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FORMULATION AND EVALUATION OF FLOATING BILAYER TABLET OF METFORMIN HYDROCHLORIDE AND CHLORPROPAMIDE

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ABSTRACT

The present investigation studied a novel bilayer tablet having an extended release system. There has been 70 years of research and development experience in the sustained drug release area since the patent, and a number of strategies have been developed to prolong drug level in the body. With many drugs, the basic goal of therapy is to achieve a steady-state blood or tissue level that therapeutically effective and non-toxic for an extended period of time. Floating Bilayer tablet of Metformin HCl as Instant Layer and Chlorpropamide as control layer were formulated using, HPMC, Sodium carboxymethyl cellulose, Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate in combination of different percentage of polymer. Nine different formulations of floating Chlorpropamide SR tablets are prepared by employing the hydrophilic polymer HPMC in different viscosity grades in the percentage. From this study it was concluded that Floating time increases, it decreases the release rate. So it suitable for sustained release formulation. The two agents were found to have a remarkable effect on glycemic control. In the present investigation a bilayer tablet was prepared in which one layer gives instant action against diabetes and another layer maintain concentration of drug in plasma for longer periods.

Keyword: Diabetes, Chlorpropamide, Metformin HCL, Bilayer tablet

1. INTRODUCTION

Bi-layer tablet is suitable for sequential release of two drugs in combination, two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. There are various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity. Bi-layer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control.

Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

IDEAL CHARACTERISTICS OF BILAYER TABLET:

• A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.

• It should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.

• It should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

• It must have a chemical stability shelf-life, so asnot to follow alteration of the medicinal agents.

OBJECTIVES BEHIND DESIGNING BILAYER TABLET:

1. To control the delivery rate of either single or two different active pharmaceutical ingredient.
2. To separate incompatible active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).
3. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for modified release
4. To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device buccal/ mucoadhesive delivery systemsand floating tablets for gastro-retentive drug delivery.

GMP REQUIREMENTS FOR BILAYER TABLET

To produce a quality bi-layer tablet, in a validated and GMP-way, it is very important to follow the following criteria for the selection of bilayer press. These requirements seem obvious but are not so easily accomplish. The press should be capable of:

1. Preventing capping and separation of the two individual layers that constitute theBi-layer tablet;
2. Preventing cross-contamination between the two layers;
3. Providing sufficient tablet hardness;
4. Accurate and individual weight control of the two layers;
5. Producing a clear visual separation between the two layers;
6. Manufacturing products of high yield.

2. Preformulation Study

Preformulation include organolaptic properties such as Colour and Morphology, Odor, Taste melting point, solubility, identification of Metformin and Chlorpropamide.

Characterization for physical-chemical properties of Metformin

A) Organoleptic Properties

Oganoleptic properties of drug were determined by direct observation of drug sample under optical microscope for its appearance color and crystal morphology.

Table 2.1 Characters of Metformin

S. No.	Sensory characters	Result
1.	Colour and Morphology	White crystalline powder
2.	Odor	Odorless
3.	Taste	Slight bitter

Table 2.2 Characters of Chlorpropamide

S. No.	Sensory characters	Result
1.	Colour and Morphology	White crystalline powder
2.	Odor	Odorless
3.	Taste	No taste

B) Solubility Study

The drug sample was qualitatively tested for its solubility in various polar, semi polar and non polar solvents**.**

Table 2.3 Solubility of Metformin

S. No.	Solvent used	Observation
1	Distilled Water	+++
2	Acetone	----
3	Ethanol	++
4	Methanol	++
5	Diethylether	--

Table 2.4 Solubility of Chlorpropamide

S. No.	Solvent used	Observation
1	Distilled Water	---
2	Dichlormethane	+++
3	Ethanol	++
4	Diethylether	+++
5	Acetone	+

C) Melting point

The melting point was determined by capillary tube method in which small quantity of finely powder drug was placed into a capillary tube and placed in the melting point determining apparatus.

Table 2.5 Melting point of the Metformin

S. No.	Melting Point of Standard Drug	Melting Point of Sample Drug	Average Melting Point of Sample Drug
1.	122-126 °C	126 °C	125 °C
2.		125 °C	
3.		125 °C	

Table 2.6 Melting point of the Chlorpropamide

S. No.	Melting Point of Standard Drug	Melting Point of Sample Drug	Average Melting Point of Sample Drug
1.	126-130 °C	126°C	128°C
2.		128°C	
3.		128°C	

D) Identification Test

FT-IR Spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound.

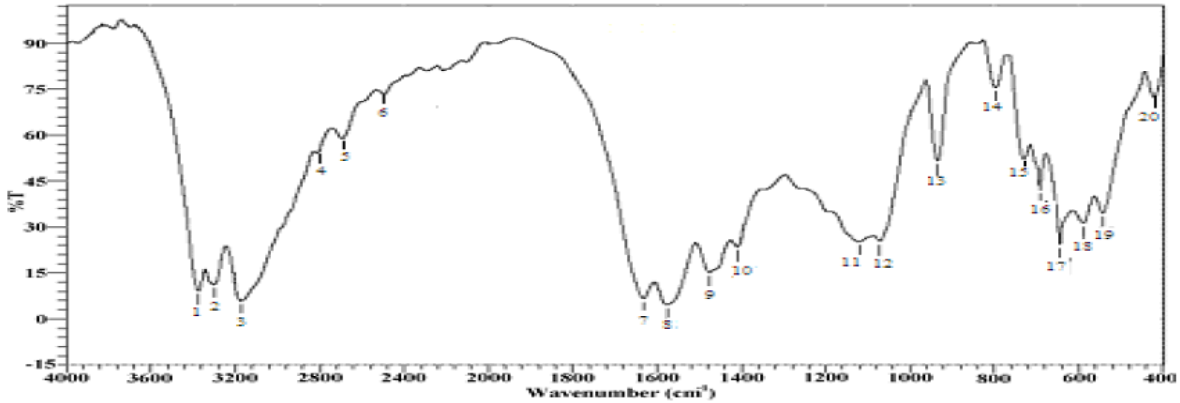

Figure 2.1: FT-IR Spectrum of Metformin (Sample)

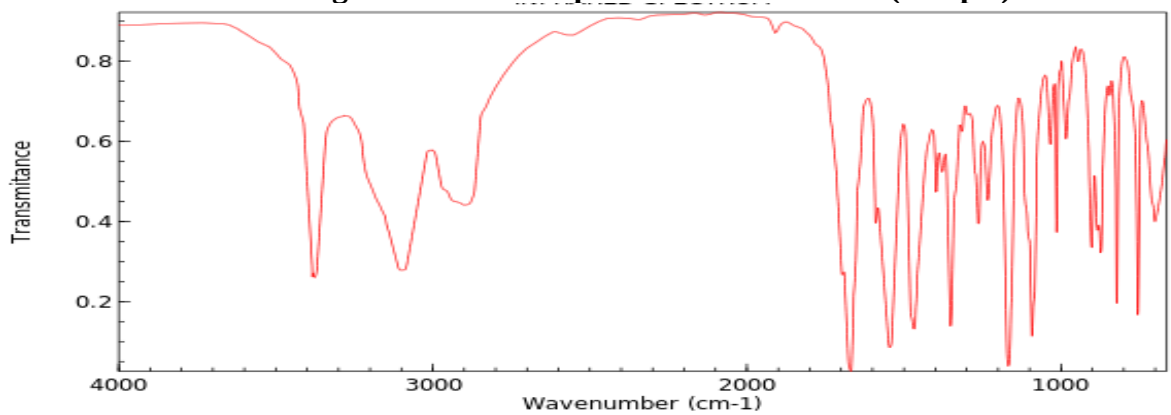

Figure 2.2: FT-IR Spectrum of chlorpropamide (Sample)

F) Determination of λ_{max} of chlorpropamide

The λ_{max} of Chlorpropamide and Metformin were determined by analyzing the drug solution in double beam ultraviolet spectrophotometer. The higher absorption peak was chlorpropamide obtained at 276 nm and The higher absorption peak was Metformin obtained at 234 nm which was the λmax of drug.

3. PREPARATION AND CHARACTERIZATION

3.1 Formulation Development

3.1.1 Preparation of Instant Layer of Metformin (Phase-1)

Fast dissolving tablets of Metformin were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio.

Precompression Parameter of Metformin

Table 3.1 Results of pre-compressional parameters of Metformin

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.524	0.634	21.825	1.256
IF2	0.527	0.637	21.559	1.264
IF3	0.534	0.638	20.493	1.236
IF4	0.527	0.636	21.412	1.262
IF5	0.533	0.640	20.427	1.232
IF6	0.538	0.638	19.373	1.256
IF7	0.534	0.634	19.781	1.269
IF8	0.537	0.634	20.045	1.232
IF9	0.534	0.637	20.403	1.257

Table 3.2 Composition of Metformin Fast Dissolving Tablets

Ingredients(mg)	**Formulation code**								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Metformin	250	250	250	250	250	250	250	400	400
Sodium Starch glycolate	40	45	50	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	40	45	50	-	-	-
Crospovidone	-	-	-	-	-	-	40	45	50
Microcrystalline cellulose	45	40	35	45	40	35	45	40	35
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	350	350	350	350	350	350	350	350	350

Post compression Parameter of Metformin

Table 3.3 Results of Post-Compression parameters of all formulations

Formulation Code	**Hardness test (kg/cm^2)**	**Friability (%)**	**Weight variation (%)**	**Thickness (mm)**	**Drug content (%)**
IF1	3.1	0.481	157	2.32	99.52
IF2	3.3	0.494	154	2.40	98.82
IF3	3.4	0.756	154	2.37	99.62
IF4	3.2	0.653	153	2.31	98.79
IF5	3.2	0.694	150	2.35	99.81
IF6	3.6	0.452	151	2.31	98.87
IF7	3.2	0.582	149	2.23	99.96
IF8	3.3	0.479	147	2.29	99.91
IF9	3.5	0.631	153	2.32	99.73

3.2 Method for Preparation of Chlorpropamide Gastroretentive tablets

Direct compression was followed to manufacture the floating tablets of Chlorpropamide. Eight different formulations were prepared by direct compression.

Table 3.4 Result of Pre-Compression Properties of Chlorpropamide Tablets

Material	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.479	0.582	16.931	1.191
F2	0.483	0.582	17.241	1.207
F3	0.481	0.587	17.709	1.221
F4	0.485	0.589	18.689	1.232
F5	0.484	0.583	17.279	1.217
F6	0.486	0.582	17.613	1.214
F7	0.480	0.581	17.324	1.209
F8	0.487	0.585	16.217	1.201
F9	0.484	0.582	16.213	1.989

Table 3.5 various formulations of Chlorpropamide gastro retentive tablets

Drug and Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorpropamide	250	250	250	250	250	250	250	250	250
Xanthan gum	75	90	-	-	-	-	15	40	15
Gaur gum	-	-	75	90	-	-	30	30	40
Karaya gum	-	-	-	-	75	90	30	40	20
PVP K30	15	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Lactose	45	30	45	30	45	30	45	30	45
Total Weight	400	400	400	400	400	400	400	400	400

Post Compression Properties of Chlorpropamide:

All the tablets were evaluated for following different parameters which includes;

Table 3.6 Results of Post Compression Properties of Chlorpropamide Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.3	5.1	501	0.802	98.91
F2	3.5	5.4	498	0.748	99.23
F3	3.7	5.3	496	0.571	98.84
F4	4.9	5.5	504	0.539	99.76
F5	4.3	5.2	506	0.613	99.06
F6	4.1	5.5	505	0.806	99.71
F7	4.5	5.1	501	0.724	99.81
F8	4.0	5.2	503	0.731	99.36
F9	4.3	5.6	502	0.736	99.14

3.3 Formulation development of bilayer tablet

Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet.

3.3.1 Evaluation of bilayer tablets-

a. Result of Post-Compressional Parameters of Optimized Formulation

Table 3.7 Post-Compressional Parameters of Optimized Formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.1±0.1	0.921	Passes	5.26

b. Drug content

Table 3.8 Results of Drug content analysis

Formulation	Chlorpropamide and Metformin (% Label Claim)
In-house Bilayer tablet	98.92

c. Dissolution rate studies of Instant layer

Table 3.9 Results of Dissolution rate studies of Instant layer

Time (min)	% Drug Release of Instant layer
15	99.03±1.28

d. Dissolution rate studies of bilayer tablets

Table 3.10 Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release
0.5	33.50±0.58
1	41.62±0.35
1.5	53.25±1.25
2	67.03±1.50
4	76.28±1.28
6	85.42±1.33
8	89.48±0.15
10	94.82±0.75
12	98.99±0.28

A dissolution study shows the release of Chlorpropamide and Metformin bilayer tablets. The Instant layer of Metformin release approx 99.03±1.28 percent drug within 15 minutes and control floating layer of Chlorpropamide shows release up to 12 Hours Approx 98.99±0.28 percent of Drug release in 12 hours.

CONCLUSION

Metformin and Chlorpropamide is white crystalline and odorless powder. The melting point of Metformin was 125°C and melting point of Chlorpropamide was 128 ^{o}C which is compliance with the standard value. Identification of Metformin and Chlorpropamide were performed by UV/VIS Spectroscopy. The 10 µg/ml solutions of Metformin and Chlorpropamide were scanned in the range of 200-400nm to determine the λ_{max} for drug. The λ_{max} of Metformin was found to be 276nm and λ_{max} of Chlorpropamide was 234 nm. From the respective stock solution (1mg/ml) different concentration of 5, 10, 15, 20 and 25µg/ml was prepared and scanned in UV region.

A study involving preparation and evaluation of bilayer tablets of Metformin and Chlorpropamide were made. Physicochemical parameters of bilayer tablets were performed using natural polymers. *In vitro* drug release profiles of bilayer tablets were performed. The Instant layer of Metformin release approx 99.03±1.28 percent drug within 15 minutes and control floating layer of Chlorpropamide shows release up to 12 Hours Approx 98.99±0.28 percent of Drug release in 12 hours.

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