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FORMULATION AND *IN VITRO* EVALUATION OF BILAYERED TABLETS OF CAPTOPRIL AND GLIPIZIDE AS SUSTAINED RELEASE AND IMMEDIATE RELEASE LAYER

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ABSTRACT

The Bilayered tablets containing Captopril SR and Glipizide IR were successfully prepared by direct compression method respectively. Various formulations were prepared and evaluated with an aim of presenting Captopril as sustained release and Glipizide as immediate release for improving the patient's compliance. The optimized formulation F4 in IR formulations contains the average thickness of 2.7mm, average hardness of 3.5 kg/cm^2, average weight of 150mg, friability of 0.36%. The optimized formulation F5 in SR formulations contains the average thickness of 2.67mm, average hardness of 5 kg/cm^2, friability of 0.45%. The F5 formulation which releases the Captopril in sustained manner in 1st hour it releases 7.0% but the remaining drug release was sustained up to 12 hours and Glipizide immediate release F4 formulation showed 99.9% drug release with in 30 min. With the data of kinetic analysis, F5 formulation showed best linearity in Zero order plot indicatingthat the release of drug from matrix tablet follows Non Fickian diffusion. The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations.

KEYWORDS

Immediate release, SR layer, Kinetic analysis and Bilayer tablet.

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INTRODUCTION

Various formulations were prepared and evaluated with an aim of presenting Captopril as sustained release and Glipizide as immediate release for improving the patient's compliance. The optimized formulation F4 in IR formulations contains the average thickness of 2.7mm, average hardness of 3.5 kg/cm^2, average weight of 150mg, friability of 0.36%. The oral route of administration still continues to be the most preferred route due to its manifold advantages including.

METHODOLOGY

Evaluation of Precompression Blend
Flow Properties
Angle of Repose
Bulk density
Tapped density
Compressibility index and Hausner ratio

EVALUATION OF TABLETS

Physical Appearance

The physical appearance including the measurement of size, shape, color, presence or absence of odour, taste etc.

Size and Shape

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Rochefriabilator.

Method

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

% friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test W_2 = Weight of tablets after test

Thickness

The thickness of the tablets was measured by vernier calipers. It is expressed in mm.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in Kg/cm^2.

Dissolution studies

In vitro Dissolution Studies for sustained release layer of Captopril

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 12hrs, at 50rpm, 0.1 N HCl was used as a dissolution medium for first 2 hours and 6.8 pH phosphate buffer for next 10hours. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free

dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 212nm.

Kinetic Analysis of Dissolution Data

$C = K_0 t$ (1)

Where, K_0 is zero-order rate constant

$LogC = LogC_0 - K_1 t / 2.303$ (2)

Where, K_1 is first order constant.

$Q = K_H t^{1/2}$ (3)

Where, K_H is the constant reflecting the design variables of the system.

$Q0^{1/3} - Qt^{1/3} = KHC\ t$ (4)

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the Hixson-Crowell rate equation.

The following plots were made using the *in-vitro* drug release data

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

Mechanism of drug release

Korsmeyer *et al*, (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer-Peppas model.

$M_t/M_\infty = Kt^n$ (5)

***In vitro* Dissolution Studies for immediate release layer of glipizide**

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 1Hr, at 75 rpm, 0.1N HCL was used as a dissolution medium. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 228nm.

Dissolution study of captopril and glipizide from bilayer tablet

The release kinetic of optimized Captopril and Glipizide from bilayer tablet was studied by conducting dissolution studies.

Dissolution tests performed using USP Type II dissolution apparatus and 900ml of 0.1N HCL at 37± 0.5°C for 2hrs.

5ml of sample were withdrawn at the intervals of every 30min, sampling was carried out and every time replaced with fresh 5ml of buffer.

After 2hrs, the 0.1N HCL buffer was replaced with 6.8pH phosphate buffer.

The absorbance of solution was recorded at 212nm and 228nm using buffer as blank.

The result was calculated as Percentage drug release of Captopril and Glipizide.

RESULTS AND DISCUSSION

***In vitro* dissolution studies for SR tablets**

Dissolution study (SR tablets)

Acidic Stage

Medium: 0.1N HCL

Type of apparatus: USP - II (paddle type) RPM 50

Volume: 900ml

Temperature: 37ºC± 0.5

Time: 2hrs

Buffer Stage

Medium: 6.8pH phosphate buffer

Type of apparatus: USP - II (paddle type) RPM 50

Volume: 900ml

Time: 12hrs

In vitro dissolution for SR tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphatebuffer for 10hrs.

***In Vitro* Drug Release Studies for SR tablets**

Discussion for *in-vitro* release of Captopril layer SR

From the table, it was confirmed that the F1, F2 of SR layer does not fulfill the sustained release theory up to 12 hrs. And also from the table, it was also confirmed that the formulationmade with HPMC K4M showed maximum drug release up to 12hrs.

Post-compression evaluation parameters for immediate release formulation

The results of the uniformity of weight, hardness, thickness and friability of the tablets are given in Table. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 148 to 151mg. The hardness of the tablets ranged from 3.3 to 3.9 kg/cm^2 and the friability values were less than 0.5% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from to 2.2 to 2.9mm. Thus all the physical attributes of the prepared tablets were found be practically within control.

Based on Dissolution profile, F4 and F5 formulations shows maximum release in 30mins, but formulation F4 was optimized as its drug release follows USP Limit

Bilayered tablet compression

After the batch was optimized in both immediate release layer (F4) and sustained release layer(F5). The optimized batch in both was compressed by using same ingredients.

Dissolution study (bilayered tablets)

Dissolution Medium for IR tablets Acidic Stage

Medium: 0.1 N HCL

Type of apparatus: USP - II (paddle type) RPM 50

Volume: 900ml

Temperature: 37ºC± 0.5

Time: 30min

In vitro dissolution for IR tablets were done in 0.1N HCL for 30 minutes.

Dissolution Medium for SR tablets

Acidic Stage

Medium: 0.1N HCL

Type of apparatus: USP - II (paddle type) RPM 50

Volume: 900ml

Temperature: 37ºC± 0.5

Time: 2hrs

In vitro dissolution for SR tablets were done in 6.8 pH for 12hrs.

Table No.1: Acceptance criteria of flow properties

S.No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	> 66	>38	>1.6

Table No.2: Limits for tablet weight variation test

S.No	Average weight of tablet (mg)	% Difference allowed
1	130 or less	10%
2	From 130 to 324	7.5%
3	> 324	5%

Table No.3: Mechanism of drug release

S.No	Diffusion exponent (n)	Overall solute diffusion mechanism
1	0.45	Fickian diffusion
2	0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
3	0.89	Case-II transport
4	n > 0.89	Super case-II transport

Table No.4: Evaluation of pre compression parameters for sustained release layer of captopril

Formulations	Angle of Repose(θ)	LooseBulk Density(g/ml)	TappedBulk Density(g/ml)	%Compressibility	Hausner's ratio
F1	27.31	0.34	0.39	12.82	1.15
F2	25.23	0.31	0.36	13.89	1.16
F3	26.09	0.37	0.42	11.90	1.14
F4	24.89	0.33	0.38	13.16	1.15
F5	26.54	0.32	0.37	13.51	1.16
F6	25.01	0.36	0.41	12.20	1.14

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

Table No.5: Post compression parameters for sustained release tablet

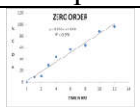
Formulations	Weight variation	*Hardness*	Thickness(mm)	Friability (%)
F1	201	4.6	2.80	0.38
F2	198	5.4	2.51	0.41
F3	200	5.1	2.61	0.37
F4	199	4.8	2.74	0.42
F5	201	5.0	2.67	0.45
F6	200	5.3	2.56	0.43

Table No.6: Cumulative percentage drug release of Sustained layer

Time(hrs)	F1	F2	F3	F4	F5	F6
Dissolution medium 0.1N HCL						
1	25.7	15.7	12.09	7.57	8.5	7.3
2	34.0	27.8	19.7	15.8	10.6	11.2
6.8pH phosphate buffer						
3	41.1	43.8	29.3	20.3	29.8	15.8
4	67.8	57.3	44.8	39.7	43.9	27.0
5	93.8	83.9	50.7	48.5	56.7	33.8
6	99.4	92.8	58.9	51.4	64.0	52.8
8	--	97.0	67.3	65.6	87.8	77.9
12	--	--	77.8	70.4	96.8	85.8

KINETIC RELEASE MODELS

Table No.7: Release kinetics for formulation for sustained release layer

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain VsT	%CDR Vs √T	Log C VsLog T
Slope	8.29272	-0.11128413	30.34942883	1.434981223
 Intercept	1.84832	2.156825431	-16.6360224	0.575980624
Correlation	0.988210211	-0.93644580	0.960563684	0.909061635
R 2	0.97655942	0.876930746	0.922682591	0.826393055

Evaluation parameters for immediate release layer of glipizide pre compression parameters

Table No.8: Pre-compression Parameters of Glipizide

Formulations	Angle of Repose(θ)	LooseBulk Density(g/ml)	TappedBulk Density(g/ml)	%Compressibility	Hausner's ratio
F1	26.09	0.37	0.42	11.90	1.14
F2	24.78	0.35	0.40	12.50	1.14
F3	25.45	0.32	0.37	13.51	1.16
F4	28.13	0.37	0.42	11.90	1.14
F5	27.46	0.34	0.38	10.53	1.12
F5	26.08	0.34	0.39	12.82	1.15

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

Table No.9: Post Compression Parameters for Immediate Release Tablets

Formulations	Averageweight (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability (%)
F1	150	3.3	2.9	0.36
F2	148	3.8	2.4	0.38
F3	151	3.6	2.6	0.42
F4	150	3.5	2.7	0.36
F5	149	3.9	2.2	0.40
F6	150	3.8	2.3	0.35

Table No.10: Dissolution for immediate release tablet of glipizide

S.No	Time inmins	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	5	26.2	23.0	18.9	36.9	35.4	30.4
3	10	35.3	39.7	30.2	60.8	66.9	59.4
4	15	75.8	76.4	58.9	85.7	79.4	70.2
5	30	89.0	87.9	77.9	99.6	99.3	86.5
6	45	98.7	99.0	87.2	--	--	99.5
7	60	--	--	96.3	--	--	--

Table No.11: Dissolution profile of bilayered tablet

S.No	Sampling time	Percentage drug released (%)	
		Glipizide	Captopril
1	15mins	86.5	3.2
2	30 mins	99.9	4.9
5	1hr	--	7.0
6	2hr	--	10.1
7	3hr	--	30.5
8	4hr	--	42.8
9	5hr	--	55.9
10	6hr	--	67.8
11	8hr	--	89.0
12	12hr	--	97.1

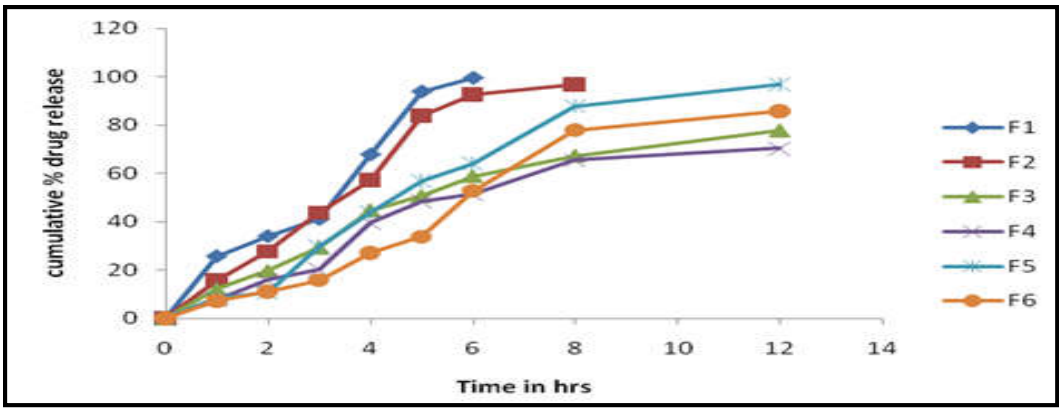


Figure No.1: Dissolution graph for sustained release formulation

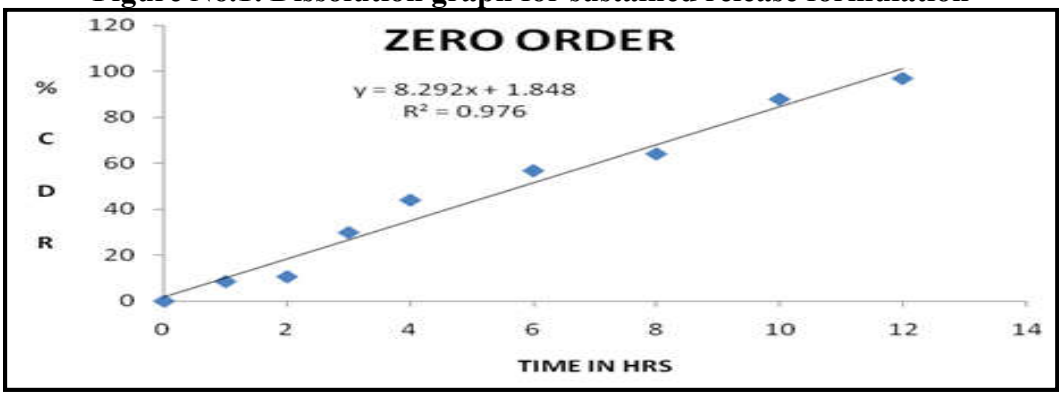


Figure No.2: Zero order release graph for F5 sustained release formulation

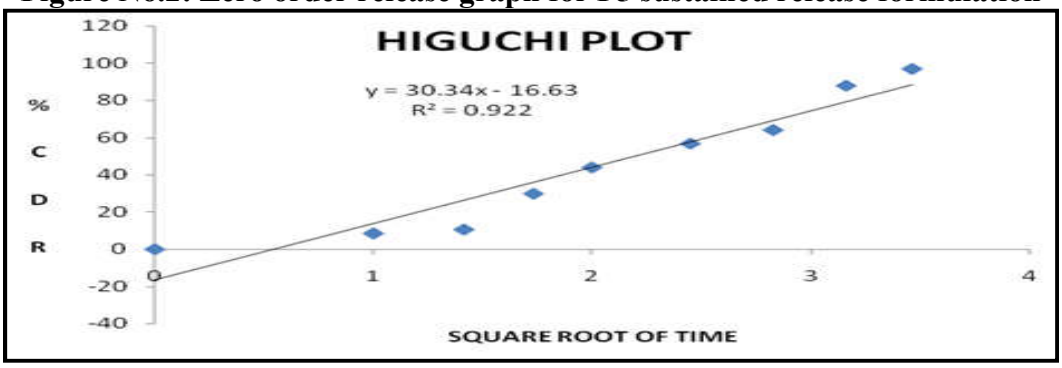


Figure No.3: Higuchi model graph for F5 sustained release formulation

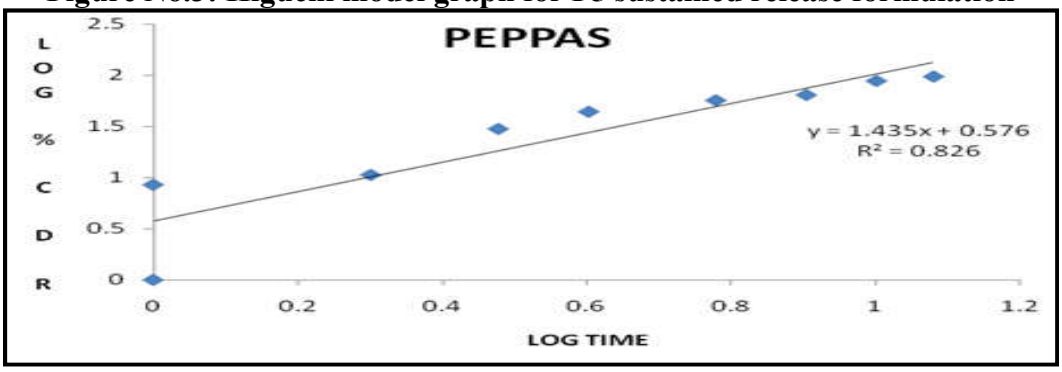


Figure No.4: Peppas model for F5 sustained release formulation

Figure No.5: First order release graph for F5 sustained release formulation

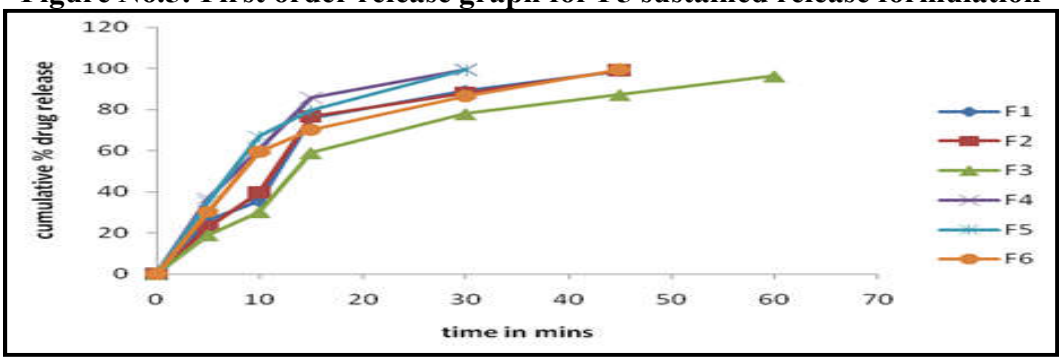


Figure No.6: Dissolution graph for formulations F1-F6

CONCLUSION

The Bilayered tablets containing Captopril SR and Glipizide IR were successfully prepared by direct compression method respectively. Various formulations were prepared and evaluated with an aim of presenting Captopril as sustained release and Glipizide as immediate release for improving the patient's compliance. The optimized formulation F4 in IR formulations contains the average thickness of 2.7mm, average hardness of 3.5 kg/cm^2, average weight of 150mg, friability of 0.36%.

The optimized formulation F5 in SR formulations contains the average thickness of 2.67mm, average hardness of 5 kg/cm^2, friability of 0.45%.The F5 formulation which releases the Captopril in sustained manner in 1st hour it releases 8.5% but the remaining drug release was sustained up to 12 hours and Glipizide immediate release F4 formulation showed 99.6% drug release with in 30 min. With the data of kinetic analysis, F5 formulation showed best linearity in Zero order plot indicating that the release of drug from matrix tablet follows Non Fickian diffusion.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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