AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Bilayered Tablets of Anti-Platelet Drugs

Krishna R. Raparla[1], YA Chowdary[*2] Sushma P[1]

1.Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Beside LMD police station, Karimnagar, Andhrapradesh, India – 505481

2.Department of Pharmaceutics, NRI College Of Pharmacy, Pothavarapadu village, Via Nunna, Agiripalli Mandal, Krishna Dist, Andhrapradesh, India – 521 212

ABSTRACT

A series of chalcones was synthesized by the Claisen-Schmidt condensation and the structures of 1-(4-bromophenyl)-3-phenylprop-2-en-1-ones were established with the help of IR and NMR study, then their effect was observed on bovine serum albumin. We have found that the synthesized chalcones interacted with bovine serum albumin irrespective of position and nature of substituent. 1-(4-bromophenyl)-3-(3-methoxyphenyl)-prop-2-en-1-one has been found to interact with BSA maximally.

Keywords: Bovine serum albumin, interaction studies, chalcones of *p*-bromoacetophenone.

*Corresponding Author Email: yarlagaddaac@yahoo.co.in

Received 26 November 2013, Accepted 01 December 2013

Please cite this article in press as: Chowdary YA. *et al.*, Formulation and Evaluation of Bilayered Tablets of Anti-Platelet Drugs. American Journal ofPharmTech Research 2014.

INTRODUCTION

Platelets have an important role in the normal haemostatic response.[1] Platelet aggregation is the main cause of cardiovascular events like angina pectoris, ischemic attack, stroke, coronary artery diseases in an individual. The dual antiplatelet therapy reduces the risk of cardiovascular events by inhibiting platelet aggregation. The combination therapy is required to reduce the risk of secondary events after attack. Combination therapy may offer several advantages such as the convenience of fewer pills a patient is required to take daily and reduced potential for medication errors. The combination drug therapy is developed to improve therapeutic efficacy, delay the development of resistance to the individual components of the combination, provides synergistic or additive potential of two or more drugs and to reduce the risk of secondary events. The dual anti-platelet therapy i.e., Aspirin and Clopidogrel bisulphate drugs are most commonly used in combination for management of patients with heart stroke and secondary events associated with it. The risk of secondary events after stroke is high and reducing the risk by administering these anti-platelet drugs (Aspirin and Clopidogrel) is very effective.[2]

For this purpose we have developed bilayered tablets containing two anti-platelet drugs. Developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayered tablet) has increased in the pharmaceutical industry, by promoting patient convenience and compliance.

Bilayered Tablet :

The term bilayered tablets refers to tablets containing subunits that may be either equivalent (homogenous) or completely different (heterogenous). Bilayered tablets allows for designing and modulating the dissolution and release characteristics.

Bilayered tablets are composed of two layers of granulation compressed together. Two layer tablets need fewer materials than compression coated tablets weigh less and may be thinner. It is appropriate 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.[3,4]

Need of developing Bi-layer tablets[5-7]

1. Controlling the delivery rate of either single or 2 completely different API'S.
2. To adapt the complete surface area available for API layer either by sandwiching with one or two inactive layers so as to attain swellable / erodible barriers for controlled release.

To separate incompatible API's with one another, to control the release of one layer by utilizing

the functional property of the other layer (such as osmotic property).

Advantages of Bilayered tablets[8-10]

- Good physical and chemical stability.
- Ease of correct dosing and low content variability.
- This formulation is also used to deliver separate two incompatible substances.
- Objectionable odour and bitter taste are often masked by coating technique.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
- Lighter and compact.
- High level of patient satisfactoriness.
- Incompatible drugs are given by separating these drugs by inert materials.

Disadvantages of Bilayered tablets[10]

- Difficult to swallow just in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

MATERIALS AND METHOD

Materials

Clopidogrel bisulphate was obtained as a gift sample from Aurabindo Pharma. Ltd, Hyd. Aspirin was obtained as a gift sample from Qualikem's Fine Chem Pvt Ltd, Vadodara. PEG-4000, Sodium starch glycolate and Aerosil was supplied by Central Drug House(P) Ltd. New Delhi. Camphor was supplied by Pawan chemicals, New Delhi. Xanthan gum was obtained from Shreeji Pharma International, Vadodara. HPMCK-4 was obtained as a gift sample from Nihal Traders (P) Ltd, Mumbai. Micro crystalline cellulose, Talc and Magnesium state was obtained from Accord Labs, Hyd. Hydrochloric acid and Sodium hydroxide was supplied from Virat Labs, Mumbai. Potassium dihydrogen ortho phosphate was obtained from HiMedia Laboratories Pvt. Ltd.

Methods

Drug Excipients Compatibility studies :

To investigate any potential interactions between the drug and excipients used, the FTIR spectra of pure Clopidogrel Bisulphate**,** and its physical mixture with PEG, Camphor and pure Asprin,

and its physical mixture with Xanthan gum, and HPMC K-4 were carried out using Bomem FTIR MB-II spectrophotometer.

Preparation of Bilayered tablet

In the preparation of Bilayered tablets direct compression method is employed for both the two layers of the dosage form i.e., immediate layer and the controlled layer. Clopidogrel Bisulphate is formulated as an immediate release layer and Aspirin was formulated as an controlled release layer.

Since Clopidogrel bisulphate is a class-II drug, its solubility is very low (i.e 0.0099 mg/ml). Therefore, "A Solid dispersion technique- Fusion method" and the Sublimation technique is employed to enhance its solubility.

Solid dispersion technique – Fusion method :

In this method the drug Clopidogrel Bisulphate and the PEG 4000 are mixed and heated until it melts. Melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final mass is then crushed, pulverized and sieved.

Sublimation technique :

In this technique volatile substance like camphor is used along with the other excipients to generate a porous matrix and later it is subjected to the process of sublimation. This volatile material is then removed by sublimation leaving behind a highly porous matrix.

Preparation of Clopidogrel Bisulphate immediate release layer :

All the ingredients were accurately weighed and are blended in a motar and pestle for 15 min and finally talc and magnesium stearate were added for the lubrication and glidant action. After thoroughly mixing these ingredients, the powder blend was passed through # 40mesh.

Preparation of Aspirin controlled release layer :

All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes then PVP K 30, micro crystalline cellulose and , talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 40mesh.

Compression of Bilayered tablet :

Optimization process is done for each and every layer in order to select the composition to form a bilayered tablet. In the preparation of bilayered tablets the first layer (immediate release) is placed in the die cavity which consists of one blend of the drug and punched with low

compressional force and then the second layer (controlled release) has been placed in the die cavity which consists of another blend of drug and it was compressed to form a bilayered tablet.

Immediate release layer controlled release layer Bilayered Tablet

Figure 1. Bilayered tablet

Table 1. Optimization of Clopidogrel Bisulphate immediate release layer

Formulation	F1	F2	F3	F4
Clopidogrel Bisulphate(mg)	75	75	75	75
PEG - 4000(mg)	75	37.5	--	--
Sodium starch glycolate(mg)	10	10	--	--
Camphor(mg)	--	--	75	37.5
Avicel(mg)	82.5	120	92.5	130
PVP K-30	--	--	--	--
Aerosil(mg)	2.5	2.5	2.5	2.5
Talc(mg)	2.5	2.5	2.5	2.5
Magnesium stearate(mg)	2.5	2.5	2.5	2.5
Total wt.	250	250	250	250

The optimized immediate release tablets F3 is formulated into bilayer tablet containing Aspirin as controlled release layer with two different polymers.

Table 2. Composition of optimized IR layer with Controlled release layer of Aspirin

Formulation	F5	F6	F7	F8	F9	F10
Immediate release layer						
Clopidogrel Bisulfate	75	75	75	75	75	75
Camphor	75	75	75	75	75	75
Avicel	92.5	92.5	92.5	92.5	92.5	92.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Controlled release layer						
Aspirin	75	75	75	75	75	75
HPMC K4	7.5	15	22.5	--	--	--
Xanthan gum	--	--	--	7.5	15	22.5
PVP K-30	7.5	7.5	7.5	7.5	7.5	7.5
Avicel	75	67.5	60	75	67.5	60
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total weight	425	425	425	425	425	425

EVALUATION

Evaluation of pre-compression parameters[11-14]

Angle of Repose :

The angle of repose of granules was firm by the funnel technique. The accurately weighed granules were taken in to a funnel. The peak of the funnel was adjusted in such a way that the tip of the funnel simply touched the apex of the head of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the subsequent equation:

$$\text{Tan } \theta = h/r$$

$$\theta = \text{Tan}^{-1}\, h/r$$

Bulk density determination:

Weighed amount of the powder (W) was taken in a graduated mensuration cylinder and volume (V_0) is measured and bulk density is calculated using the formula.

Bulk Density = weight of the powder/ volume of the powder

Tapped density determination :

Weighed amount of powder was taken in a graduated cylinder and therefore the volume is measured (V_0). The graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The ultimate reading was denoted by (V_f).

$$\text{Tapped density (TD)} = \frac{W}{V_f}$$

Hausner ratio:

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The connection between Hauser's ratio and flow property are given in the table below.

Hausner's ratio = Tapped Density / Bulk density

Compressibility Index :

The Compressibility Index of the powder blend was firm by Carr's compressibility index. It is indirectly associated with the relative rate of flow, cohesiveness and particle size. It is easy, quick and popular technique of predicting powder flow characteristics Carr's index was calculated by using the formula given below.

$$\text{Compressibility Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Evaluation of Post-compression parameter [15-17]

Weight variation :

This test is done by weighing 20 tablets randomly and average weight is calculated. Not more

than two of the individual weights deviate from the average weight by more than the percentage and none deviate by more than twice the percentage The mean and standard deviation were determined.

Tablet thickness and Diameter :

Thickness and diameter of tablets were important for uniformity of tablet size. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. Thickness and diameter were measured using vernier calipers. Tablet thickness should be controlled within a ±5%.

Hardness :

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability :

The friability test was carried out to evaluate the hardness and stability instantly to withstand abrasion in packing, handling and transporting. In Roche Friabilator in which twenty tablets were weighed (W_o) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w). The percent loss in weight or friability (f) was calculated by the formula given below.

$$\% \text{ Friabilty} = \boldsymbol{f = (1 - W/Wo)\, x\, 100}$$

Disintegration time :

The disintegration time was determined at 37±0.5^{0}C using disintegration test apparatus in 0.1 N HCl.

In vitro dissolution studies :

Dissolution test was carried out using USP apparatus type I rotating basket type. The stirring rate was 50 rpm. 0.1 N Hydrochloric acid was used as dissolution medium for the first two hours and it is replaced with the 6.8 pH Phosphate buffer for the remaining hours.900ml of dissolution medium was taken and was maintained at 37±0.5^{0}C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the drug Clopidogrel Bisulphate at 270 nm and Aspirin at 265 nm by using a double beam UV spectrophotometer (Shimadzu-2000). Each dissolution study was performed for three

times and the mean values were taken.

Drug release Kinetics :

To study the mechanism of Aspirin drug release from the Bilayered tablet, the release data were fitted into the following equations:

Zero order equation : $Q_t = Q_0 + k_0 t$ **;**

Where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution and k_0 is the zero order release rate.

First order equation : $\ln Q_t = \ln Q_0 + k_1$ **;**

Where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the solution and k_1 is the first order release rate.

Higuchi's equation : $Q = k_H t^{1/2}$ **;**

Where Q_t is the amount of drug release in time t, k_H is the Higuchi diffusion rate constant.

Koresmeyer peppas equation : $M_t / M_\infty = Kt^n$ **;**

Where M_t is the amount of drug release in time t, M_∞ is the amount of drug released after infinite time, k is kinetic constant and n is the diffusional exponent indicative of the drug release mechanism.

Study of similarity factor of test batch and marketed batch :

For the determination of similarity factor, marketed product Clopitab A-75 (Lupin Pvt.Ltd, India) was taken as the innovator and the in- vitro drug release of optimized formulation was compared with the marketed product. Comparison between innovators product and test batches was done using statistical factors called similarity factor (F2).The similarity factor (F2) was defined by CDER and FDA as the logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference products. This was calculated to compare the test with reference release profiles.

The data were analyzed by the formula as shown in below

F2=50 X log {[1-(1/n)n t=1(Rt-Tt)2]-0.5 X 100}

Stability studies

The optimized Bilayered tablets were packed in glass bottle and subjected to accelerated stability studies as per ICH guidelines (initial, 25^0 C ± 2^0 C / 60 ± 5% RH, 40^0 C ± 2^0 C / 75 % ± 5 % RH). The samples were withdrawn periodically (0, 30, 60 and 90days) and evaluated for the different physico-chemical parameters viz.., appearance, weight variation, thickness , hardness, drug content, and in-vitro drug studies.

RESULTS AND DISCUSSION

Drug Excipients Compatibility studies:

In this, IR spectra of Clopidogrel bisulfate, Aspirin, and optimized formulations of both the polymers were shown in the figure (2-4). It was observed that the spectrum of pure Clopidogrel showed a distinct C-O stretch at 1172 cm-1, C=O stretch at 1752 cm-1, C-H stretch at 715 cm-1 and for pure drug Aspirin C=C stretch at 1455cm-1, C=O stretch at 1749cm-1, C-O stretch at 1182 cm-1, O-H stretch at 2830 cm-1. The FTIR spectra of drugs with other excipients and the combination of drugs showed characteristic peaks within the range. The FT-IR studies revealed that Clopidogrel and Aspirin is compatible with the excipients used in the formulation and the peak results were shown in the table 3.

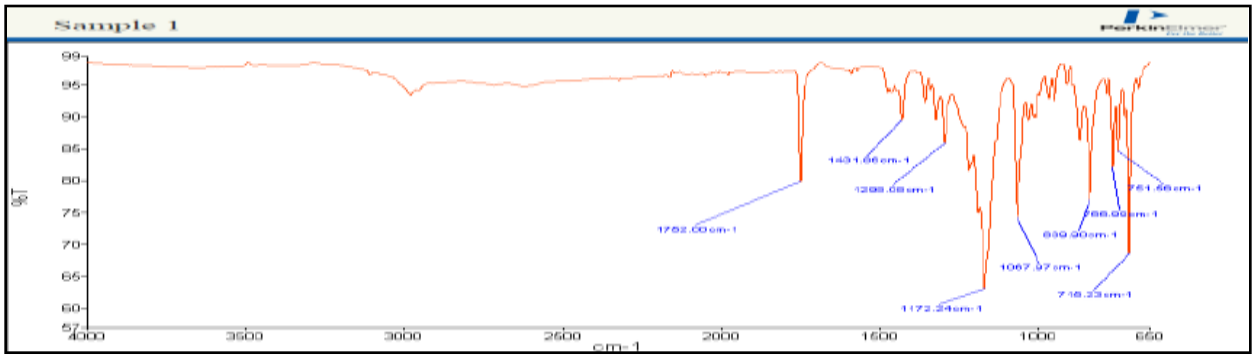

Figure 2. IR spectra of Clopidogrel bisulphate sample

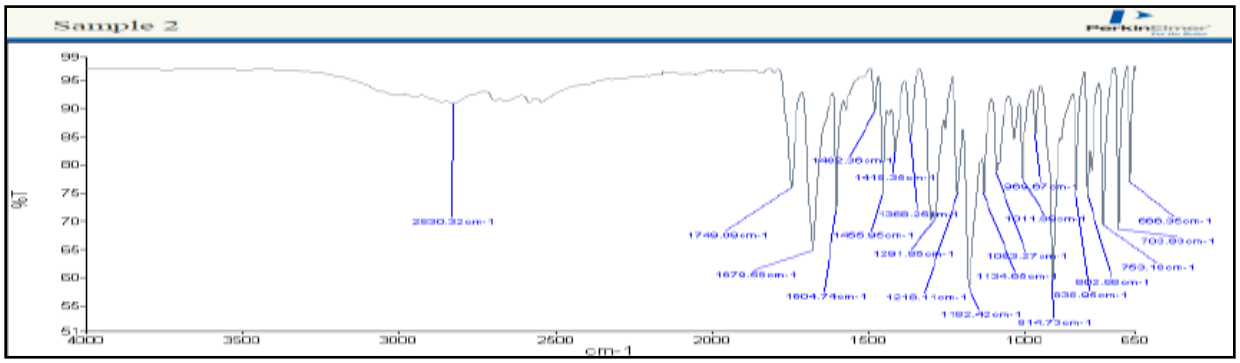

Figure 3. IR spectra of Aspirin sample

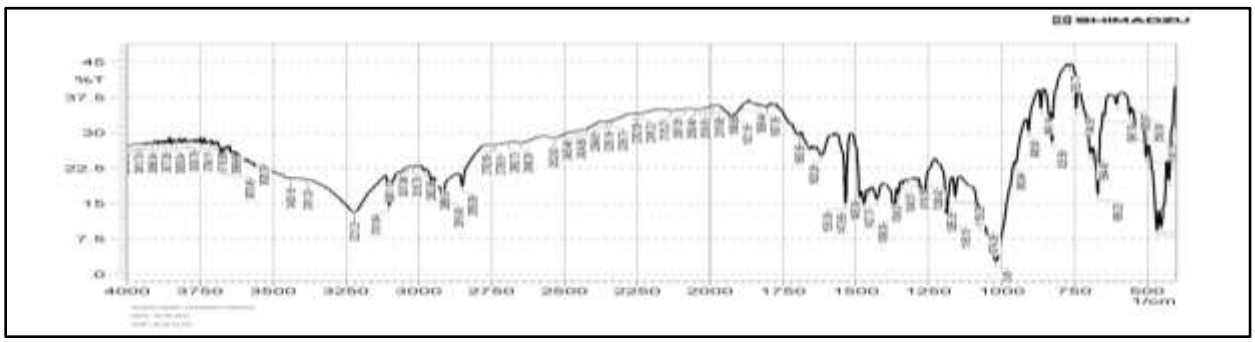

Figure 4. IR spectra of mixture of drugs with excipients

Table 3. Characteristic peaks of FTIR graphs

Bond & frequency(cm^{-1})	Pure drugs		Optimized Bi-layered tablet formulated with Xanthan gum (cm^{-1})
	Clopidogrel bisulphate(cm^{-1})	Aspirin (cm^{-1})	
C-O 1320-1000	1172	--	1009
C=0 1760-1665	1752	--	1748
C-H 675-900	715	--	753
C=C 1600-1400	--	1455	1458
C=0 1750-1730	--	1749	1748
C-O 1300-1000	--	1182	1288
O-H 3300-2500	--	2830	2891

Evaluation of post compression parameters :

The prepared bilayered tablets were subjected to various physical properties. All the formulations i.e., immediate release and controlled release layer were subjected to various physical parameters like thickness, weight variation, hardness, friability, disintegration. All the tablets compiled with the pharmacopoeial specifications for these tests. All these results were reported in the table 6.

Table 4. Physical properties of granules for Immediate release layer

Batch no	Angle of repose	Loose bulk density(g/ml)	Tapped density(g/ml)	Compressibility index(%)	Hausner's ratio	Drug content
F1	22.28 ±0.03	0.42 ±0.04	0.49±0.03	14.24 ±0.04	1.16 ±0.02	99.52±0.6
F2	24.65 ±0.05	0.46 ±0.05	0.53±0.05	13.24 ±0.03	1.15 ±0.03	98.85±0.5
F3	23.92 ±0.06	0.41 ±0.03	0.48±0.03	14.50 ±0.06	1.17 ±0.08	100.65±0.7
F4	25.45 ±0.04	0.45 ±0.04	0.52.±0.04	13.43 ±0.03	1.15 ±0.04	101.56±0.4

Table 5. Physical properties of granules for controlled release layer

Batch no	Angle of repose	Loose bulk density(g/ml)	Tapped density(g/ml)	C.I (%)	Hausner's ratio	Drug content
F5	26.35 ±0.05	0.45 ± 0.08	0.52±0.03	13.42 ± 0.04	1.15 ± 0.05	99.35±0.5
F6	28.52 ±0.04	0.42 ± 0.03	0.48±0.04	12.58 ±0.07	1.14 ±0.04	102.1±0.3
F7	25.86 ±0.03	0.47 ± 0.05	0.53±0.06	12.73 ±0.03	1.12 ±0.07	100.2±0.7
F8	26.3 ±0.08	0.42 ±0.06	0.48 ± 0.04	12.5 ±0.04	1.14 ±0.06	99.36 ±0.7
F9	28.6 ±0.05	0.49 ±0.05	0.57 ±0.05	14.0 ±0.05	1.16 ±0.04	101.45 ±0.4
F10	27.6 ±0.06	0.45 ±0.06	0.52±0.06	13.4 ±0.05	1.15 ±0.07	98.45 ±0.9

Table 6. Post compression parameters

Batch no	Weight in mg	Hardness	Thickness (mm)	Friability (%)	Disintegration time (sec)
F1	249.5 ±0.2	2.5 ±0.3	2.38±0.2	0.71 ±0.04	4′ 30″
F2	250.6 ±0.4	2.7 ±0.4	2.40 ±0.3	0.65 ±0.03	12′ 20″
F3	249.2 ±0.3	2.6 ±0.3	2.39 ±0.3	0.53 ±0.04	10′ 15″
F4	249.3 ±0.2	2.3 ±0.4	2.40 ±0.5	0.56 ±0.05	16′ 25″
F5	425.5 ±0.2	5.4 ±0.3	3.61 ±0.4	0.45 ±0.04	--
F6	426.2 ±0.3	5.5 ±0.3	3.58 ±0.2	0.56 ±0.03	--
F7	425.7 ±0.3	5.5 ±0.4	3.61 ±0.4	0.59 ±0.04	--
F8	425.6 ±0.5	5.5 ±0.5	3.59 ±0.5	0.65 ±0.03	--
F9	426.2 ±0.4	5.4 ±0.3	3.56 ±0.3	0.54 ±0.04	--
F10	425.4± 0.3	5.5 ±0.4	3.58 ±0.4	0.72 ±0.07	--

In-vitro dissolution studies :

The dissolution studies of the immediate release tablets which were formulated with PEG and Camphor (F1 – F4) were shown in the table 7. The formulation prepared with PEG (F1) shown maximum drug release in 15 min and the formulation prepared with camphor shown maximum release in 30 min and it matches the innovator as a result it was selected as the optimized formulation for the IR layer.

Both the methods i.e., Solid dispersion and Sublimation techniques were used to study the drug release pattern. Among both the techniques the desired drug release profile was achieved by sublimation technique. Hence formulation prepared with sublimation technique was selected as optimized formulation.

in-vitro drug release data prepared with optimized immediate release layer and controlled release layer formulated with HPMC K4 and Xanthan gum were shown in figure. 5 and 6. The F5 formulation which is composed of 10% HPMC K-4 shown a maximum drug release i.e., 97.4% over a period of 10 hrs and the formulation F8 which is composed of 10% xanthan gum shown a slow, controlled, maximum drug release i.e., 99.3% over a period of 10 hours. The drug release with both the polymers was found to be decreasing with the increase in the concentration of both the polymers. Hence the formulation F8 with a percent drug release of 99.3% was selected as the optimized formulation as it passed all the pharmacoepial limits.

Drug release kinetics from formulations F5 to F10 is shown in the table no. 8 and it obeys zero order drug release and the mechanism of drug release was found to be fikian diffusion by fitting the data to Higuchi and Kosmeyer-peppas equation.

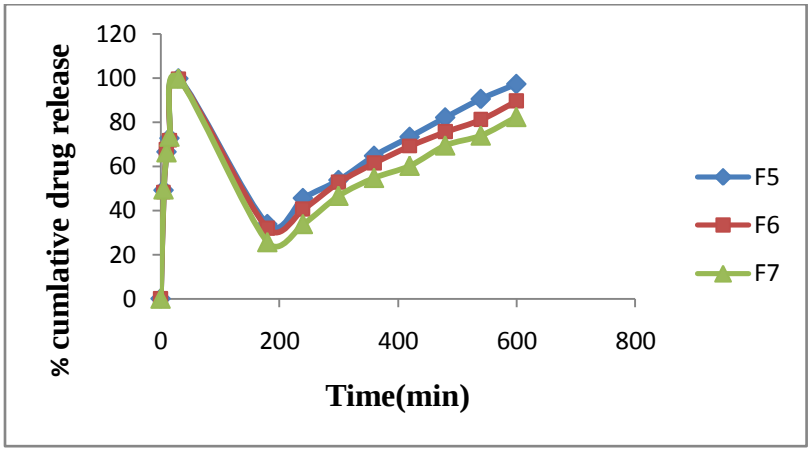

Figure 5. Plot showing Aspirin controlled release layer formulated with HPMC, Batch F-5, F-6, F-7

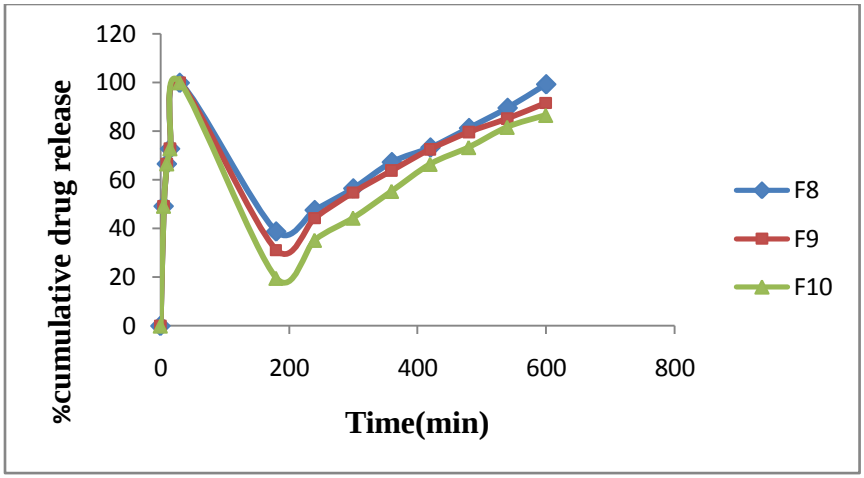

Figure 6. Plot showing Aspirin controlled release layer formulated withXanthan gum, Batch F-8, F-9, F-10

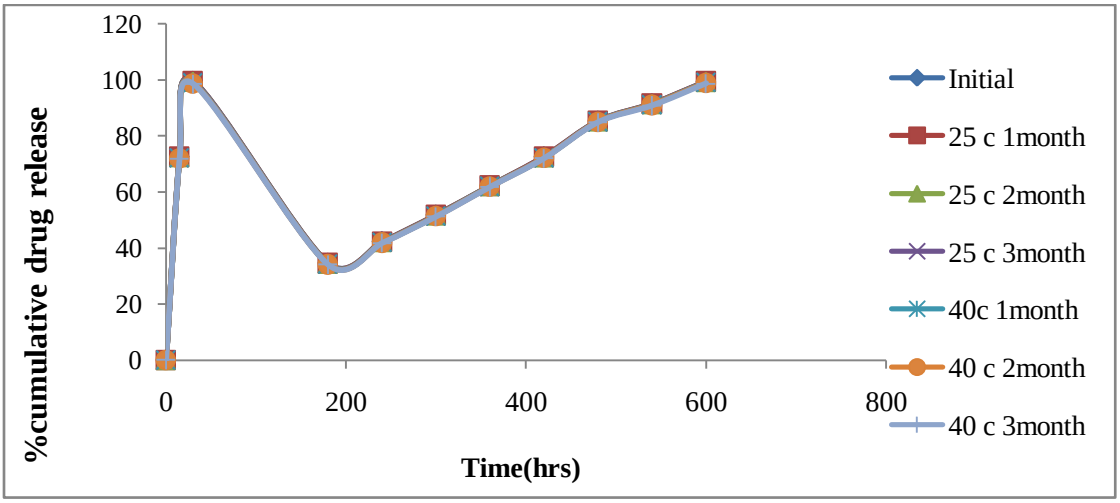

Figure 7. In- vitro release profile of optimized Bilayered (F8) tablets stored at various temperatures

Table 7 Dissolution of Clopidogrel bisulphate immediate release layer

Time(min)	% Cumulative Drug release			
	F1	F2	F3	F4
0	0	0	0	0
5	67.2	44.3	49.2	28.8
10	78.1	62.9	66.6	43.2
15	99.9	81.5	72.8	51.6
30	--	99.8	99.9	63.6
45	--	--	--	93.6
60	--	--	--	99.9

Table 8 Release rate kinetics of different formulations

Batch	Correlation co-effiecient (r2)			
	Zero order	Higuchi	Korsemeyer peppas	First order
F5	0.993	0.864	0.051	0.536
F6	0.987	0.870	0.063	0.572
F7	0.992	0.841	0.138	0.558
F8	0.994	0.866	0.054	0.366
F9	0.984	0.869	0.042	0.532
F10	0.988	0.786	0.167	0.563

Stability studies

Stability studies were carried out at (Initial 25 ± 2^0 C /60 ± 5% RH, 40± 2^0 C /75 ± 5% RH) for a period of 3 months for the best optimized formulation (F8). No significant changes occurred for the parameters like hardness, physical appearance, dissolution studies. All these indicates that the formulation was quite stable and the in- vitro release profile of optimized.

CONCLUSION

The present investigation was carried out to develop bilayered tablets of anti-platelet drugs containing 75 mg of Clopidogrel bisulphate as immediate release component and 75 mg of Aspirin as controlled release component for management of heart stroke and prevention of recurrent attacks in susceptible individual. The optimized concentration of disintegrants, polymers gave the desired release rate (zero order). The comparison of these bilayered tablets made with marketed formulation (Clopitab A-75), also suggests its suitability for this purpose.

REFERENCES

1. Kamath S , Blann A.D and Lip G.V.H. Platelets and atrial fibrillation. European Heart Journal 2001; 22 : 2233-2242.
2. Mahajan YY[2], Pawar TO, Vispute HK, Jadav SD, Pawar PB. Development and in-vitro evaluation of tablet in capsule drug delivery system for simultaneous administration of two antiplatelet drugs. Int. J. Pharma Res Bio-science 2012; 1(3) : 355-372.
3. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of

Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm Sci Tech 2008; 9(3): 818-827.

4. Guncel W.C, Compression-Coated and layer tablet. In, Lieberman AH(ed). Pharmaceutical dosage forms- tablets. Newyork: Decker; 1989; 274-284.
5. Panchal Hiten Ashok, Tiwari Ajay Kumar. A Novel Approach of Bi-layer Tablet Technology a review. IRJP 2012; 3(5): 44-49.
6. Kulakarni A, Bhatia. Development and evaluation of bi-layer floating tablets of atenolol and lovastatin for biphasic release profile. Iran. J. Pharm. Res. 2009; 8: 15-25.
7. Nirmal J, Saisivam S, Peddamma C, Muralidharan S, Nagarajan M. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem. Pharm. Bull 2008; 56: 1455-1458.
8. Sowmya C, Suryaprakash Reddy C, Tabasum S.G, Varma V. An overview on Bi-layer tablets. Int. J. Pharm Technology 2012; 4: 2143-2156.
9. Swati Aggarwal, Navneet Syan, Pooja Mathur. Bi-Layer Tablet Technology - Opening New Ways in Drug Delivery Systems: An Overview. Int. J. Res Pharma Bio-Medical Sci 2013; 4(1).
10. Ronak K. Gokani, Jalpa S. Paun. Bilayered tablet – An Emerging Trend. Int. J. Pharm Res Develop 2011; 04: 102-111.
11. Cooper J, Gunn. C. Powder flow and compaction. In, Carter SJ (ed). Tutorial Pharmacy. New Delhi ; 1986; 211-233.
12. Raymond C Rowe, Paul J Shaskey, Marian E Quinn. Handbook of excipients. 6th edition., 1-915.
13. Government of India. Ministry of Health and Family Welfare. Indian Pharmacopeia. vol II. The Controller of Publication, Ghaziabad; 2007: 457.
14. Government of India. Ministry of Health and Family Welfare. Indian Pharmacopoeia. vol III. The Controller of Publication, Ghaziabad; 2007: 1156.
15. Lachman L, Lieberman HA, Kaing JL. The Theory and Practice of Industrial Pharmacy. 3rd ed., Bombay:Varghese publishing house; 1987: 294, 336,413.
16. Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms. 2nd ed., New York : Marcel Dekker Inc; 1989; 195-229.
17. Martin A. Micromeretics. In: Martin A, Physical pharmacy. Baltimores: Lippincott Williams and Wilkins ; 2001: 423-54.