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FORMULATION AND EVALUATION OF ASPIRIN AND CLOPIDOGREL BILAYER TABLETS

M. Lakshmi Prasanna*, K. Ambika, K. Vijayalakshmi,

K. Jhansi Bai, L. Mohitha and M.V. Sitamahalakshmi

VJ'S College of Pharmacy, Rajahmahendravaram,
3-124, Diwancheruvu, Andhra Pradesh-533 296, India.

ABSTRACT

Aspirin and clopidogrel are considered the most important oral platelets aggregation inhibitors. So it is widely used for treatment and prophylaxis of cardiovascular and peripheral vascular diseases related to platelets aggregation.In this study aspirin and clopidogrel were formulatedtogether as bilayer tablet system.Three different formulas of 75 mg aspirin were prepared by wet granulation method as immediate release layer anddifferent formulas of 75 mg clopidogrel were prepared as sustained release tablets by wet granulation (effervescent) method.The prepared bilayer tablets were further subjected to evaluation of their physical, floating properties and release behavior. Finally the kinetic study reflects acceptable shelf life for aspirin and clopidogrel

Keywords: Platelet aggregation inhibitors, wet granulation method, aspirin and clopidogrel.

INTRODUCTION

TABLET- A CONVENTIONAL DOSAGE FORM

Tablet is a solid dosage form in which powder, crystalline or granular form of drug is compressed in a disk or molded. Most of the tablet is administered orally

Oral route is the most convenient and extensively used route for drug administration.

Types of tablet

1. Tablet may be uncoated or coated. Uncoated tablets are chewable tablet, effervescent tablet, lozenge tablet, soluble tablet, and sublingual tablet. Coated tablets are enteric coated tablet, film coated tablet, implant, sugar coated tablet, and modified-release tablet. A broken section of a coated tablet shows a core which is surrounded by a continuous layer of a different texture.

The reasons for coating a tablet are:

a) to protection of the active ingredients from air, moisture, light,

b) to mask the unpleasant tastes and odor; and

c) to improve appearance

Chewable tablet

The tablet which is intended to be broken and chewed in between the teeth before ingestion. Antacid and vitamin tablets are usually prepared as chewable tablets. It is given to the children who have difficulty in swallowing and to the adults who dislike swallowing.

Effervescent tablet

The tablet that contains acid substances and carbonate or hydrogen carbonate that react rapidly in the presence of water to release carbon dioxide. Sodium bicarbonate, citric acid and tartaric acid are added to the active ingredients to make the tablet effervescent. This preparation makes the tablet palatable.

Lozenge tablet

The tablet that is intended to produce continuous effect on the mucous membrane of the throat. There is no disintegrating agent. The quality of the binding agent is increased so as to produce slow dissolution. Suitable sweetening (sugar), coloring and flavoring agents must be include in this formulation. Gum is used to give strength and cohesiveness to the lozenge and facilitating slow release of the active ingredient.

Soluble tablet

The tablet that dissolves completely in liquid to produce solution of definite concentration. Mouth wash, gargle, skin lotion, douche; antibiotic, certain vitamins, and aspirin are given in this formulation.

Sublingual tablet

The drug which is destroyed or inactivated within the gastrointestinal tract but can be absorbed through the mucosal tissue of the oral cavity is usually given in this formulation. The tablet is required to be placed below the tongue for the slow release of drug. But for immediate effect some medicaments are formulated in such a way to dissolve within 1 to 2 minutes. Nitroglycerin is prepared in this formulation.

Table 1: LIST OF MATERIALS AND SUPPLIERS

S.NO	INGREDIENTS	SUPPLIERS
1	Aspirin	Supplied By Pharma Train
2	Clopidogrel	Supplied By Pharma Train
3	Crosspovidone	SD Fine Chemicals, Mumbai
4	Pregelatanized starch	SD Fine Chemicals, Mumbai
5	HPMC K 100M	SD Fine Chemicals, Mumbai
6	Guar gum	SD Fine Chemicals, Mumbai
7	Xanthum gum	SD Fine Chemicals, Mumbai
8	MCC	SD Fine Chemicals, Mumbai
9	Sodium bicarbonate	SD Fine Chemicals, Mumbai
10	Red oxide of Iron	SD Fine Chemicals, Mumbai
11	Talc	SD Fine Chemicals, Mumbai
12	Magnesium stearate	SD Fine Chemicals, Mumbai

Table 2: FORMULATION TABLE
CLOPIDOGREL SUSTAINED RELEASE TABLETS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clopidogrel	98	98	98	98	98	98	98	98	98
HPMC K1000M	40	-	-	60	-	-	80	-	-
Guar gum	-	40	-	-	60	-	-	80	-
Xanthum gum	-	-	40	-	-	60	-	-	
MCC	78	78	78	58	58	58	38	38	38
Sodium bicarbonate	30	30	30	30	30	30	30	30	30
Talc	2	2	2	2	2	2	2	2	2
Mg.Stearate	2	2	2	2	2	2	2	2	2
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table 3: ASPIRIN IMMEDIATE RELEASE TABLETS

INGREDIENTS	IR1	IR2	IR3
Aspirin	7	7	7
Crospovidone	5	10	15
Pregelatinized Starch	10	10	10
Mcc	124	119	114
Red Oxide Of Iron	1	1	1
Mg. Stearate	1.5	1.5	1.5
Talc	1.5	1.5	1.5
Total Weight (Mg)	150	150	150

Table 4: LIST OF EQUIPMENT'S

S.NO	NAME OF THE EQUIPMENT	MODEL
1	Electronic weighing balance	Scale-tec
2	Frilator	Roche FriabilatorElectrolab, Mumbai
3	Laboratory oven	Dtc-00r
4	Compression machine	Cmd(Cadmach)
5	Tablet hardness tester	Pfizer Hardness Tester, Mumbai
6	UV	LabindiaUv 3000+
7	Dissolution apparatus	Electrolab TDT-08L
8	Vernier calipers	Cd-6"Cs

RESULTS AND DICUSSION

1. Construction of Standard calibration curve of Aspirin in0.1N HCL

The absorbance of the solution was measured at 272nm, using UV spectrometer with 0.1N HCL as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml

Table 5: Standard Calibration graph values of Itopride in 0.1N Hcl

Concentration (µg / ml)	Absorbance
0	0
2	0.128
4	0.242
6	0.349
8	0.474
10	0.603

Standard plot of Aspirin plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown figure

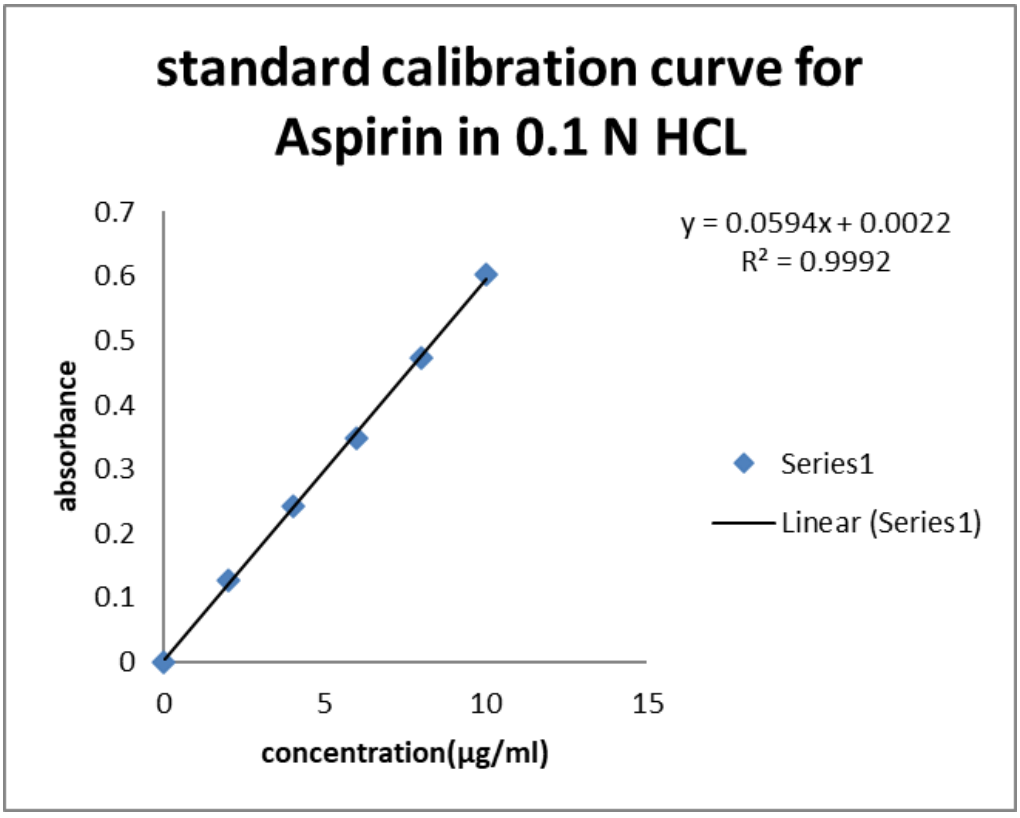

Fig. 1: Standard calibration curve of Aspirin in 0.1N Hcl

Inference

The standard calibration curve of Aspirin 0.1N HCl showed good correlationwith regression value of 0.999

2. Construction of Standard calibration curve of Clopidogrel in 0.1N HCL

The absorbance of the solution was measured at 238nm, using UV spectrometer with 0.1N HCl as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 10 to 30 µg/ml

Table 6: Calibration Curve

Concentration (µg / ml)	Absorbance
0	0
10	0.165
15	0.254
20	0.317
25	0.399
30	0.481

Standard Calibration graph values of Clopidogrel in 0.1N Hcl

Standard plot of Clopidogrel plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig.

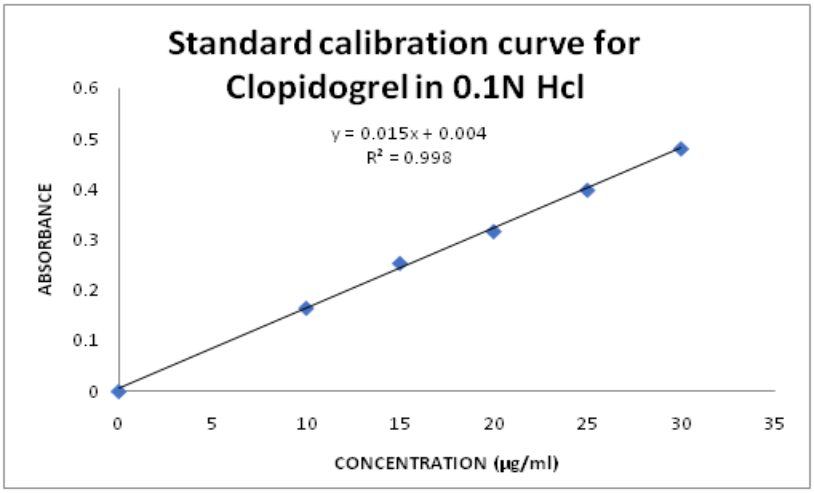

Fig. 2: Standard Calibration graph of Clopidogrel in 0.1N Hcl

III. Evaluation of Tablets

Table 6: Pre compression studies of clopidogrel Floating tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.43	0.52	17.3	1.41	12.62
F2	0.40	0.46	13.0	1.5	12.29
F3	0.50	0.58	13.0	1.16	11.58
F4	0.44	0.51	13.7	1.25	9.29
F5	0.39	0.47	17.0	1.56	18.23
F6	0.42	0.52	19.2	1.45	13.24
F7	0.36	0.39	7.60	1.0	11.03
F8	0.41	0.50	18.00	1.5	17.4
F9	0.39	0.48	18.00	1.23	11.96

Table 7:

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
IR1	0.58	0.63	7.93	1.08	27.72
IR2	0.59	0.67	11.94	1.13	33.45
IR3	0.54	0.61	11.47	1.12	32.83

Inference

- The bulk density and the tapped density for all formulations were found to be almost similar
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.06 to 1.14 resectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 26.82-33.13˚ which indicating passable flow (i.e. incorporation of glidant will enhance its flow)

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Table 8: Post compression studies of Aspirin IR tablets

Formulation Code	% weight variation	Thickness (mm)	% friability	% Drug Content	Hardness (Kg/cm^2)
IR1	pass	3.01±0.10	0.213	100.5 ±1.5	4.16 ±0.17
IR2	pass	3.07±0.14	0.158	99.8 ±1.2	4.05 ±0.15
IR3	pass	3.03±0.09	0.211	100.2 ±1.4	4.03 ±0.1

*Test for Friability was performed on single batch of 20 tablets

Inference:

- The variation in weight was within the limit
- The thickness of tablets was found to be between 3.01 – 3.07 mm.
- The hardness for different formulations was found to be between 3.45 to 3.56 kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.

Table 9: Post compression studies of Clopidogrel Floating tablets

Formulation Code	% weight variation	Thickness (mm)	%friability	%Drug Content	Hardness (Kg/cm^2)
F1	pass	3.16±0.11	0.22	102.0 ±1.1	4.78 ±0.17
F2	pass	3.53±0.15	0.15	101.3 ±1.5	5.13 ±0.15
F3	pass	4.06±0.057	0.12	99.8±1.3	5.58 ±0.13
F4	pass	5.1±0.1	0.43	101.7 ±0.8	5.28 ±0.04
F5	pass	3.03±0.05	0.32	100.6±1.2	4.83 ±0.05
F6	pass	3.83±0.15	0.14	98.9 ±2.1	5.20 ±0.02
F7	pass	4.93±0.05	0.20	99.2± 1.7	5.70 ±0.10
F8	pass	5.26±0.1	0.33	99.5± 1.4	5.53 ±0.05
F9	pass	3.02±0.2	0.18	99.2±1.3	4.99 ±0.02

Inference:

- The variation in weight was within the limit
- The thickness of tablets was found to be between 3.03 -5.26 mm.
- The hardness for different formulations was found to be between 4.78 to 5.70kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98.9 to 102 %.

Table 10: In vitro Buoyancy Studies of Clopidogrel floating tablets

Time (hrs)	% Drug released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	**0**	0	0	0	0	0
1	36	48	47	**18**	40	39	16	37	35
2	45	68	58	**26**	51	47	23	48	46
4	68	85	81	**47**	73	70	46	56	65
6	81	100	98	**66**	89	81	59	78	80
8	98	100	100	**78**	95	100	65	91	96
10	100	100	100	**89**	100	100	78	97	100
12	100	100	100	**100**	100	100	83	100	100

Table 11: In-vitro Dissolution results for formulation trails

Formulation Code	Floating lag time(sec) n = 3	Total floating time n = 3	Matrix Integrity upto 12 hrs. n = 3
F1	20 ± 0.51	Up to 10	-
F2	52 ± 0.21	Up to 6	-
F3	75 ± 0.61	Up to 8	-
F4	25 ± 0.71	Up to 12	+
F5	28 ± 0.81	Up to 12	+
F6	53 ± 0.51	Up to 6	-
F7	29 ± 0.31	Up to 12	+
F8	38 ± 0.81	Up to 12	+
F9	51 ± 0.71	Up to 8	-

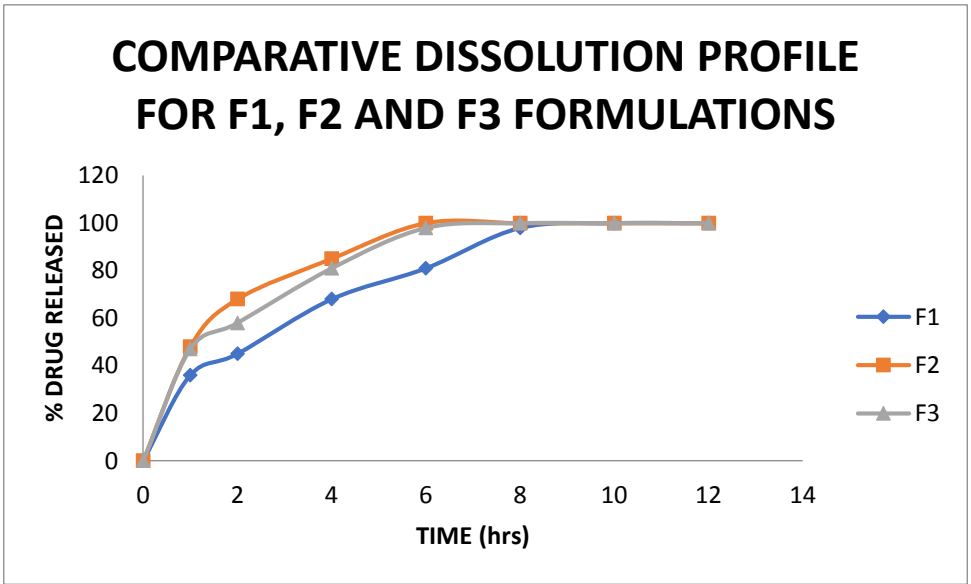

Fig. 3: Comparative dissolution profile for F1, F2 and F3 formulations

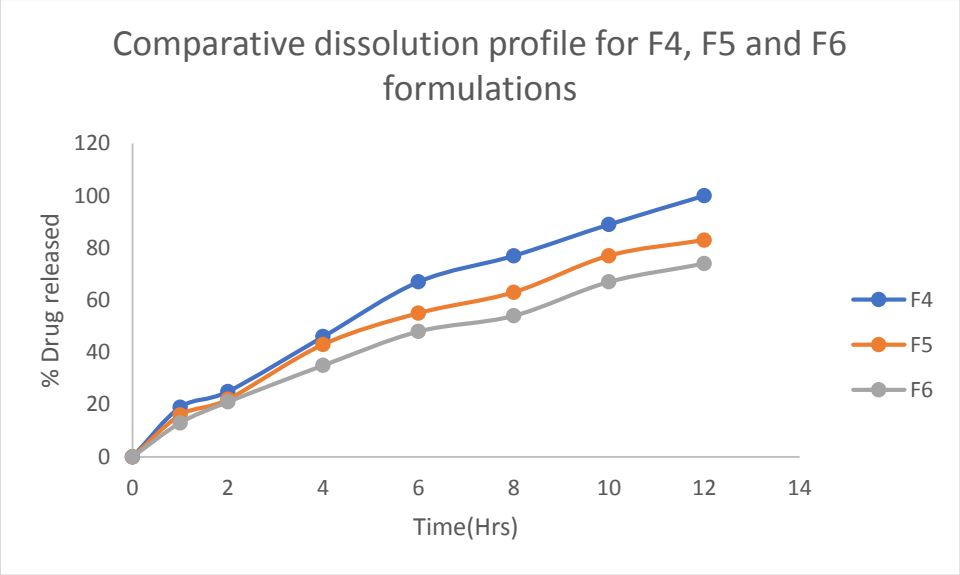

Fig. 4: Comparative dissolution profile forF4, F5 and F6 formulations

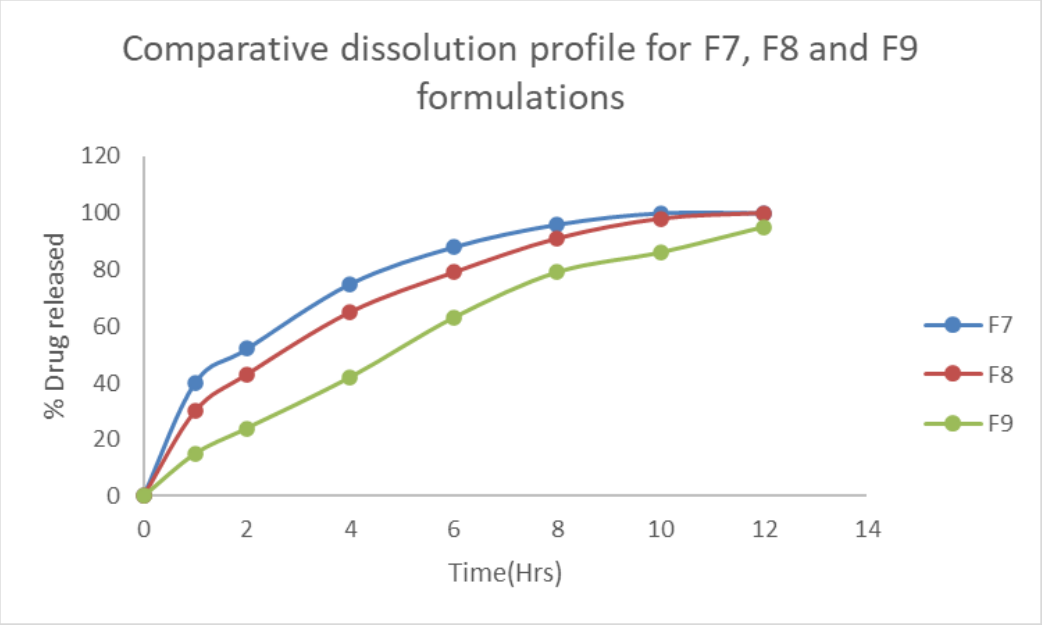

Fig. 5: Comparative dissolution profile for F7, F8 and F9 formulations

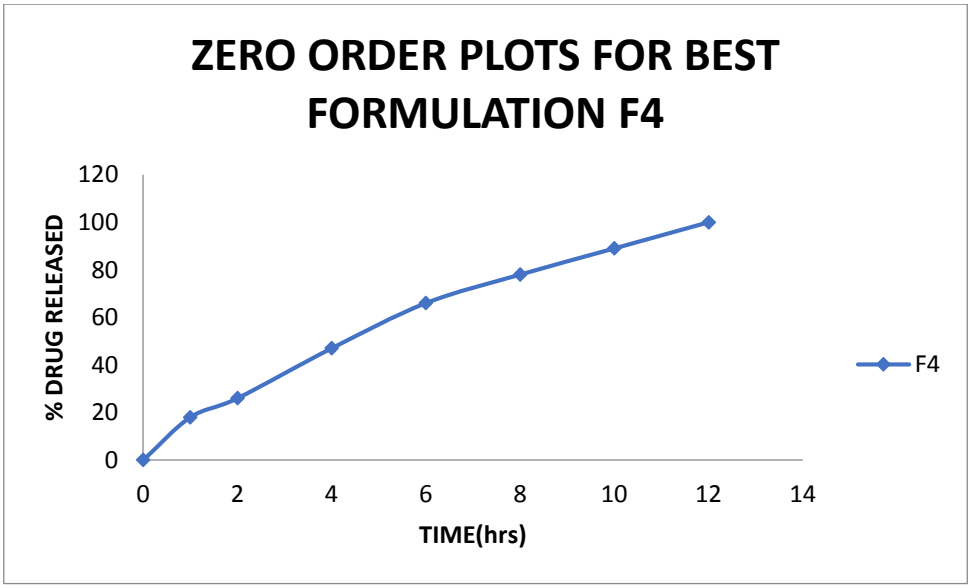

Fig. 6: Zero order plot for best formulation F4

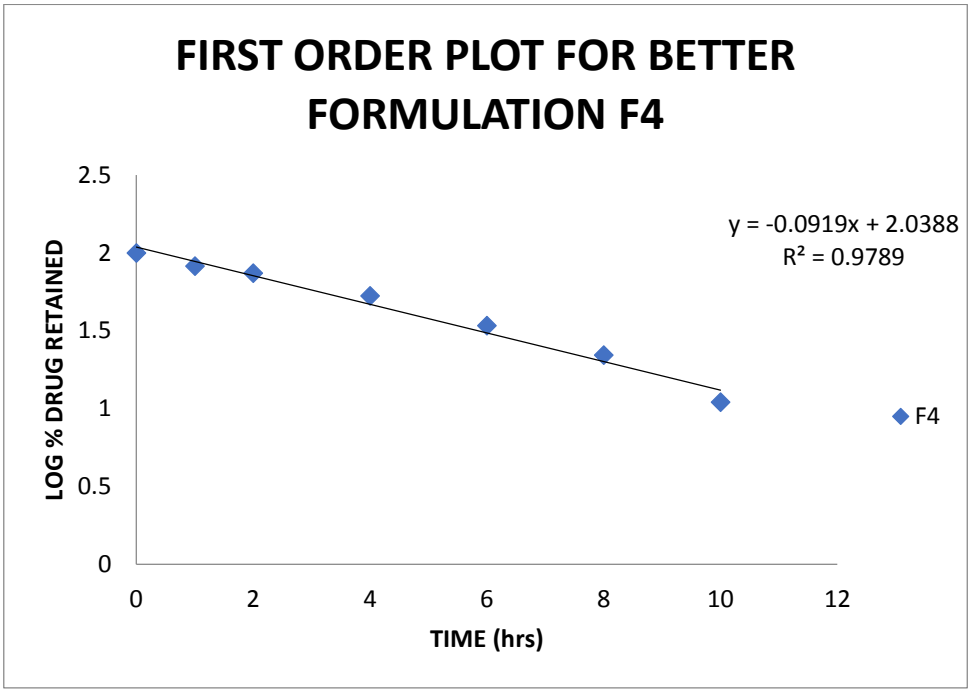

Fig. 7: First order plot for best formulation F4

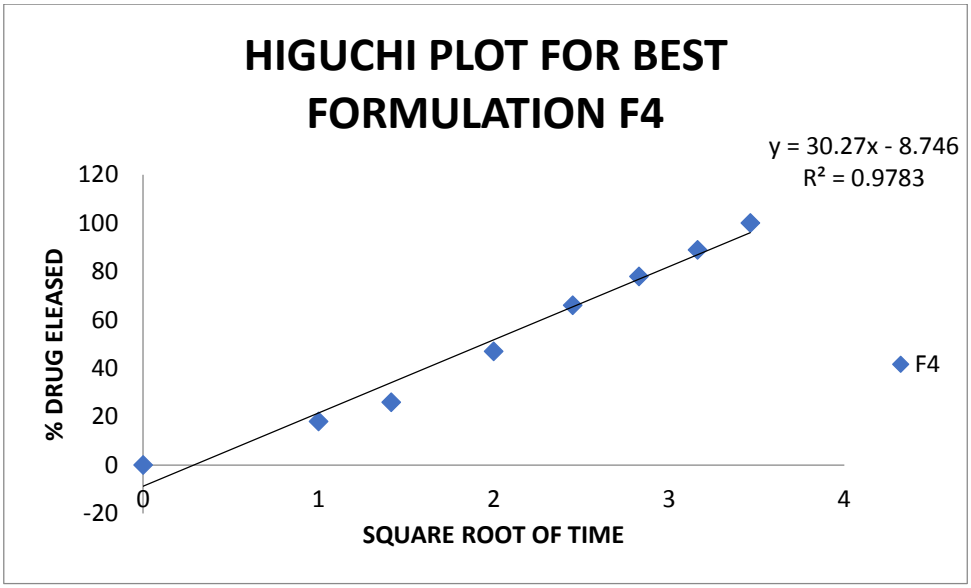

Fig. 8: Higuchi plot for best formulation F4

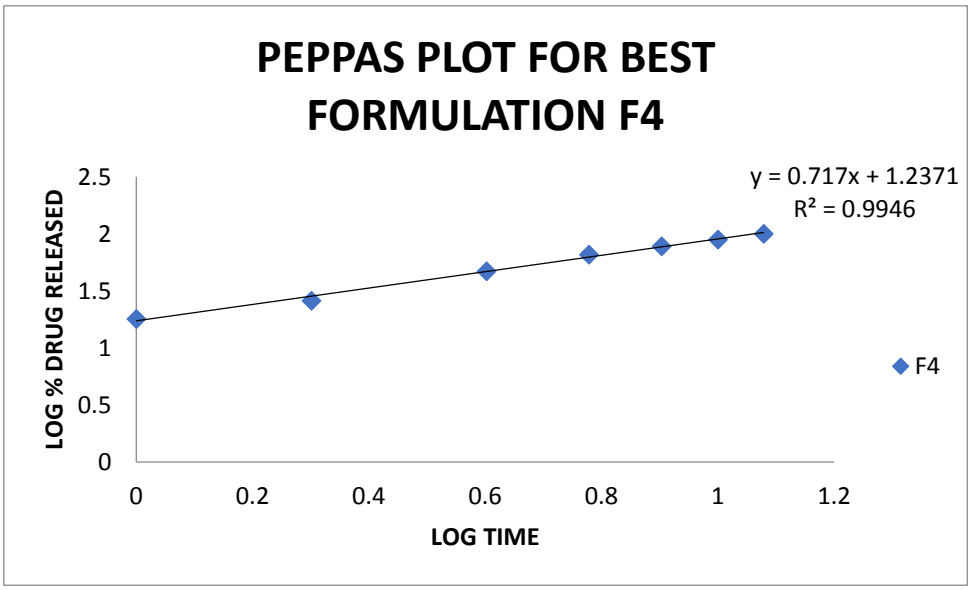

Fig. 9: Peppas plot for best formulation F4

Table 12: R^2 value and N result table

Formulation Code	r^2 values(Regression coefficient)				n value
	Zero order	First order	Higuchi	Peppas	
F4	0.969	0.983	0.964	0.994	0.723

Inference

- Among the different control release polymers HPMC K100M was showing highest drug release retarding capacity
- F4 was showing the satisfactory results and it was having better sustainability
- When we plot the release rate kinetics for best formulation F4 was following first order because correlation coefficient value of first order is more than zero order value.
- The F4 formulation diffusion exponent n value is in between 0.45 to 0.89 so they are following non ficki ananmolous diffusion model
- Higuchi plots for F4 formulation is having good correlation value so the drug is releasing diffusion mechanism

SUMMARY AND CONCLUSION

From the experimental data, it can be concluded that

1. Floating Tablets of Clopidogrel are formulated to increase gastric residence time and thereby improve its therapeutic efficacy.
2. HPMC K100M was respectively showed better Sustained drug release of Clopidogrel.
3. Synthetic polymers was showing more rate retarding drug release and matrix integrity,
4. When drug:polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases
5. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and *in vitro* drug release.
6. Formulation F4 gave better-controlled drug release and floating properties in comparison to the other formulations.
7. The release pattern of the F4 formulations was best fitted to Korsmeyer-Peppas model, Higuchi and first-order model.
8. The most probable mechanism for the drug release pattern from the formulation was non-Fickian diffusion or anomalous diffusion.
9. From immediate release tablets of Aspirin IR3 gave better release when compared to all formulations.
10. The angle of repose, bulk density, tapped density and compressibility index results shown that the formulation is suitable for direct compression method.
11. The drug release kinetics of the optimized bilayered tablets correspond best to Korsmeyer-peppas model and the drug release mechanism as per n value of Korsmeyer - peppas is anomalous (nonfickian) diffusion and the tablets showed no significant change in physical appearance, drug content or in vitro dissolution pattern.

Hence, it is finally concluded that, the bilayer tablet technology can be successfully applied for sustained release of Clopidogrel and immediate release of Aspirin.

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