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Research Article

FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS CONTAINING ANTI-PLATELET DRUGS

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Abstract: Various types of therapeutic intervention should be considered for prevention of ACS (Acute coronary syndrome), a clinical syndrome of acute cardiac ischaemia related to coronary artery disease (CAD). These include therapeutic interventions aimed at preventing coronary plaque formation (mainly primary prevention and treatment of risk factors), interventions aimed at preventing plaque rupture (with potential for an anti-inflammatory approach), and interventions aimed at interfering with the final step of thrombosis, i.e., formation of the clot. ASA has for a long time been recommended as a first approach to treating all types of ACS indications, the use of clopidogrel in combination with ASA was approved in Europe, US, and 89 countries worldwide. Clopidogrel in combination with ASA has been more recently approved in Europe, in the US and several other countries for the prevention of atherothrombotic events. This present work, which contains a fixed-dose combination of clopidogrel (75 mg) and acetylsalicylic acid (ASA) (100 mg) as film-coated immediate-release tablet formulations. The use of a fixed-dose combination tablet instead of the individual administration of the two compounds is expected to be more convenient to patients by limiting the number of tablets they need to take.

Key words: Acute coronary syndrome, coronary artery disease, thrombosis, Acetyl salicylic acid, Clopidogrel

INTRODUCTION

Now a days various developed & developing countries move towards combination therapy for treatment of various diseases & disorders requiring long term therapy such as ACS, CAD, hypertension & diabetes. Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects minimized, a low-dose combination of two different agent reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other. Using low dosage of two different agents minimizes the clinical & metabolic effects that occur with maximal dosage of individual component of the combined tablet & thus dosage of the single component can be reduced[1]. Oral route of drug administration has wide acceptance and of the drugs administered orally in solid dosage forms represents the preferred class of products. The reasons are Tablets and Capsules represent unit dosage form in which one usual dose of drug has been accurately placed. By comparison liquid oral dosage forms such as syrups, suspensions, emulsions, solutions, and elixirs are usually designed to contain one dose medication in 5-30ml. Most of the mortality and morbidity associated with non-ST-segment elevation acute coronary syndromes (ACS) arises from disruption of atheromatous plaques, followed by platelet aggregation and thrombus formation. Aspirin is the most commonly prescribed antiplatelet agent, which is known to reduce the risk of fatal and nonfatal myocardial infarction in patients with unstable angina. Clopidogrel, a different antiplatelet agent, inhibits platelet aggregation induced by adenosine diphosphate, thereby reducing ischaemic events. Combining clopidogrel with aspirin may therefore have an additive effect as each act via a different inhibitory pathway. The main undesirable side effects of aspirin are gastrointestinal ulcers, stomach bleeding, and tinnitus, especially in higher doses.

So in order to minimize the side effects of aspirin in the gastric region the dose of aspirin was taken 100mg which does not cause the gastric irritation. The aim of the present study is to prepare a stable formulation of aspirin and clopidogrel tablets[2,3,6,7,8,9,10,11].

EXPERIMENTAL SECTION

Materials

Aspirin powder drug was given by the Suven life sciences, Clopidogrel bisulfate powder drug was given by the Orchid chemical labs, Mannitol, hydroxyl propyl cellulose, microcrystalline cellulose was given by the Signet chemicals, poly ethylene glycol 6000 was given by the Clariant chemicals, hydrogenated castor oil by Cosph care chemicals, colloidal silicon dioxide was

given by Gem corporation,Opadry pink was gifted by Colorcon, India.

Equipments

The powdered ingredients were blend and granulated in Double cone blender and Rapid mixing granulator manufacture by Sam Techno PVT.LTD, Roller compaction and Oscillating granulator using model PRC 100/25 and manufacture by Prism machinery, coating the table by using Neo cota manufacture by Neomachine. Finally packing of tablet by Elmach packer. Dissolution test was carried out by using Disso 2000 model of Labindia dissolution apparatuses. Aligent 1200 series integrated high performance liquid chromatographic system was used for assay, Disintigration test was done by TD20S model of tab machines, Friability test was carried by FTA20 of Thermonik.

Method of manufacturing:

Fourier transform infrared (FT-IR) studies[10,15,16] :

Fourier transform infrared (FT-IR) spectroscopy was employed to characterize the possible interactions between the drug and the excipients in the solid state on Perkin Elmer Spectrum GX (organic Chemistry Unit, IISc, Bangalore) by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000–400 cm^{-1}.

Clopidogrel Blend: (Dry Granulation)

Sifting: Sifted Clopidogrel bisulfate and mannitol together through mesh # 20. Microcrystalline cellulose and low substituted hydroxy propyl cellulose and lactose monohydrate , together passed through mesh # 20.The Polyethylene glycol and Hydrogenated castor oil through mesh # 20.

Dry mixing: Loaded the materials of Clopidogrel bisulfate, mannitol, hydroxyl propyl Cellulose, lactose monohydrate in rapid mixing granulator. Rapid mixing granulator is used for dry mixing of ingredients at 100 RPM for 5mints.In this processes challenges were take such as like at different times points 3, 5, 7 mints sample were collected and it determines the uniformity of mixing of ingredients.

Pre compaction lubrication: Transfer the dry mixing material in double cone blender and add hydrogenated castor oil (cutina HR). Lubricated for 5 mints and samples were collected and uniformity of mixing has been seen.

Roller compaction: Transfer the pre lubrication material in to roller compactor to form slugs. In this processes challenges were taken such as like roller speed, vertical and horizontal feed of screw and roller pressure and they were kept constant over the process and the slugs were passed over1.0mm screen mesh which was fixed on oscillating granulator and the granules were collected. pass the granules through # 60 meshes.

Blending: Microcrystalline cellulose and colloidal silicon dioxide were taken and added to the granules and Blend the material for 20 mints. In this stage challenges were taken at different time point such as like 10, 15, 20 mints sample were collected to know the blend uniformity.

Lubrication: Load the above material, polyethylene glycol and hydrogenated castor oil were added and it was lubricated for 5 mints. Samples were drawn for 5 mints and pooled sample 100mg was also collected to check the water content.

Aspirin Blend(Direct Compression)

Sifting: Sifted Aspirin and Citri acid anhydrous together through mesh # 30. Microcrystalline cellulose, Starch and Lactose anhydrous, together passed through mesh # 40.

Mixing: Mix all the excipients for 5mins.

Lubrication: Lubricate the above mixture with stearic acid for 2mins and study PSA.

Compression: Finally the lubricated blend was transfer into bilayer tablet compression machine with 12mm SC punches with Aspirin as first layer and Clopidogrel as second layer. Compression was done at speed of 15±2 RPM.

Coating: The uncoated tablet was coated with ophadry pink solution till the average tablet weight gains 2.5±0.5%w/w of core tablet weight. After coating, the tablets were collected and sent for analysis to check whether they are meeting the specifications.

Characterization of formulation blend[13,14]

The formulation blend was characterised by Bulk density, Tapped density, Angle of repose, Carr's index, Hausner ratio.

Evaluation of prepared tablets

Weight variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

Hardness: Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Thickness: Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Friability (F): Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were

dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

Assay by HPLC :

10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in suitable ethanol. The solution was filtered and diluted suitably. Further dilutions were done suitably to get a concentration of 10 µg/ ml with buffer pH 1.2.The drug content was analysed by HPLC at 235 nm.

Stability study[17]:

An accelerated stability study was conducted by storing tablets in amber bottles at 25oC/60%RH and 40oC/75%RH. The content of the drugs and the dissolution of the drug from the bilayer tablets were tested monthly for three months.

In-Vitro drug release:

Preparation of 0.1N HCL (pH 2.0) :

pH 2.0 Buffer:

1. 0.2M kcl – Dissolve 14.91g kcl in 1000mL
2. 0.2M Hcl- dissolve 17.5mL of Hcl in 1000mL
3. 2.0pH buffer- 250mL of 0.2M kcl and 65mL of 0.2M Hcl and make up the volume upto 1000mL with water and adjust pH to 2.0 with 0.2 Hcl and Kcl.

Dissolution test:

Chromatographic condition:

Column develosil Ods, 150*46 mm, Flow rate 1mL/min, Wavelength 225nm, Column temp 25^{0}c, Run Time 10min, Injection Volume 5 microlitre.

Dissolution conditions: Clopidogrel:

Medium Acid buffer, PH 2.0, Volume 1000ml, Temperature 37^{o}C ± 0.5^{o}C, Apparatus USP type –II (paddle), RPM 50, Time interval 5, 10, 15, 30 and 45

Dissolution conditions: Aspirin

Dissolution parameters:

Medium Acetate buffer, PH 4.5, Volume 500ml, Temperature 37^{o}C ± 0.5^{o}C, Apparatus USP type –I (basket), RPM 100, Time interval 5, 10, 15, 30 and 45.

pH 4.5 Buffer:

2.99g of sodium acetate and 14mL of 2N acetic acid in 1000mL of purified water and adjust pH to 4.5 with 2N acetic acid(11.3mL of aceic acid in 1000mL).

Standard Stock:

Weigh and transfer about 50mg of clopidogrel working standard into 50mL flask, dissolve the mobile phase and make up the volume with mobile phase.

Standard preparation:

5mL of stock into 25mL of volumetric flask and make up the final volume with mobile phase.

Calculation:

%Drug release=

$$\frac{\text{test area}\times\text{std weight(mg)}\times\text{media volume}\times\text{test dilution}\times p\times 1000}{\text{Std.area}\times\text{Std.dilution}\times\text{abel claim}\times 100}$$

RESULTS AND DISCUSSION

Drug and Excipients Compatibility studies by FTIR spectrophotometer

The infrared spctra of pure drug and mixture of polymers and excipients were studied by FT IR spectroscopy using the KBR. Here spectral changes in the mixture are the basis for the determination of compatibility. The obtained spectrums of different formulation combinations were shown below. The spectral analysis of the pure drug and excepient mixture were done. From the graphs based on peaks and wave numbers that specific functional group, no additional peaks were obtained which indicates that there is no significant interaction between drug and excipients.

Table no.1. Characterisation of granules of Aspirin(A) blend and Clopidogrel(C) blend

S.No	Formulation	Bulk density g/cm^3	Tap density g/cm^3	Hausner ratio	Carr's Index(%)	Angle of repose(^{0})
1	A1	0.445±0.03	0.52±0.014	1.105±0.03	10±3.11	29.3±0.98
2	A2	0.45±0.01	0.52±0.014	1.1±0.0	12.45±3.74	27.75±1.48
3	A3	0.45±0.0	0.49±0.014	1.085±0.03	10.85±1.2	29.8±0.28
4	A4	0.571±0.02	0.63±0.028	1.13±0.07	11.47±0.56	27.1±1.69
5	C1	0.445±0.03	0.52±0.014	1.105±0.03	10±3.11	29.3±0.98
6	C2	0.45±0.01	0.52±0.014	1.1±0.0	12.45±3.74	27.75±1.48
7	C3	0.45±0.0	0.49±0.014	1.085±0.03	10.85±1.2	29.8±0.28
8	C4	0.455±0.02	0.53±0.028	1.15±0.0	14.1±0.56	27.1±1.69

Table No.2: Evaluation study for Bilayer tablet formulations

Formulations	Thickness(mm) n=10	Hardness(kp) n=6	Friability(%) n=10	Deviation in weight variation (mg) n=20	Disinteg--ration (mins)
F1	4.5 ± 0.1	16.7 ± 0.1	0.94±0.02	501.1±4.06	6.3±0.57
F2	4.7 ± 0.2	8.96±0.32	0.93±0.04	504.9±4.29	9±1
F3	4.75±0.05	11.93±0.51	0.67±0.01	505.6±4.30	5.75±0.95
F4	4.74±1.34	13.33±0.20	0.93±0.04	504.3±4.46	4.33±0.5

Formulation: Table No.3

TRIAL ⇨ / INGREDIENTS ⇩		F1(mg/tab) Film coating	F2(mg/tab) Film coating	F3(mg/tab) Film coating	F4(mg/tab) Film coating
CLOPIDOGREL BLEND					
INTRA GRANULAR					
1	Clopidogrel bisulphate	97.875	97.875	97.875	97.875
2	Mannitol	12.5	12.5	12.5	-
3	MCC	82	82	85.5	72.0
4	L-HPC	5.00	5.00	5.00	5.0
5	PEG6000	5.00	5.00	5.00	5.0
6	Colloidal silicon dioxide	-	-	-	2.5
7	Crosspovidone	-	-	-	12.5
8	Lacose anhydrous	-	-	-	17.5
9	Sodium stearyl fumarate			-	2.5
10	Cutina HR	2.5	2.5	2.5	-
EXTRA GRANULAR					
11	Colloidal silicon dioxide	5.00	5.00	-	2.5
12	Cutina HR	7.50	7.50	2.50	4.0
13	Aerosil200	-	-	5.00	-
14	Sodium stearyl fumarate	-	-	-	4.5
15	crosspovidone	7.5	7.5	9.0	-
ASPIRIN BLEND					
1	Aspirin	100.00	100.00	100.00	100.00
2	Avicel PH 112	22.5	30.00	110.00	110.00
3	Supertab 22 AN	80	105.00	-	-
3	Starch 1500	15.00	24.00	55.00	55.00
4	Citric acid anhyrous	-	7.00	9.00	9.00
5	Colloidal silicon dioxide	1.2	-	-	-
5	Stearic acid	-	-	1.50	1.50
6	Cutina HR	2.5	8.25	-	-

Formulation: Table No.4

Trial ⇨ Specification and Time Interval ⇩	F1	F2	F3	F4
Clopidogrel (min)				
10	17	19	21	40
20	75	75	54	65
30	85	87	85	90
45	89	97	95	98
60	91	108	100	99
Recovery	107	108	112	100
Assay	95	105	100.4	102
Aspirin(min)				
10	3	4	75	50
20	6	9	85	70
30	15	16	91	85
45	36	40	95	95
60	69	65	97	98
Recovery	100	100	99	100
Assay	95	95	94.8	99

***IN-VITRO* DISSOLUTION STUDY**

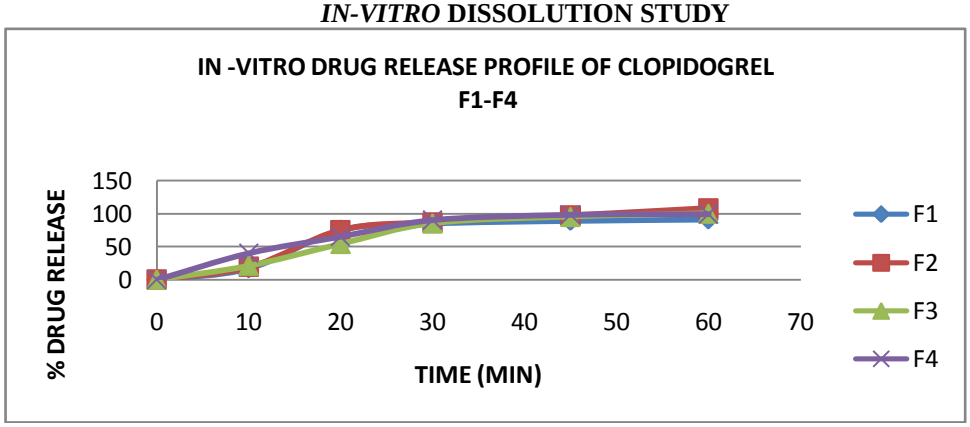


Fig 1: *In-vitro* dissolution clopidogrel in F1, F2, F3, F4

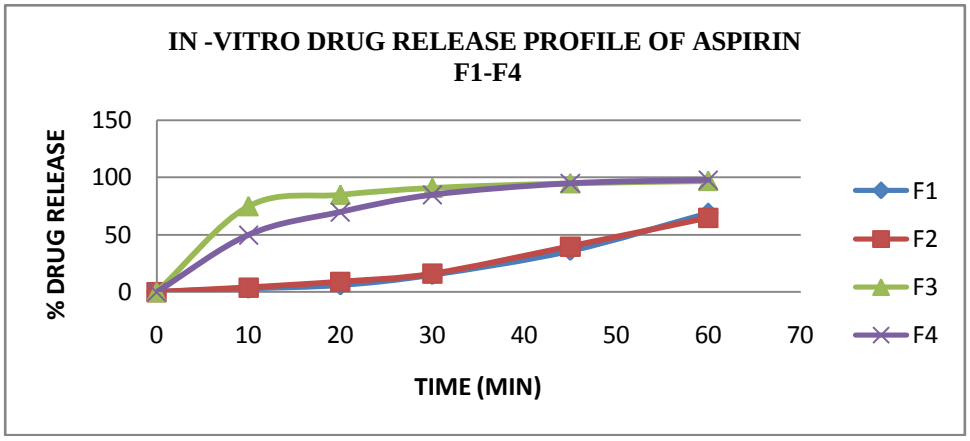


Fig 2: *In-vitro* dissolution Aspirin in F1, F2, F3, F4

Table-5: Stability data Formulation No. F3 and F4

SPECIFICATION TESTING PERIOD	DESCRIPTION		DT (Mins)		Hardness(Kp)		Assay	
	F3	F4	F3	F4	F3	F4	F3	F4
INITIAL	Pink round, SC, coated, 12mm	Pink round, SC, 12mm	4-5	5-6	7-9	7-9	A-94% C-100%	A-96% C-102%
1M, 60^{0}c /90%RH,	NC	NC	5-6	5-6	6-7	6-7	A-92% C-98%	A-96% C-102%
1M, 40^{0}c/75%RH	Slight acetic acid smell	NC	5-6	5-6	6-7	6-7	A-92% C-98%	A-96% C-102%
2M, 40^{0}c/75%RH	NC	NC	7-8	6-7	5-6	6-7	A-92% C-98%	A-96% C-102%
3M, 40^{0}c/75%RH	NC	NC	8-9	6-7	5-6	6-7	A-90% C-95%	A-96% C-102%

Table No.6. In-vitro dissolution data of F3 and F4 after stability

Trial Specification and Time Interval	F7	F8
Clopidogrel (min)		
10	15	35
20	35	60
30	50	75
45	75	98
60	80	99
Recovery	100	100
Assay	97	102
Aspirin(min)		
10	65	45
20	75	68
30	87	80
45	95	92
60	97	98
Recovery	99	100
Assay	94	99

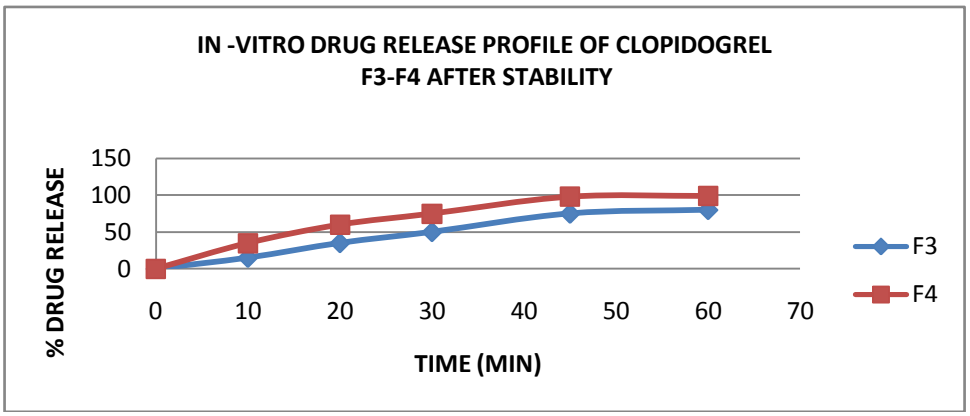


Fig 3: Invitro dissolution of clopidogrel in F3 & F4 after stability

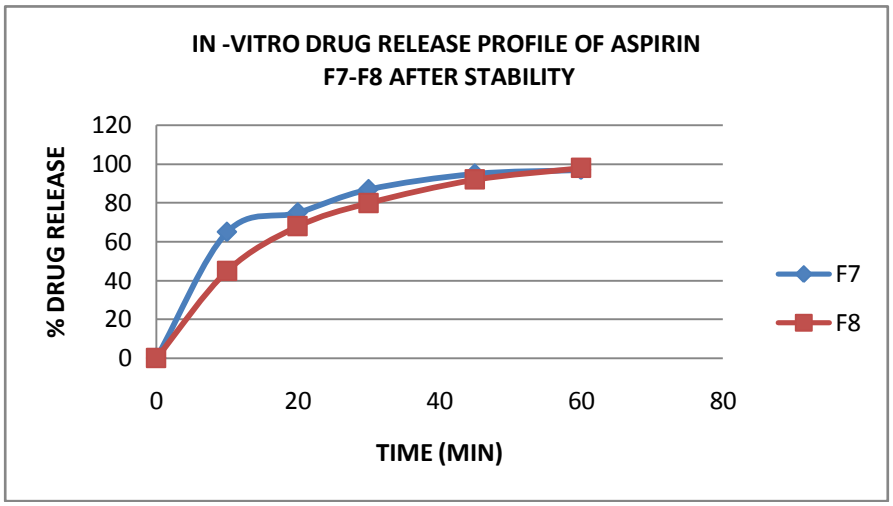
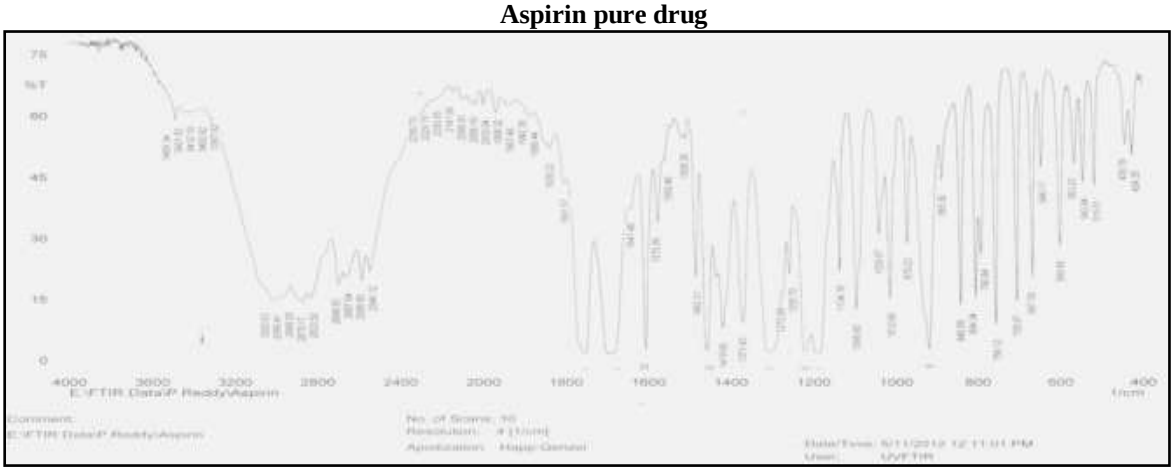


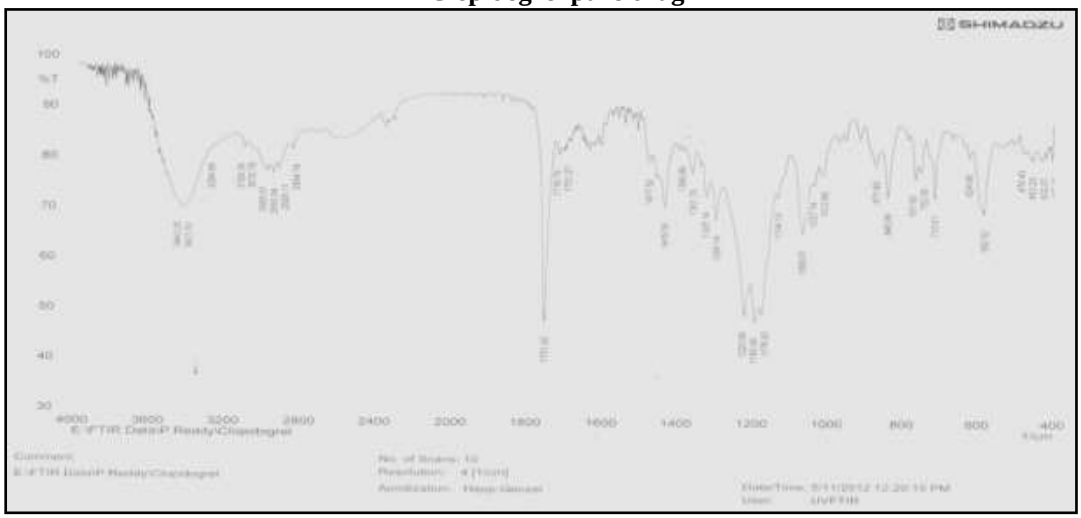
Fig 4: Invitro dissolution of aspirin in F3 & F4 after stability

FT-IR Chromatograms:

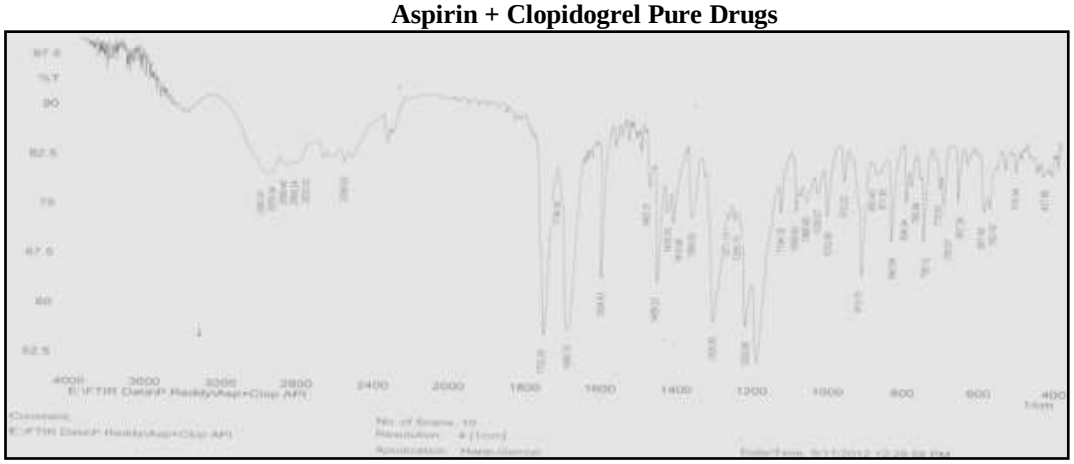
Aspirin pure drug



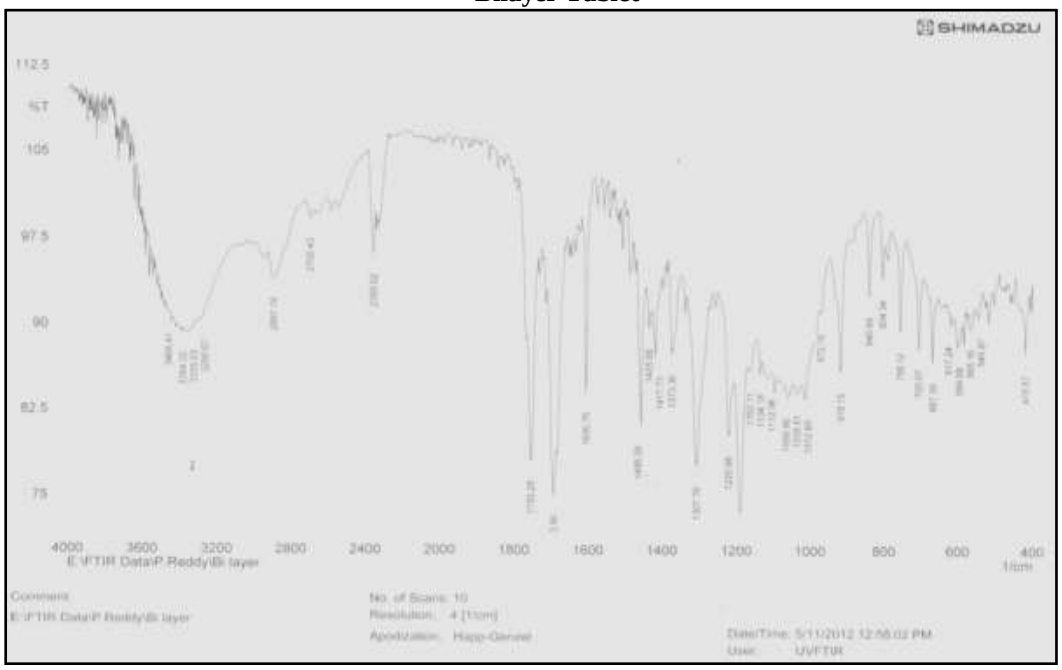
Clopidogrel pure drug



Aspirin + Clopidogrel Pure Drugs



Bilayer Tablet



CONCLUSION

The present research was carried out to develop a stable tablet of Aspirin and Clopidogrel using different excipients for immediate release. The present study was undertaken with an aim to design oral immediate release tablet of Aspirin and Clopidogrel. By drug excipients compatibility studies and FTIR studies, all the compositions were compatible. The preformulation studies of all excipients and blends were expressed the good packing and desirable flow property of blend. Based on the drug-excipient compatability study it was concluded that the single layer strategy was not possible because of stability problem of aspirin. Results of physical test of all formulation (F1 to F4) were within the prescribed limit which indicates strength and good handling properties of the prepared bilayer tablets. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances of same category and also for immediate release tablet to get synergistic effect. Results indicated that stability of the dosage form and release of the drug from the tablet was influenced by content of different excipients in the formulation. Formulation 8 is showing maximum drug release and good stability. So, bilayer tablets could be a potential dosage form for delivering Aspirin and Clopidogrel. Success of the *In vitro* drug release studies recommends the product for further in vivo studies.

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