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Formulation and Evaluation of Gastro retentive Bilayer Tablets- Glimepiride as Sustained Release and Lisinopril as Immediate Release

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ABSTRACT

The Bilayer tablets containing Glimepiride SR and Lisinopril IR were successfully prepared by Wet granulation and direct compression method respectively. Various formulations were prepared and evaluated with an aim of presenting Glimepiride as sustained release and Lisinopril as immediate release for improving the patient's compliance. The physiochemical evaluation results for the blends of all trials pass the official limits in all tests including Angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner's ratio. The prepared blend for SR layer tablets and IR layer tablets were also maintained the physiochemical properties of tablets such as weight variation, hardness, thickness, friability. The optimized formulation F9 in IR formulations contains the average thickness of 2.4 mm, average hardness of 4.9 kg/cm^2, average weight of 150 mg, friability of 0.46% and disintegration time of 2 minutes. The optimized formulation F7 in SR formulations contains the average thickness of 2.64mm, average hardness of 5.9kg/cm^2, average weight of 250 mg, friability of 0.52%, and optimum mucoadhesive strength. The F7 formulation of Glimepiride Sustained Release Layer releases 10.5% in 1st hour but the remaining drug release was sustained up to 24 hours and F9 formulation of Lisinopril Immediate Release showed 99.92% drug release with in 30min. With the data of kinetic analysis, F7 formulation showed best linearity in zero order plot indicating that the release of drug is independent upon concentration and the mechanism from mucoadhesive layer follows Higuchi diffusion mechanism. The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations. Stability studies were carried out for 6 months. All physical and chemical parameters were found to be satisfactory based on the stability data.

Keywords: Wet granulation, Direct compression, Angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner's ratio.

INTRODUCTION

Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They are intended for oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in water before being administered and

some are retained in the mouth, where the active ingredient liberated. Tablets are used mainly for systemic drug delivery but also for local drug action. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated. Bilayer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is a suitable for sequential release of two drugs in combination, separate 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.[1-12] Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages.[13] Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. [14] Formulating oral gastro retentive bilayer tablet may give several advantageous outcomes with major patient compliance.

AIM AND OBJECTIVE

The aim of the present study was to design and evaluate Gastro retentive bilayer tablets of Glimepiride and Lisinopril. An attempt was made to develop bi-layer tablet suitable for delivering different drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as mucoadhesive layer for sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

Objectives

- To optimize the concentration of polymer for sustaining layer, Glimepiride.
- To select and optimize the concentration of disintegrant for immediate release layer, Lisinopril.
- To select the suitable filler to produce the bulkiness and desired weight.
- To select the dissolution media, by performing solubility studies.
- To perform the drug – excipient compatibility studies as per ICH guideline.
- To perform evaluation tests.
- To perform stability studies.

METHODOLOGY

Formulation of Immediate Release Tablet of Lisinopril by Direct Compression Method

Immediate Release tablets of Lisinopril were prepared by direct compression method. Cross povidone, Sodium starch glycolate and Cross caramellose sodium were used as Super disintegrants. The concentrations of the above ingredients were optimized as shown in below table on the basis of preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release super disintegrants and other excipients, except magnesium stearate and Talc, in ascending order of their weight. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate and Talc was added and mixed for not more than 1 min (to ensure good lubrication.) About 150 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 8mm round surface punches.

Composition of Immediate Release Layer

Table of Composition for Immediate Release Layer

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Cross carmellose sodium(CCS)	7.5mg	11.25mg	15mg	--	--	--	--	--	--
Crospovidone	--	--	--	7.5mg	11.25mg	15mg	--	--	--
Sodium Starch Glycolate	--	--	--	--	--	--	7.5mg	11.25mg	15mg
PVPK 30	7.5mg	7.5mg	7.5mg	7.5mg	7.5mg	7.5mg	7.5mg	7.5mg	7.5mg
Lactose mono hydrate	109mg	105.25mg	48.5mg	109mg	105.25mg	48.5mg	109mg	105.25mg	48.5mg
Mg stearate	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
talc	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Total tablet weight	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg

Formulation of Mucoadhesive Sustained Release Tablet of Glimepiride by Wet Granulation Method

The tablet was prepared by wet granulation method.

Sieving

The active ingredient was passed through the sieve#40 followed by the other ingredients were passed the same sieve.

Dry mixing

Glimepiride, HPMC, Xanthan gum, Micro crystalline cellulose were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug.

Preparation of binder solution with IPA

Weigh binding material accurately and it is mixed with IPA to form a paste is used as binder solution and kept separately.

Granulation

The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules.

Drying

Then the wet granules were dried in trays and pass the air for drying since the IPA is corrosive and also get evaporated quickly. So air drying is only suitable for drying, samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content

Sieving

The dried materials were passed through the sieve#20, after sieving dry granules were lubricated using Magnesium stearate. After lubrication granules were sent to compression. Glimepiride layer was compressed using 12mm round punch.

Composition of Sustained Release Layer

	F1	F2	F3	F4	F5	F6	F7	F8
Glimepiride	4mg	4mg	4mg	4mg	4mg	4mg	4mg	4mg
Xanthan gum	75mg	87.5mg	100mg					
HPMC K100M				75mg	87.5mg	100mg	100mg	100mg
Ethyl cellulose	50mg	50mg	50mg	50mg	50mg	50mg	75mg	87.5mg
Micro crystalline cellulose	161mg	148.5mg	136mg	161mg	148.5mg	136mg	61mg	48.5mg
Mg stearate	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Colloidal silicon dioxide	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Total tablet weight	250mg	250 mg	250mg	250mg	250 mg	250mg	250mg	250mg

Table Of Composition For Sustained Release Layer

MCC- Micro crystalline cellulose, EC – Ethyl cellulose, HPMC – Hydroxy Propyl methyl cellulose.

RESULTS AND DISCUSSION

Preformulation Study of Lisinopril

Organoleptic Properties (Color, odor, taste and appearance)

S.NO	Parameter	Drug
1	Color	White to off White color
2	Odor	Odorless
3	Taste	Tasteless
4	Appearance	Crystalline powder

Results of Identification Tests of Drug

Melting point determination

Reported Melting Point	Observed Melting Point
147ºC	147-149ºC

Results of Melting Point Determination Test of Drug

Determination of solubility

Soluble in methanol water and DMSO, dimethylsulfoxide, and N, N-dimethylformamide, sparingly soluble in ethanol, propylene glycol, and very slightly soluble in hexane, dichloromethane, and methylbenzene.

D. UV-Spectroscopy - Analysis of drug

Ultraviolet Visible (UV-visible) spectroscopy

Drug sample showed wavelength of maximum absorption (λ-max) 216 nm.

Preformulation Study of Glimepiride

Organoleptic Properties (Color, odor, taste and appearance)

S.NO	Parameter	Drug
1	Color	White
2	Nature	Hygroscopic
3	Appearance	Crystalline powder

Organoleptic Properties of Glimepiride

Melting point determination

Reported Melting Point	Observed Melting Point
212ºC	215ºC

Melting Point Determination of Glimepiride

Determination of solubility

Soluble in DMSO (>10 mg/ml), water (<1 mg/ml at 25° C), and ethanol (<1 mg/ml at 25° C).

Evaluation of Lisinopril IR

UV-Spectroscopy - Analysis of drug

Ultraviolet Visible (UV-visible) spectroscopy:
Drug sample showed wavelength of maximum absorption (λ-max) 229 nm in 0.1 N HCl

Evaluation of Blend

Bulk density, Tapped density, % Compressibility index, Hausner ratio and Angle of repose.

Precompression studies of Lisinopril

Formulation code	Angle of repose(θ)	Bulk density (gm /ml)	Tapped density(gm/ml)	Carr's index (%)	Hausner's ratio
F1	25^0	0.541	0.691	11.62	1.17
F2	26^0	0.484	0.615	11.30	1.16
F3	29^0	0.710	0.873	15.76	1.15
F4	26^0	0.712	0.870	17.12	1.20
F5	26^0	0.718	0.871	18.51	1.22
F6	25^0	0.410	0.483	15.11	1.17
F7	26^0	0.671	0.832	15.34	1.18
F8	29^0	0.711	0.823	16.12	1.16
F9	29^0	0.698	0.843	15.12	1.17

Precompression Studies of Lisinopril IR

From the above pre-compression parameters it was clear evidence that powdered blend has excellent flow properties.

Post compression studies of Lisinopril

Formulation code	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friabilty (%)	Content uniformity (%)	Disintegration Time (min)
F1	0.6	4.3	2.3	0.42	99.28	2
F2	0.6	4.5	2.3	0.48	97.16	2.4
F3	0.3	4.9	2.4	0.49	101.1	2.4
F4	1.3	4.4	2.4	0.46	97.68	2.2
F5	1.3	4.7	2.3	0.48	98.19	2.3
F6	0.2	4.8	2.3	0.45	99.41	2.4
F7	0.12	4.6	2.3	0.48	96.23	2.6
F8	0.6	4.7	2.3	0.48	98.12	2.8
F9	0.1	4.9	2.4	0.46	97.23	2.9

Post compression Studies of Lisinopril IR

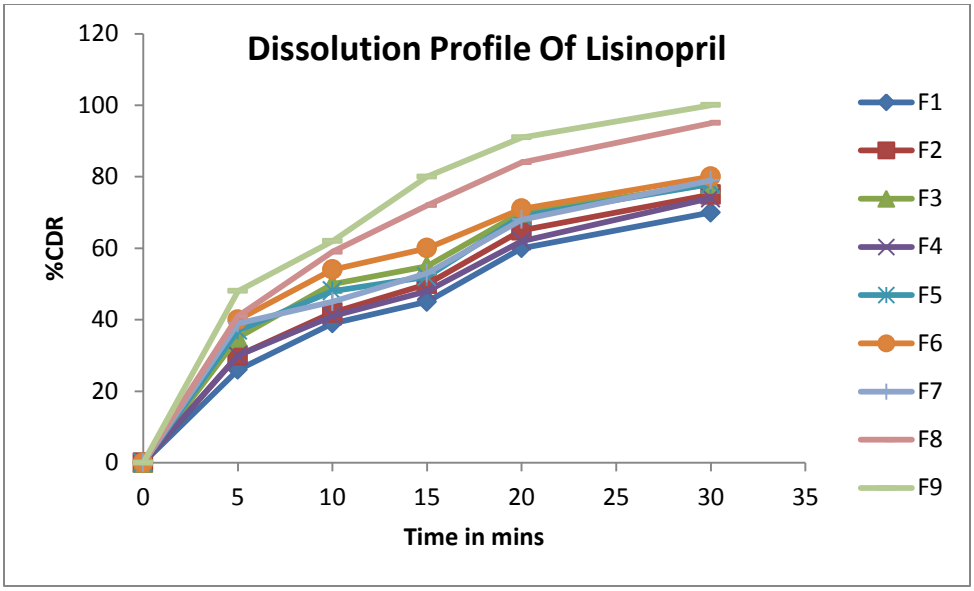
In -vitro drug release study of Lisinopril

Paddle method Dissolution data of tablets formulations of Lisinopril by Paddle method (USP II) are reported

Dissolution Data of Lisinopril

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	26	30	35	30	37	40	39	41	48
10	39	42	50	41	48	54	45	59	62
15	45	50	55	48	52	60	53	72	80
20	60	65	70	62	69	71	68	84	91
30	70	75	78	74	78	80	79	95	100

Dissolution Data of Tablets of Formulations of Lisinopril



Dissolution Profile of Tablets of Formulations of Lisinopril

Evaluation of Glimepiride Mucoadhesive Layer

Table No: 7.11 Evaluations of Glimepiride Tablets of Formulations

Formulations	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's index(%)	Hausner's ratio
F1	25^0 73'	0.318	0.352	13.23	1.12
F2	25^0 16'	0.315	0.342	14.23	1.14
F3	26^0 68'	0.323	0.354	13.58	1.13
F4	27^0 58'	0.314	0.338	15.19	1.16
F5	28^0 38'	0.312	0.335	15.48	1.18
F6	26^0 42'	0.315	0.332	14.48	1.15
F7	26^0 18'	0.332	0.351	14.48	1.16
F8	26^0 78'	0.378	0.362	16.17	1.20

From the above pre-compression parameters it was clear evidence that powdered blend has excellent flow properties.

Post Compression Parameters of Glimepiride Mucoadhesive Layer

Formulations	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Content uniformity (%)
F1	0.4%	4.6	2.80	0.38	99.28
F2	0.8%	5.4	2.51	0.41	97.16
F3	0.1%	5.1	2.61	0.37	101.1
F4	1.2%	4.8	2.74	0.42	97.68
F5	0.4%	5.0	2.67	0.45	98.19
F6	0.2%	5.3	2.56	0.49	99.41
F7	0.2%	5.9	2.64	0.52	98.23
F8	0.1%	6.0	2.57	0.51	98.12

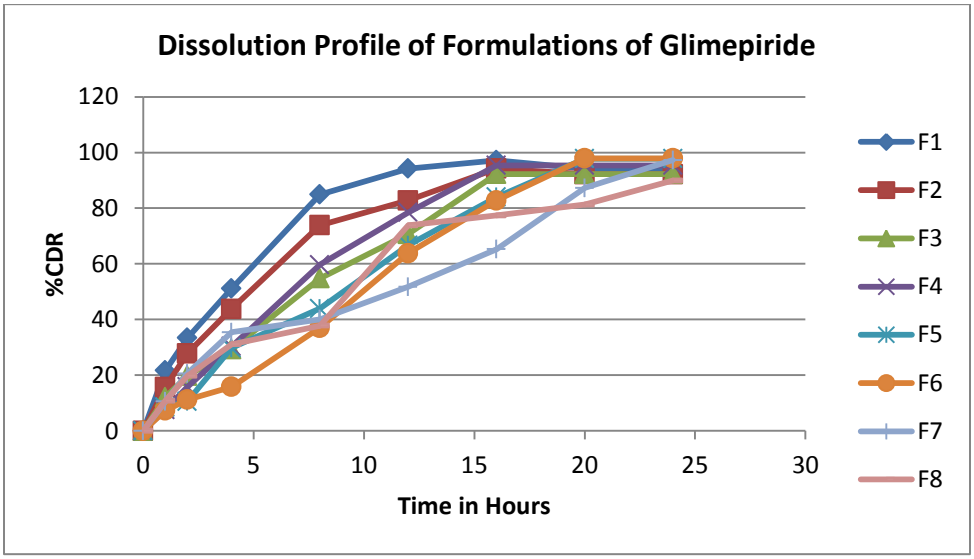
Post Compression Parameters for Glimepiride Tablets of Formulations

In-Vitro Drug Release Studies of Glimepiride Mucoadhesive Layer

Cumulative percentage drug release of Glimepiride Mucoadhesive Layer

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	21.7	15.7	12.09	7.57	8.5	7.3	10.5	10.8
2	33.4	27.8	19.7	15.8	10.6	11.2	20.6	19.7
4	51.1	43.8	29.3	30.3	29.8	15.8	35.4	31.1
8	84.9	73.9	54.8	59.7	43.9	37.0	40.05	37.8
12	94.23	82.8	70.7	78.5	66.7	63.8	51.75	73.8
16	97.23	94.24	92.3	95.4	84.0	82.8	65.25	77.4
20	94.23	92.24	92.3	95.4	97.8	97.9	87.3	81.32
24	94.23	92.24	92.3	95.4	97.8	97.9	97.3	89.9

Cumulative Percentage Drug Release of Glimepiride Tablets Of Formulations

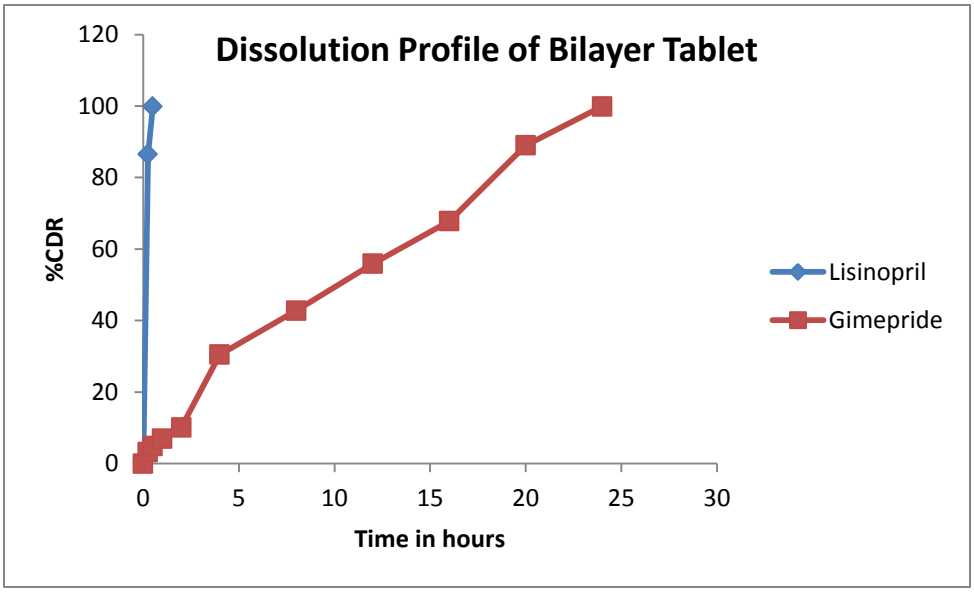


Dissolution Profile of Tablets of Formulations of Glimepiride

Dissolution Study (Bilayer Tablets)

S.No	Time	Dissolution profile of Lisinopril	Dissolution profile of Glimepiride
0	**0**	**0**	**0**
1	**15mins**	**86.5**	**3.2**
2	**30 mins**	**99.9**	**4.9**
5	**1hr**	**--**	**7.0**
6	**2hr**	**--**	**10.1**
7	**4hr**	**--**	**30.5**
8	**8hr**	**--**	**42.8**
9	**12hr**	**--**	**55.9**
10	**16hr**	**--**	**67.8**
11	**20hr**	**--**	**89.0**
12	**24hr**	**--**	**99.89**

Dissolution Profile of Bilayer Tablet



Dissolution Profile of Optimized Bilayer Tablet

COMPARISION STUDIES WITH PREVIOUS WORK

Sustained release layer

F1- glimepiride present work

F2- glimepiride previous work

Comparision with Previous Work

Formulations	Polymers	Site Of Drug Release	Drug Release %	
			12th Hour	24th Hour
F1	HPMC K100M	Stomach	51.75	97.3
F2	GUAR GUM	Stomach, Intestine	58.21	100

% Drug Release of Formulations

Formulations	% DR at 2nd Hour	% DR at 4th Hour	% DR at 8th Hour	% DR at 12th Hour	% DR at 16th Hour	% DR at 20th Hour	% DR at 24th Hour
F1	20.5	35.3	40.1	51.74	65.24	87.2	97.4
F2	30.1	40.2	47.9	58.21	70.1	95.2	100

IMMEDIATE RELEASE LAYER

F1- Lisinopril Present Work

F2- Captopril Previous Work

Comparision With Previous Work

Formulations	Disintegrants	Drug Release %
		30 Min
F1	Sodiun Starch Glycolate	100
F2	Crospovidone	97.50

% Drug Release of Formulations

Formulations	% DR at 5 min	% DR at 10 min	% DR at 15 min	% DR at 20 min	% DR at 30 min
F1	49	65	90	95	100
F2	48.9	64.5	89.1	94.5	97.50

Stability Data of Optimized Bilayer Formulation

Stability Data of Lisinopril IR Layer

S.No	Time points (hrs)	Initial	Cumulative % Drug Release (mean) (SD) (n)					
			25C/60%RH			40C/75%RH		
			1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month
1	15 minutes	86.5	84.525	82.535	82.50	85.52	81.54	81.50
2	30 minutes	99.5	94.525	92.535	92.50	95.52	91.54	91.50
3	Assay	99.5	99.46	92.52	92.5	95.5	91.54	91.5

Stability Data of Optimized Bilayer Formulation

Stability Data of Glimepiride SR Layer

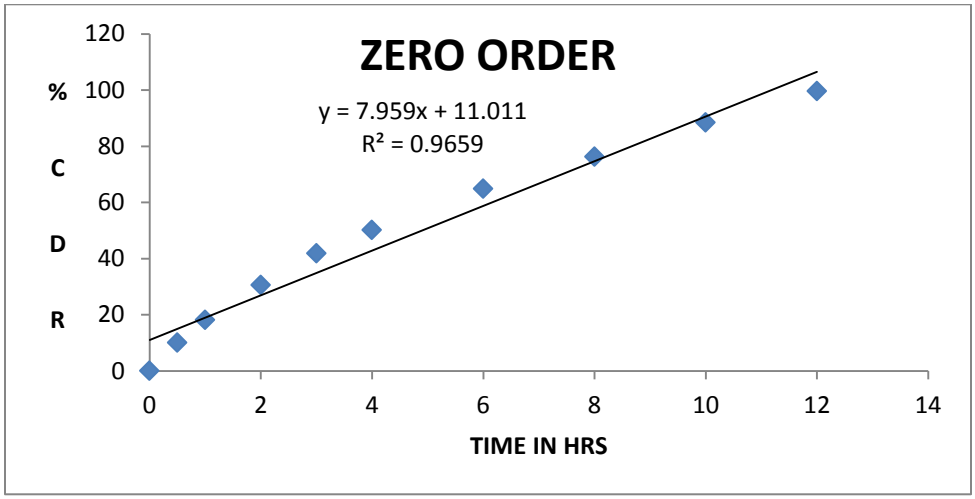
S.No	Time points (hrs)	Initial	Cumulative % Drug Release (mean) (SD) (n=3)					
			25C/60%RH			40C/75%RH		
			1st Month	3rd Month	6th Month	1st Month	3rd Month	6th Month
1	1 hour	7	6.65	6.51	6.50	6.72	6.44	6.42
2	2 hour	10.1	9.595	9.393	9.390	9.696	9.292	9.290
3	4 hour	30.5	28.975	28.365	28.360	29.28	28.06	28.02
4	8 hour	42.8	40.66	39.804	39.801	41.088	39.376	39.372
5	12 hour	55.9	53.105	51.987	51.982	53.664	51.428	51.422
6	16 hour	67.8	64.41	63.054	63.052	65.088	62.376	62.372
7	20 hour	89	84.55	82.77	82.72	85.44	81.88	81.84
8	24 hour	99.89	94.8955	92.897	92.894	95.894	91.898	91.892
9	Assay	99.7	94.715	92.721	92.701	95.712	91.724	91.720

Stability Data of Optimized Bilayer Formulation

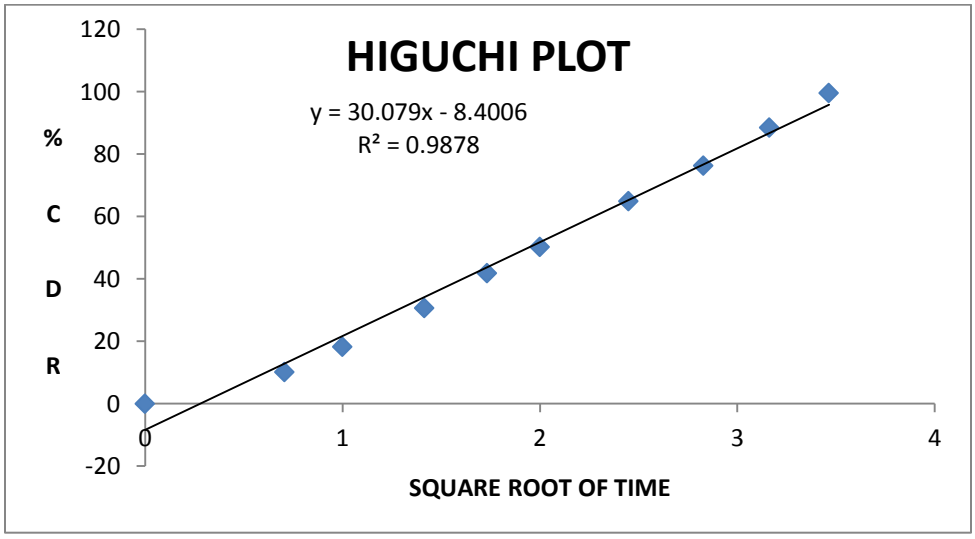
Kinetic Release Models

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.95899383	-0.150882018	30.07869811	1.010492678
Intercept	11.01067869	2.176885193	-8.400621175	0.98215819
Correlation	0.982792061	-0.878758474	0.99386347	0.790554881
R 2	0.965880235	0.772216456	0.987764597	0.62497702

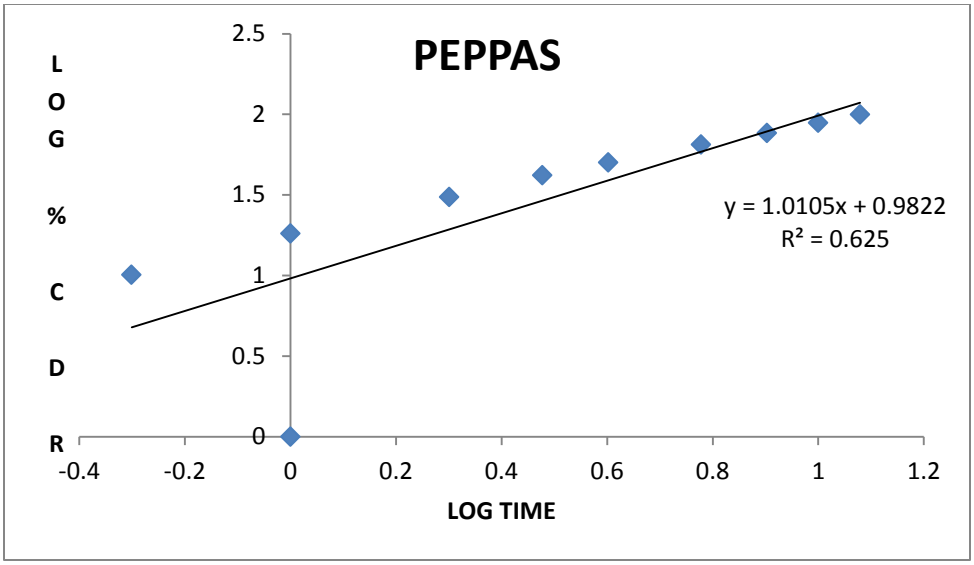
Release Kinetics for F7 Mucoadhesive Layer



Zero Order of Release of F7 Formulation Of SR Layer



Diffusion Type of Release model On F7 Formulation of SR Layer



Peppas Model for Release of F7 Formulation of SR Layer

First Order Release Model for F7 Formulation of SR Layer

DISCUSSION

The release profile of Lisinopril - Immediate release formulations F_1, F_2, F_3, F_4 F_5,F_6, F_7, F_8 and F_9 comprising various disintegrating polymers like ,croscarmellose sodium, crospovidone and sodium starch glycolate with similar concentrations is 70%, 75%, 78%, 74%, 78%, 80%, 79%, 95%, 100% respectively. F_9 shows maximum drug release at the end of 30 mins. Hence it was optimized and decided to develop for further formulation. The release profile of Glimepiride - Sustained release formulations F_1, F_2, F_3, F_4 F_5,F_6, F_7, F_8 comprising various rate retarding polymers like Xanthan gum, HPMC K100M with similar concentrations is 94.23%, 92.24%, 92.3% at 16^{th} hour to 20^{th} hour, 95.4%, 97.8%, 97.9% at 16^{th} hour to 20^{th} hour, 97.3%, 89.9% at 24^{th} hour. From all the formulations F7 released 97.3% of drug at 24^{th} hour with optimum mucoadhesive strength and hence it was optimized and decided to develop for further formulation.

SUMMARY

The Bilayer tablets containing Glimepiride SR and Lisinopril IR were successfully prepared by Wet

granulation and Direct compression method respectively. Various formulations were prepared and evaluated with an aim of presenting Glimepiride as sustained release and Lisinopril as immediate release for improving the patient's compliance. The physiochemical evaluation results for the blends of all trials pass the official limits in all tests including Angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner's ratio. The prepared blend for SR layer tablets and IR layer tablets were also maintained the physiochemical properties of tablets such as weight variation, hardness, thickness, friability. The optimized formulation F9 in IR formulations contains the average thickness of 2.4 mm, average hardness of 4.9 kg/cm^2, average weight of 150 mg, friability of 0.46% and disintegration time of 2 minutes. The optimized formulation F7 in SR formulations contains the average thickness of 2.64mm, average hardness of 5.9kg/cm^2, average weight of 250 mg, friability of 0.52%, and optimum mucoadhesive strength. The F7 formulation of Glimepiride Sustained Release Layer releases 10.5% in 1st hour but the remaining drug release was sustained up to 24 hours and F9 formulation of Lisinopril Immediate Release showed 99.92% drug release with in 30min. With the data of kinetic analysis, F7 formulation showed best linearity in zero order plots indicating that the release of drug is independent upon concentration and the mechanism from mucoadhesive layer follows Higuchi diffusion mechanism. The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations. Stability studies were carried out for 6 months. All physical and chemical parameters were found to be satisfactory based on the stability data.

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