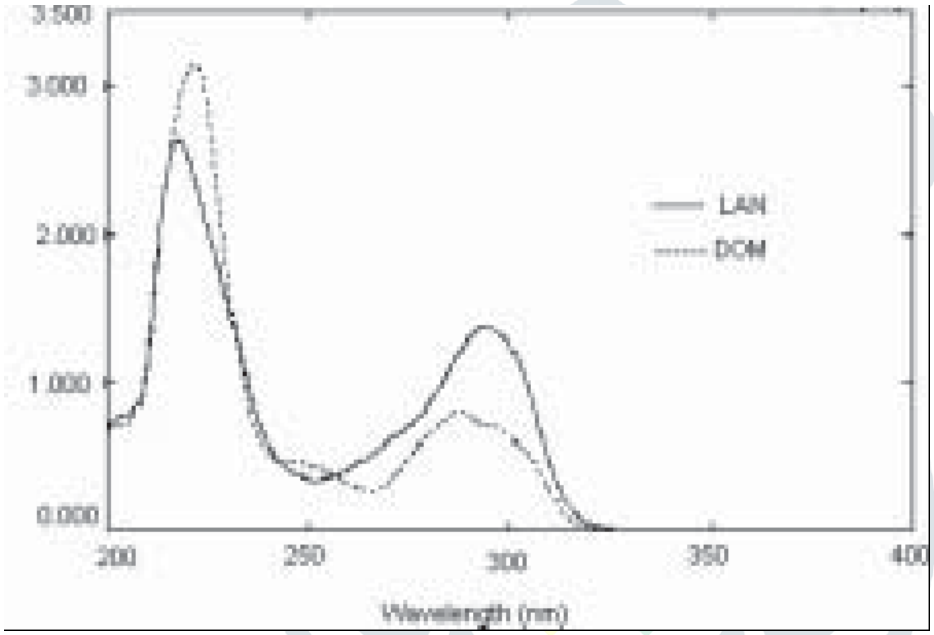

Fig No..1 λ_{max} Scan of Lansoprazole andMetoclopramide

A spectrum of the working standards is obtained by scanning from 200-400nmagainst the reagent blank to fix absorption maxima. The λ_{max} is found to be 256.0nm. Hence standard curve and dissolution testings are being carried out at the same wavelength.

3.7 Drug-Excipient compatibility study at 40° C / 75 % RH

The various drug excipient mixtures are subjected to compatibility studies by keeping the blends under accelerated conditions, 40° C / 75 % RH for a period of 4 weeks. After 4 Weeks of study physical appearance of these compositions were made and compared with the initial observations. These observations are recorded in Table

Table No. 12 Excipients compatibility studies for Lansoprazole

S.No	Composition	Ratio	Physical Appearance				
			Initial	1st week	2nd week	3rd week	4th week
1.	Lansoprazole		A white or almost white crystalline powder	NCC	NCC	NCC	NCC
2.	Lansoprazole + Mannitol	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
3	Lansoprazole + $NaHCO_3$	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
4.	Lansoprazole + Povidone	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
5.	Lansoprazole + Avicel PH102	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
6	Lansoprazole + Aerosil	1:0.25	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
7.	Lansoprazole + Mg. stearate	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
8.	Lansoprazole + Talc	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC

*** NCC – No characteristic change**

Table No. 13 Excipients compatibility studies for Metoclopramide

S.No	Composition	Ratio	Physical Appearance				
			Initial	1st week	2nd week	3rd week	4th Week
1.	Metoclopramide		A white or almost white crystalline powder	NCC	NCC	NCC	NCC
2.	Metoclopramide + HPMC K4	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
3	Metoclopramide + HPMC K15	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
4.	Metoclopramide + Lactose monohydrate	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
5.	Metoclopramide + Avicel pH101	1:1	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
6.	Metoclopramide + Magnesium stearate	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC
7.	Metoclopramide + Talc	1:0.5	A white or almost white crystalline powder	NCC	NCC	NCC	NCC

*** NCC – No characteristic change**

3.8 DRUG –POLYMER COMPATIBILITY STUDIES BY FTIR:

The FTIR spectra of Lansoprazole and the combination of drug and excepientsshows no significant interaction between drug and excepients.

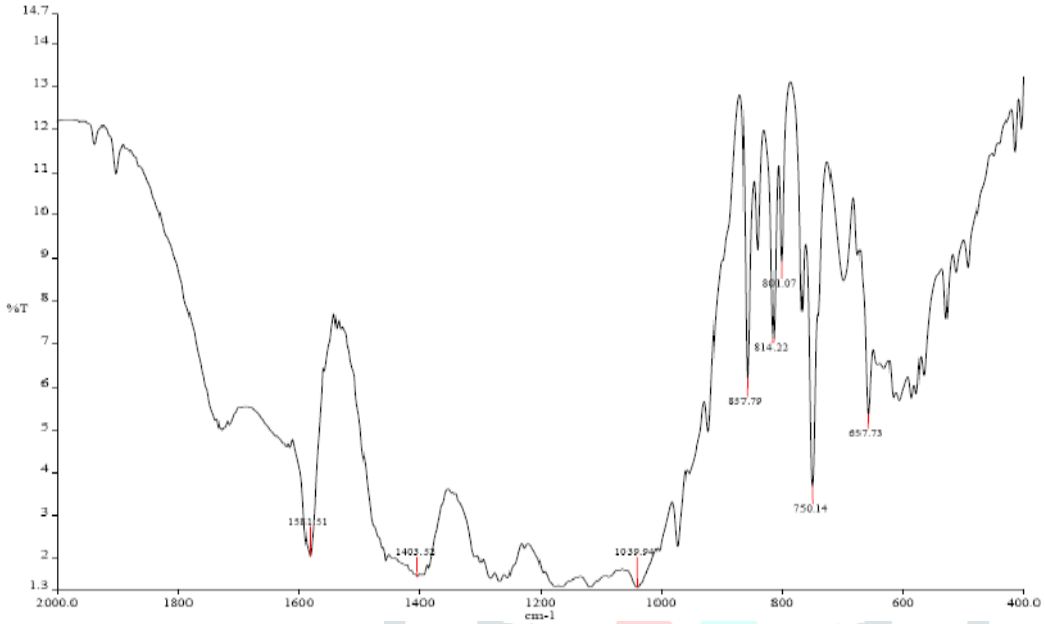

Fig No. 2 FTIR Spectra of Lansoprazole Drug

3.9 Characterization of tablets

3.9.1 Pre-compression parameters

The derived properties of the formulated blends are studied at ambientconditions using standard protocols and the data is tabulated in the tables.

Table No.13 Pre-compression parameters of Lansoprazole batches F1 to F6

Batch	Derived Properties			Flow Properties		
	Bulk Densit (gm/ml)	Tapped Density (gm/ml)	Loss on Drying	Angle of Repose (°)	Compress ability Index	Hausner's Ratio
F1	0.36±0.002	0.39±0.006	1.35±0.07	26.33±0.31	13.52±0.86	1.15±0.011
F2	0.32±0.003	0.38±0.001	1.36±0.07	28.05±0.13	11.28±0.42	1.12±0.005
F3	0.35±0.01	0.36±0.003	1.47±0.10	29.15±0.20	8.16±3.44	1.08±0.041
F4	0.33±0.008	0.37±0.005	1.51±0.05	31.83±0.22	10.84±3.58	1.12±0.045
F5	0.35±0.010	0.35±0.003	1.42±0.16	28.41±0.26	12.87±2.96	1.14±0.039
F6	0.32±0.006	0.40±0.004	1.37±0.08	27.72±0.13	9.62±1.10	1.10±0.013

Table.No.14 Pre-compression parameters of Metoclopramide batches F1 to F7

Batch	Derived Properties			Flow Properties		
	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Loss on Drying	Angle of Repose (°)	Compressibility Index	Hausner's Ratio
F1	0.37±0.005	0.40±0.004	1.45±0.07	31.6±0.34	10.13±0.48	1.13±0.006
F2	0.36±0.004	0.41±0.002	1.39±0.14	30.7±0.13	12.73±1.58	1.12±0.020
F3	0.34±0.004	0.39±0.004	1.42±0.05	32.71±0.50	10.19±1.67	1.13±0.020
F4	0.38±0.006	0.43±0.008	1.50±0.12	31.63±0.36	15.24±2.31	1.17±0.032
F5	0.35±0.005	0.44±0.005	1.48±0.08	29.52±0.65	14.65±1.39	1.15±0.018
F6	0.36±0.009	0.47±0.003	1.39±0.13	27.81±0.75	15.47±1.81	1.16±0.025
F7	0.39±0.005	0.39±0.001	1.41±0.06	28.14±0.35	9.53±1.19	1.11±0.014

3.9.2 Post compression parameters:

Table No.15 Post compression Parameters of Lansoprazole and Metoclopramide Bilayer tablet

Batch	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Content uniformity (%)	
					LANSO	METO
F1	8.26±0.08	2.99±0.04	357.1±1.9	0.45±0.02	98.11±0.38	98.84±0.32
F2	8.29±0.04	3.05±0.01	359.7±1.5	0.51±0.03	99.18±0.19	98.14±0.35
F3	8.27±0.03	3.02±0.01	358.0±1.6	0.57±0.04	101.16±0.6	98.58±0.68
F4	8.25±0.03	3.03±0.07	362.8±3.1	0.46±0.03	98.69±0.68	98.77±0.56
F5	8.26±0.02	2.97±0.02	359.4±1.9	0.47±0.01	99.85±0.39	98.58±0.35
F6	8.29±0.07	2.95±0.10	360.7±2.2	0.55±0.02	100.00±0.4	98.81±0.55
F7	8.28±0.05	2.99±0.13	362.1±3.4	0.60±0.03	98.80±0.05	97.38±0.57

3.10 *IN-VITRO* RELEASE PROFILES OF THE FORMULATIONS

Table No.16 *In-vitro* release profiles of Lansoprazole formulations F1 to F6

S.No	Time (min)	Cumulative % of drug release					
		F1	F2	F3	F4	F5	F6
1	**0**	0	0	0	0	0	0
2	**0.5**	19.07	17.18	11.32	7.82	10.64	6.95
3	**1**	46.18	40.51	39.65	38.58	43.72	38.05
4	**2**	58.84	57.72	49.95	48.95	55.02	52.10
5	**4**	72.36	68.83	65.36	62.84	68.20	61.62
6	**8**	88.59	82.69	79.65	71.25	83.74	76.65
7	**10**	97.91	99.85	98.14	95.91	97.06	98.17
8	**12**	_	_	_	99.99	_	_

3.11 Drug release criteria according to USP

Table No.17 *In-vitro* release profiles of Metoclopramide formulations F1 to F7

S.No	Time (hrs)	Cumulative % of drug release						
		F1	F2	F3	F4	F5	F6	F7
1	**0**	0	0	0	0	0	0	0
2	**0.5**	9.96	8.65	7.82	6.02	7.81	7.80	12.74
3	**1.0**	19.35	16.06	13.06	11.36	14.02	15.80	19.58
4	**2**	34.54	32.85	23.65	19.71	29.16	28.26	37.92
5	**4**	54.98	48.96	35.25	33.45	45.92	40.32	59.32
6	**8**	91.37	82.69	63.21	58.65	78.36	67.32	81.57
7	**10**	98.15	94.21	75.02	74.91	91.79	75.12	90.38
8	**12**	_	_	92.38	86.52	_	89.36	99.75

3.12 STABILITY STUDIES

The formulation is stored at Accelerated conditions like 40°C and 75% RH fora period of three months

Table No.18 Characteristics of the tablets during stability studies

Evaluation Parameters	Storage condition 40°C / 75 % RH			
	Initial	1st month	2nd month	3rd month
Description	White and red color round shape	complies	complies	Complies
Hardness (kg/cm^2)	8.5±0.4	8.4±1.2	8.4±0.6	8.4±0.8
Thickness (mm)	3.06±0.01	3.04±0.02	2.99±0.01	3.01±0.03
Weight Variation (mg)	361.4±0.45	359.8±0.12	361.3±0.07	361.2±0.13
Friability (%)	0.657	0.589	0.751	0.657

CONCLUSION

In the present study an attempt has been made to Formulate and evaluate the multiparticulate delayed release Lansoprazole as one layer and sustained release Metoclopramide as another layer. The Lansoprazole compressible enteric coated granules were prepared by using different enteric coated polymers such as HPMC Phthalate, Eutragit NE30D and Kollicoat MAE30DP with different ratios and plasticized with PEG. The Lansoprazole granules which are coated with 8% Eutragit and plasticized with 2%PEG meet the USP criteria in drug release. From the above data it is evident that the formulation F7 shows satisfactory drug release both on acid phase and buffer phase and complies with all the pharmacopoeial limits before and after the stability studies and is the most suitable composition for the delayed release of Lansoprazole.

Two different grades of HPMC polymer are used to study the release retarding activity. Different concentrations of polymer are used in the sustained release layer and their effect on the release of Metoclopramide is explored. The formulation F7 is found to be the best formulation since it meets the USP criteria in the drug release. HPMC of grade K4M and K15M at a concentration of 20% and 10% releases the drugas per the USP specifications. The cumulative drug release at the end of twelfth hour is 100%.From the above data it is evident that the formulation F7 shows satisfactory sustained release and complies with all the pharmacopoeial limits before and after the stability studies and is the most suitable composition for the sustained release of Metoclopramide.

Finally I conclude that F7 formulation shows the best release in both the layers (Lansoprazole and Metoclopramide) and that may fulfils the objective of the study. The stability studies were performed according to in-house specifications for the optimized formulation. The tablets were kept at accelerated condition (40±2° C/ 75±5% RH) for a period of three months. The obtained results were within the specifications.

REFERENCES

1. Ding X, Alani AWG, Robinson JR. Extended release and targeted drug delivery systems. In : The Science and Practice of Pharmacy. 2005; (Remington, Ed.), Twenty first edition, volume 1, pp. 939-964 ; Lippincott Williams and Wilkins.
2. Karande A.D., Dhoke S.V., Yeole P.G. Formulation and evaluation of bilayer tablets with antihypertensive drugs having different release patterns. Indian Drugs, 2006; 43(1): 44-50.
3. R.Nagaraju and Rajesh Kaza. Formulation and evaluation of bilayer sustained release tablets of Salbutamol and Theophylline. International Journal of Pharmaceutical Sciences and Nanotechnology, 2009; 2(3): 638-646.
4. Shailesh kumar, Venkata Bala Krishna Rao, N.Kannapan, Amitsankar Dutta. Formulation and evaluation of Atorvastatin calcium and Nicotinic acid in a bilayer tablets. Journal of Pharmacy Research, 2009; 2(7): 1256-1258.
5. Pharmaceutics, The science of dosage form design, Aulton M.E, 2nd edition, 1998, 1, 289-306, 412.
6. Modern Pharmaceutics, Gilbert S.Banker Christopher T.Rhodes, 4th edition, 2006, 121, 501-514.
7. The Theory and practice of Industrial Pharmacy, Leon Lachamnn., Herbert A.Liebermann., Joseph L.Kanig, 2nd edition, 2003,1, 330-331.
8. Martino Fusca, Dagmer Farber, Heppinheim, Patented on Multilayer tablets, 2001 Patent No. US 6,254,886 B1
9. Sachin S. Kale, Viraj S. Saste, Prajkta L. Ughade, Dheeraj T. Baviskar. Review article on Bilayer Tablets. International Journal of Pharmaceutical Sciences Review and Research.2011, Volume 9, Issue 1: 25-30
10. Jitendra R. Amrutkar, Mohan G.Kalaskar,Varsha G.Shrivastav, P.G.Yeole. Bilayer tablets of Metformin hydrochloride and Glilclazide. A Novel approach in treatment of diabetes, international Jour of Pharm Research and Development,2009; 1(2).
11. Wen H, Park K. Fluid bed coating and granulation for CR delivery In : Oral controlled release formulation design and drug delivery: theory to practice. 2010:. 115-121 ; John Wiley and Sons.
12. Brahmankar DM, Jaiswal BS. Controlled release medication. In: Biopharmaceutics and Pharmacokinetics a treatise. 1995: pp. 335-371, Vallabh Prakashan
13. Sansom LN. Oral extended release products. Aust Prescr. 1999 ; 22: 88-90.
14. Richards JH. Role of polymer permeability in the control of drug release. In: Polymer permeability. 1985; (Comyn J, Ed.,), pp : 220-256; Springer

15. Chinam Niranjan Patra, Arethi Bharani Kumar, Hemat Kumar Pandit, Satya Prakash singh, Meduri vimala devi. Design and evaluation of Sustained Release Bilayer tablets of propronalol hydrochloride. Acta Pharm; 2007; 57: 479-489.
16. Physical Pharmacy, Martin's, P.S Patrick J. 5th edition, 2006, 1, 337-354, 553-558.
17. Rane M, Parmar J, Rajabi-Siahboomi. Hydrophilic matrices for oral extended release: influence of fillers on drug release from HPMC matrices. Pharma Times. 2010 ; 42: 41-45.
18. Brahmankar DM, Jaiswal BS. Controlled release medication. In: Biopharmaceutics and Pharmacokinetics a treatise. 1995: pp. 335-371, Vallabh Prakashan.
19. Sanjahan Abdul, Anil V. Chandewar, Sunil B. Jaiswal, A flexible technology for Modified-Release drugs, J. Of Controlled release, 147 (2010) 2-16.
20. V.S.N. Murthy, and J.Vijaya Ratna, Key formulation variables in Tabletting of Coated Pellets, Indian J.of Pharmaceutical Sciences, 2008, pp.555-564
21. Ann Debunne, Chris Vervaet, Debby Mangelings, Jean-Paul Remon, Compaction of enteric-coated pellets: influence of of formulation and process parameters on tablet properties and *invivo* evaluation, European J. Of Pharmaceutical sciences, 22(2004): 305-314.
22. A.Dashevsky, K.Kolter, R.Bodmeier,Compression of pellets coated with various aqueous polymer dispersions, International J.of Pharmaceutics 279(2004): 19-26
23. Volker Buhler, Functional polymers for pharmaceutical Insustry, BASF, 2007 pp 69-97
24. Raymond C Rowe, Paul J Sheskey,Sian C Owen Hand book of Pharmaceuticalexcipients Fifth edition.
25. R. Baselt, *Disposition of Toxic Drugs and Chemicals in Man*, 8th edition, Biomedical publications, Foster City, CA, 2008: 1146-1147
26. Meyers RA. Interpretation of IR spectra, a practical approach. Encyclopedia of analytical chemistry. 2000 : 10815 – 10837.
27. Indian pharmacopeia volume-2 2007
28. Leon Lachman et.al; The Theory and Practice of Industrial Pharmacy, 3rd edition, Page. No: 293- 345
29. Duphar BV, Weesp. Design for drug excipient interaction studies. Drug development and Industrial pharmacy. 1983; 9 : 43-55.
30. Indian pharmacopeia volume-2 2007
31. Huanjo kim.reza fassihi. Pharma Resea,vol.14(10).1997 :1415-1421
32. Mamajek RC, Moyer ES. Drug dispensing device and method. US Patent 4 207 890. June 17, 1980.
33. Rakesh patil, ashok bariaijps vol.1 issue 2, 2009 31-32.
34. Leon Lachman et.al; The Theory and Practice of Industrial Pharmacy, 3rd edition, Page. No: 293- 345
35. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 515 Fifth Edition, 2004

36. Chapter 905, Uniformity of Dosage Units and Chapter 1151, Pharmaceutical Dosage Forms, United States Pharmacopoeia, 2008
37. FDA guidance on “Dissolution Testing of Immediate Release Solid Oral Dosage Forms
38. Korsmeyer RW, Gurny R, Doelker E, Buri P. Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm*. 1983