Formulation and Evaluation of Bilayer Tablets Containing Immediate Release Aspirin Layer and Floating Clopidogrel Layer

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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 formulated together as floating bilayer tablet system. Three different formulas of 75 mg aspirin were prepared by wet granulation method as immediate release layer; different disintegrants used to achieve rapid disintegration. Formula with crosscarmellose as disintegrant achieve rapid disintegration was selected for preparation of bilayer tablet.

Different formulas of 75 mg clopidogrel were prepared as sustained release floating layer by wet granulation (effervescent) method ;the physical and floating properties for compressed clopidogrel matrix were studied in addition to study the effect of polymer concentration(HPMC) ,and its combination with ethyl cellulose and carbapol ,effect of different diluents and effect of increasing sodium bicarbonate amount on the release from compressed matrix .

Formula prepared with HPMC and EC in a ratio of 1:1 was capable to retard the release of clopidogrel for 6 hours in addition to its good floating behavior and therefore selected to prepare bilayer tablets in combination with selected aspirin layer.

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.

Key words: Aspirin, Clopidogrel, Bilayer tablet, Floating tablet.

تصييغ وتقييم الحبوب الثنائية الحاوية الاسبرين كطبقة فورية التحرر واللكوبيدوكريل كطبقة طافية

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الخلاصة

يعتبر الاسبرين والكلوبيدوكريل من اهم مثبطات تجمع الصفائح الدمويه المعطاة عبر الفم ,لذا فهي تستخدم بشكل واسع للوقاية والعلاج من امراض القلب الوعائيه والامراض المحيطيه المرتبطه بتجمع الصفيحات الدمويه .في هذه الدراسه تم تصييغ الاسبرين والكلوبيدوكريل على شكل حبوب طافيه بنظام ثنائي الطبقه . تم تحضير ثلاث صيغ مختلفه للاسبرين بطريقه التحبيب الرطب كطبقه سريعة التفكك باستخدام مفككات مختلفه من اجل تحقيق التفكك السريع .لقد اظهرت النتائج ان الصيغه التي تحوي الكروسكارملوز كمفكك حققت اسرع وقت للتفكك وتم اختيارها لتصنيع الحبوب ثنائيه الطبقة .تم تحضير العديد من الصيغ المختلفه للكلوبيدوكريل بطريقة التحبيب الرطب (الفواره),تم دراسة الخصائص الفيزياويه وخواص الطوفان للحبوب المحضره كقالب بالاضافة لدراسة تاثير التراكيز المختلفه للبوليمر المستخدم (الهايدروكسي بروبيل مثيل سيللوز)وتاثير دمجه مع بوليمرات اخرى مثل الاثيل سيللوز والكاربابول وتاثير استخدام مخففات مختلفه اضافه لدراسة تاثير زيادة كميه بيكاربونات الصوديوم على تحرر الكلوبيدوكريل .

لقد وجد ان الصيغه المحضره من الهايدروكسي بروبيل مثيل سيل وز والاثيل سيللوز بنسبه 1:1لها القابليه على اعاقة تحرر الكلوبيدوكريل لست ساعات اضافه لامتلاكها خواص طوفان جيده لذا فقد تم اختيارها لتحضير الحبوب ثنائية الطبقة بالدمج مع الطبقه المنتقاة من الاسبرين.لقد تم اخضاع الحبوب ثنائية الطبقه المحضره لاختبارات الخواص الفيزياويه وخواص الطوفان والتحرر خارج الجسم .اظهرت دراسة حركيه الدواء عمر رف مقبول بالنسبة لكلا الاسبرين والكلوبيدوكريل.

الكلمات المفتاحية: الاسبرين ،الكلوبيدوكريل ، حبوب ثنائية الطبقة ،الحبوب الطافية .

Introduction

The oral route remains the most considered one for administration of drugs and tablets of various types still the ruling dosage form since years. Multilayered tablets are a form of modified release tablets [(1)] and they are designed for many reasons:

- To control the delivery rate of either single or two different active pharmaceutical ingredient(s).
- To separate incompatible active pharmaceutical ingredients from each other, to control the release of active pharmaceutical ingredients from one layer by utilizing the functional property of the other layer (such as, osmotic property).

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- To modify the total surface area available for active pharmaceutical ingredients layer either by sandwiching with one or two inactive layers in order to achieve swell able /erodible barriers for modified release.
- To administer fixed dose combinations of different active pharmaceutical ingredients, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery [(2).]

One of the most important aspects of layered tablets is gastro retentive system which is shown to improve bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [(3)].

Aspirin and clopidogrel are a well known platelets aggregation inhibitors; the combination of both drugs was shown to be synergistic because they have different mechanism of action.

Aspirin has a significant effect on platelets this action is mainly due to decrease in production of thromboxane A2 which consider the main promoter of platelets aggregation; aspirin in low doses (60-80mgdaily) can irreversibly inhibit thromboxane production [(4),] while clopidogrel interfere with the binding of adenosine diphoshate ADP to its receptors, ADP is the second most important trigger to platelets aggregation behind thromboxane A2 [(5).]

It appears that rapid release formulation of aspirin should be preferred in anti platelets therapy either alone or in combination with other anti platelets drugs [(6).]

Clopidogrel solubility is strongly pH dependent and it is very soluble and stable at pH value <3 [(7).] In addition to that clopidogrel has low oral bioavailability (50%), undergoes extensive first pass metabolism (85%) and frequent high doses are required to maintain the therapeutic level as a result, dose related toxic effects developed [(8).]

The goal of this study is to utilize bilayer tablet approach to administer aspirin as immediate release layer and clopidogrel as sustained release floating layer in an attempt to improve bioavailability and to get maximum therapeutic benefits by patients that need the combination of aspirin and clopidogrel in cases of in acute coronary syndromes, including acute myocardial infarction and unstable angina, and in coronary stenting.

Materials and Methods

Aspirin supplied by "SDI, Iraq", Carbapol (Goodrich,USA), Clopidogrel Powder (Zhejiang Menovo Pharmaceutical Co.,LTD,China), Croscarmellose (Hekma Drug Industry,Jordan), Ethylcellulose (EC) (BDH Chemicals ,Ltd, England) , Explo tab(BDH Chemicals, Ltd, England) Hydrochloric acid (BDH Chemical LTD, England) , Hypromellose USP(Metolose 90SH-4000SR) (HPMC4000) (Shin-Etsu Chemicals Co.Ltd., Japan) , Lactose(Riedel-deltaen /Germany), Microcrystalline Cellulose (Avicel PH 101)(Whatman intrnational , England), Polyvinylpyrrolidone (PVP)(Riedel De Haen AG Seelze, Honnover, Germany), Sodium Bicarbonate(Riedel-deltaen/Germany), Starch(Afco ,India), Talc(Afco ,India).

Table (1) summarizes three formulas to prepare aspirin immediate release layers by non aqueous wet granulation method. .A known weight of granules were mixed with calculated amount of talc powder for 5minutes then compressed to first layer of tablet using 9mm flat face punch tabletting machine.

Table 1: Different formulas of aspirin immediate release layer.

Ingredients in mg / Formula No.	Aspirin	Lactose	Explo tab	Croscarmellose	10% alcohol starch paste	Talc	Total wt .(mg)
Asp1	75	57	------	----------	15	3	150
Asp2	75	54	3	----------	15	3	150
Asp3	75	54	------	3	15	3	150

Evaluation of compressed aspirin immediate release Layer

The different prepared formulas of immediate release layer were compressed and their disintegration time was recorded. The disintegration time of the prepared tablets was measured using the disintegration apparatus and method as described in the USP, a disintegration media of 0.1 N HCl held at 37ºC.

The in vitro release study of each formula were conducted in USP dissolution apparatus (paddle)in 900 ml 0.1 N HCl solution as dissolution media at 37˚C, Samples of 5ml were withdrawn at different time intervals ,filtered and measured at the UV of maximum absorbance which is 230 nm .

Preparation of clopidogrel floating sustained release layer

Different formulas of clopidogrel floating controlled release layer were prepared as shown in table (2) using non aqueous wet granulation method. A known weight of granules was mixed with calculated amount of talc powder for 5minutes then compressed using 9mm flat face punch tabletting machine.

Table2: Different formulas of clopidogrel tablet as sustained release layer.

Ingredients In mg / Formula No	CLO	HPMC	EC	Carbapol	SodiumBicar.	MCC	Lactose	DCP	PVP	Talc	Total wt.(mg)
CL-1	75	70	-	-	17.5	156	-	-	17.5	14	350
CL-2	75	140	-	-	17.5	86	-	-	17.5	14	350
CL-3	75	210	-	-	17.5	16	-	-	17.5	14	350
CL-4	75	157.5	52.5	-	17.5	16	-	-	17.5	14	350
CL-5	75	105	105	-	17.5	16	-	-	17.5	14	350
CL-6	75	157.5	-	52.5	17.5	16	-	-	17.5	14	350
CL-7	75	105	-	105	17.5	16	-	-	17.5	14	350
CL-8	75	210	-	-	-	33.5	-	-	17.5	14	350
CL-9	75	210	-	-	8.75	24.75	-	-	17.5	14	350
CL-10	75	140	-	-	17.5	-	86	-	17.5	14	350
CL-11	75	140	-	-	17.5	-	-	86	17.5	14	350

Evaluation of compressed clopidogrel floating sustained release layer

The prepared formulas were subjected to following tests:

Friability test

The friability test was done for the prepared tablet using Roche friabilitor ,the friability was calculated as the percent weight loss.

Hardness

The hardness of six tablets from each of the prepared formulas was measured using Monsanto hardness tester**.**

Content uniformity test

Content uniformity test was done as described in USP, the amount of clopidogrel was determined by employing UV absorption at the wave length of maximum absorbance at about 270nm.

Determination of floating lag time and floating duration

The floating lag time and floating duration was determined by placing tablets in a 100-ml beaker containing 0.1 N HCl .

Dissolution test

The in vitro release study of each formula were conducted in USP dissolution apparatus (paddle)in 900 ml 0.1 N HCl(pH1.2)solution as dissolution media at 37˚C, Samples were measured at the UV of maximum absorbance which 270 nm.

Variables affecting release profile from clopidogrel floating matrix tablets

Effect of polymer concentration

Formulas CL-1, CL-2, CL-3, were used to study the effect of polymer concentration on the release profile .These formulas (CL-1, CL-2, CL-3) contains HPMC in concentration of 20%, 40%, 60%w/w respectively.

Effect of polymer combination and ratio

Formulas CL- (4,5,6,7) were used to study the effect of polymer combination and how the ratio of these combination will affect the release from the floating matrix tablet . Formulas CL-4,CL-5 contain EC in a ratio of 3:1and 1:1 respectively while formulas CL-6,CL-7, contain Carbapol in a ratio of 3:1and 1:1 respectively.

Effect of the amount of sodium bicarbonate

Different amounts of sodium bicarbonate were used in formulas CL- (3,8 ,9) ,Formula 8 has no sodium bicarbonate in its composition ,formula 3 contain the standard amount used in the study which is 5%,while formula 9 contain half the amount present in formula 3.T he effect of increasing the concentration of sodium bicarbonate on the release were studied.

Effect of diluent type

Formulas CL- (2, 10, and 11) were used to study the effect of different types of diluents on the release profile of the prepared matrix tablets. All three formulas have the same concentration of diluents but different types of diluents used .These fillers are Microcrystalline cellulose ,Lactose ,Dibasic calcium phosphate.

Bilayer tablets preparation

Optimized formula of aspirin and clopidogrel was selected for formulation of bi-layer tablet. The required weight from each layer which is equivalent to active ingredients of both aspirin and clopidogrel were individually weighed, the clopidogrel layer manually filled into the 9mm die and compressed slightly so that flat rough surface required for adhesion of the aspirin layer was created. Then aspirin granules was poured into the die above the clopidogrel layer; both layers finally were subjected to the final compression; Bilayer tablet of aspirin and clopidogrel was ejected from the die.

Evaluation of bi-layer tablet

Determination of friability, hardness, floating lag time and floating duration were done as per the procedures previously mentioned in the evaluation of clopidogrel floating controlled release layer.

Content uniformity test:HPLC analytical method

The assay was done by High Pressure Liquid Chromatography (HPLC) method according to the following condition. Column: C18 250X4.6MM, 5µm: Mobile phase: was acetonitrile: 50mM potassium dihydrogen phosphate buffer: methanol (50:30:20v/v, PH3). Flowrate: 1.5ml/min, Detection: UV, 240nm.

Drug release study

The in vitro release study of the prepared bilayer tablet were conducted in USP dissolution apparatus (paddle)in 900 ml 0.1 N HCl (pH1.2)solution as dissolution media at 37˚C,samples were analayzed by HPLC method.

Kinetic study

The effect of temperature on the degradation rate of aspirin and clopidogrel in the optimized floating bilayer tablet was studied at three different temperatures: 40˚C, 50˚C, 60˚C for 16 weeks .Samples were taken at different time intervals and analyzed for aspirin and clopidogrel content by HPLC method.

Results and Discussion

Evaluation of compressed aspirin immediate release layer

The disintegration times of the compressed aspirin immediate release layers shown in table (3); all the prepared formulas show fast disintegration time but formula Asp3 is the fastest one and it is selected as first layer for preparation of bilayer tablets.

Table 3: The disintegration time of the compressed aspirin immediate release layer

Formulas	Disintegration time (min)
Asp1	12
Asp2	7
Asp3	4

All the prepared formulas of aspirin immediate release layer show rapid and complete release of aspirin within short period of time ;formula Asp3 showing rapid disintegration and complete release of aspirin within 30 minutes therefore it is selected for preparation of bilayer tablets ,the results of dissolution test are shown in figure (1).

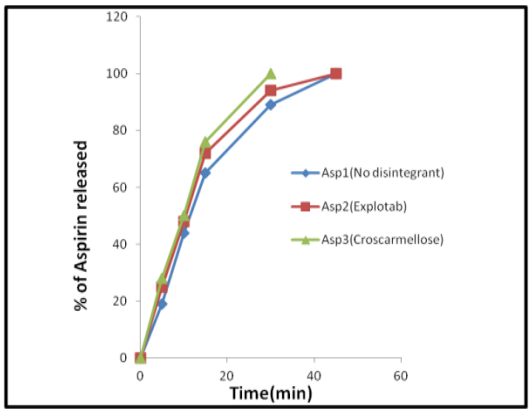

Figure1: The effect of different disintegrants on the dissolution profile of aspirin layer in 0.1N HCl and 37˚C .

Evaluation of compressed clopidogrel floating sustained release layer

The results of friability, hardness , content uniformity , floating lag time and floating duration are summarized in table(4).

All the prepared formulas showing acceptable results regarding to friability, content uniformity, while hardness was kept constant.

Formula (1)shows bad floating properties and disintegrate rapidly leading to fast release of tablet in addition to that the tablet loss its integrity ;the evolved CO2 causes rapid disintegration of the tablet ;also the concentration of polymer used in this formula was not enough to form proper matrix that can swell upon hydration and form coherent gel capable of entrapping liberated CO2[9]. with the increase in the polymer concentration in formulas 2and 3, the viscosity of the gel layer around the tablet increases, thereby limiting the release of active ingredient. The higher concentration of polymer also helps to retain the generated carbon dioxide for a longer period thereby conferring good floating properties on the formulations[10].this lead to prolongation of floating lag time and total floating duration.

Table 4: Evaluation parameters of clopidogrel floating sustained release layer

Formulas	Friability(%)	Hardness(kg)	Content uniformity%	Floating lag time(seconds)	Floating duration(hrs)
CL-1	0.56	5	97.5	1	<1
CL-2	0.39	5	92.2	5	20
CL-3	0.27	5	96.8	30	>24
CL-4	0.36	5	94.7	42	>24
CL-5	0.3	5	99	60	>24
CL-6	0.28	5	99.3	200	14
CL-7	0.46	5	92.9	240	12
CL-8	0.44	5	99.4	480	12
CL-9	0.42	5	98.1	160	20
CL-10	0.42	5	97.7	20	>24
CL-11	0.39	5	94	45	>24

As the ethylcellulose was added in formula (4and5) floating lag time and floating duration was increase by increasing concentration of ethylcellulose; ethylcellulose has a well known release retardant effect due to its hydrophobic nature so it can retard the diffusion of dissolution medium to the matrix and this will delay the reaction between the dissolution medium and sodium bicarbonate ; generation of CO_2 will affected and hence floating time will be prolonged [11].Incorporation of carbapol in formulas (6and7) lead to prolongation of floating lag time and decrease in total floating duration .Carbapol has a well known negative effect on floating behavior of the delivery system. This can be explained by the fact that carbapol has a much higher moisture absorption compared to HPMC. This results in a dramatic increase in the density of the floating system which, in turn,

shows a corresponding decrease in the floating capacity of floating system [12].

Formula CL-8 was prepared without addition of sodium bicarbonate while formula CL- 9 contains half the standard amount used in all formulas ,floating lag time was decreased with increasing the amount of sodium bicarbonate and the total floating duration was prolonged [13].

FormulaCL- (10, 11) contains lactose and dicalcium phosphate respectively .lactose is a well known water soluble filler while although dicalcium phosphate is hydrophobic in nature, but soluble in acidic solution [9] this property facilitates the penetration of medium to matrix lead to floatation of the tablet in a short period.

Variables affecting release profile from the floating matrix tablets

Effect of polymer concentration

Formulas CL- 1,2and 3 were prepared to show the effect of different amount of HPMC used on the release profile; formula CL- 1 failed to control the release of clopidogrel because the concentration of polymer used which is 20%w/w was insufficient to maintain the matrix integrity so rapid disintegration of the tablet was shown[9]

By increasing the amount of polymer used to 40% and 60% w/w in formulas 2and 3 respectively it was found that there is a decrease in the amount released with increasing the amount of polymer ;in general the greatest percentage of polymer corresponds to a lower porosity of the matrix, which achieves slower drug release rates[14].the results are shown in figure 2.

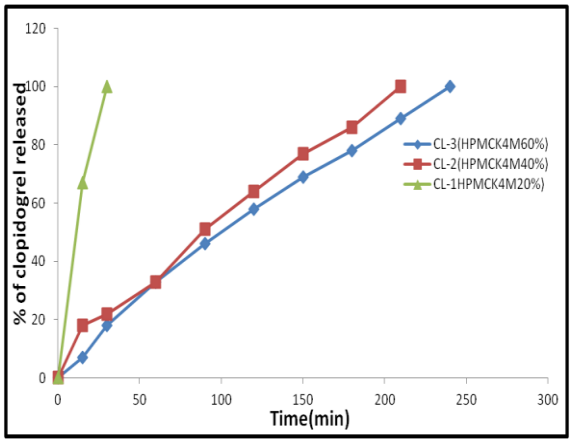

Figure2: Effect of HPMCK4M concentration on the release of clopidogrel in 0.1 N HCl and 37˚C.

Effect of polymer combination and ratio

Formulas (4, 5) and (6, 7) were designed to study the effect of incorporation of ethylcellulose and carbapol respectively on the release profile of clopidogrel.

Addition of ethylcellulose to formulas 4and **5** lead to decrease in the release of clopidogrel from the matrix tablet in comparsion with formula 3 which contain no ethylcellulose; The retardation in the release from formulas containing ethylcellulose is related to hydrophobic nature of ethyl cellulose which restrict the penetration of medium inside the matrix and also restrict the formation of gel layer around the matrix as compared to the hydrophilic HPMC [15].The results are shown in figure 3.

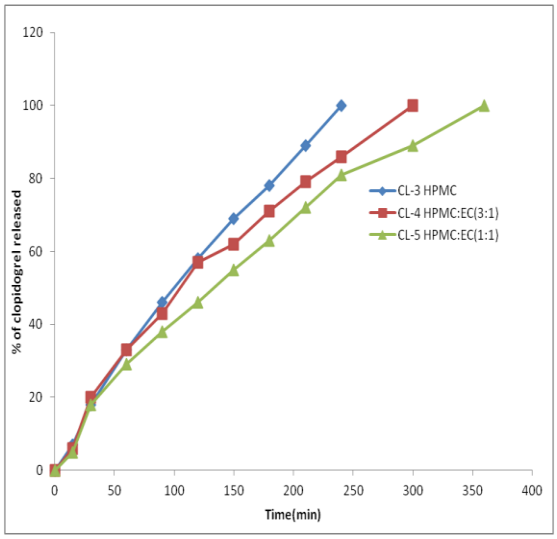

Figure 3: The effect of EC concentration on the of clopidogrel in 0.1 NHCl and 37°C release.

Incorporation of carbapol in the formulas 6and **7** lead to decrease the clopidogrel released from the matrix ;although at acidic pHs carbapol forms a weak gel not capable of controlling the drug release but addition of sodium bicarbonate which elevates pH may improve their retarding effect in acidic media by making the matrices form a stronger polymer network [16] also combination of anionic polymer (carbopols) with nonionic (HPMC) produces a synergistic increase in viscosity. The results are shown in figure 4.

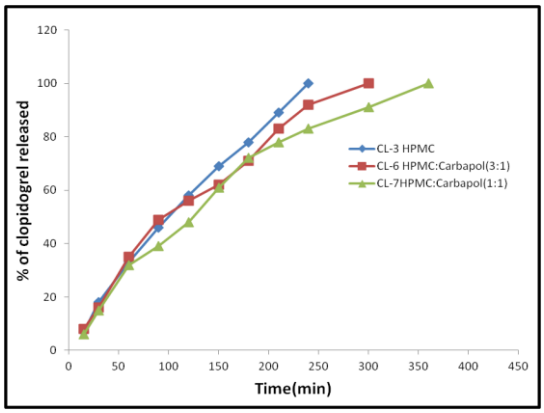

Figure4:The effect of carbapol concentration on the release of clopidogrel in 0.1NHCl and37˚C.

Effect of the amount of sodium bicarbonate

FormulaCL- 8 andCL- 9 were designed to study the effect of decreasing the amount of sodium bicarbonate on the release of clopidogrel from compressed matrix .The results obtained indicate that there is a direct relationship between the amount of sodium bicarbonate incorporated in the formula and the amount released of clopidogrel. The rate of drug release was found to increase with increasing weight ratio of sodium bicarbonate. This is the direct result of the porous nature of the sodium bicarbonate containing tablet; the high amount of gas generating agent (sodium bicarbonate), which creates path for drug release by increasing pore size of matrix and increasing gas pressure inside the matrix [(17).]The results are shown in figure 5 .

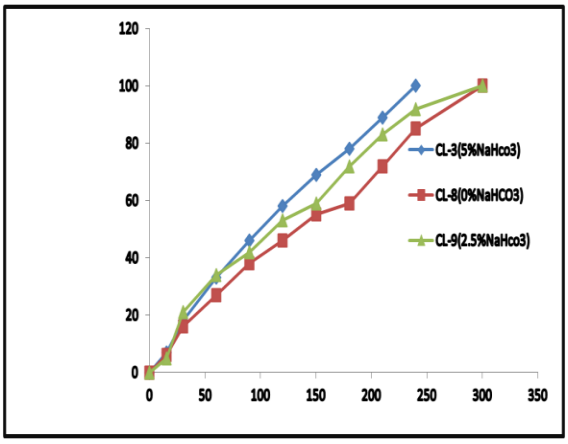

Figure5:The effect of sodium bicarbonate amount on the release of clopidogrel in 0.1N HCl and 37˚C.

Effect of Diluent Type

The effect of different types of diluents on release profile was studied using three different diluents differ in their properties each one can affect the release in different manner .Microcrystallineellulose (MCC) was used as diluents in formulaCL- 2,in formula CL-10 MCC was replaced by lactose and in formula CL-11 dicalcium phosphate(DCP) was utilized as a diluent.

Replacement of MCC with lactose in formulaCL- 10 and by DCP in formula CL-11lead to acceleration of release.

Lactose is well known water soluble filler; so incorporation of lactose leads to increases in the hydration rate and relaxation of the polymer chains, resulting in more dissolved drug diffusing out from the matrix.

Also when the drug solubility increases, the enhanced osmotic stress accelerates water penetration into the matrix resulting in a higher degree of polymer swelling and formation of more micro-cavities; therefore Lactose, by its water-soluble and hydrophilic nature, facilitates gel formation and shortens the penetration time of the dissolution medium into the matrix[(18).]The results are shown in figure6.

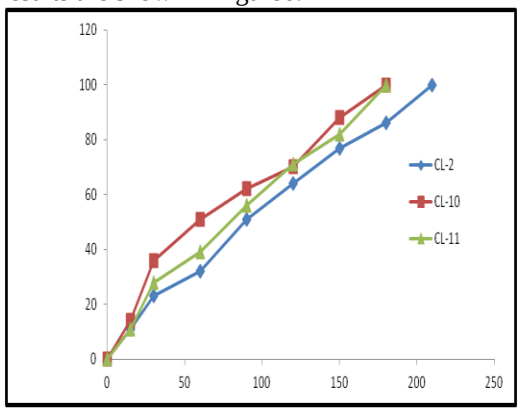

Figure6: The effect of diluent type on the release of clopidogrel in 0.1N HCl and 37˚C

Bilayer tablets preparation

Formula Asp3 (fast disintegration and rapid release) was chosen as optimized formula for rapidly disintegrating first layer while formula Cl-5 was chosen as optimized formula for floating sustained release layer(prolonged release for 6 hours with good floating properties). 350 mg of clopidogrel floating sustained release layer was manually poured into 9mm die and compressed slightly .150 mg of immediate release aspirin layer was poured into the die above the clopidogrel layer and finally subjected

to final compression . Bi layer tablet of aspirin and clopidogrel was ejected from die.

Evaluation of Bi-layer Tablet

The prepared bilayer tablets were subjected to friability, hardness, floating lag time ,floating duration and content uniformity test tests and the results are shown in table (5).

Table 5: Evaluation parameters of bilayer tablets

Hard -ness	Friability	Floating Duration	Floating lag Time	Content uniformity%
5kg	0.4	>24 hr	80 sec	Aspirin98 %,Clopidogrel99.3 %

Dissolution study

Dissolution study was performed for prepared bilayer tablet ;.there is no significant difference in the release of clopidogrel from bilayer tablet in comparison with compressed clopidogrel matrix alone . rapid and complete release of aspirin was occurred with 30 min of test .The results are shown in figure 7 and figure 8.

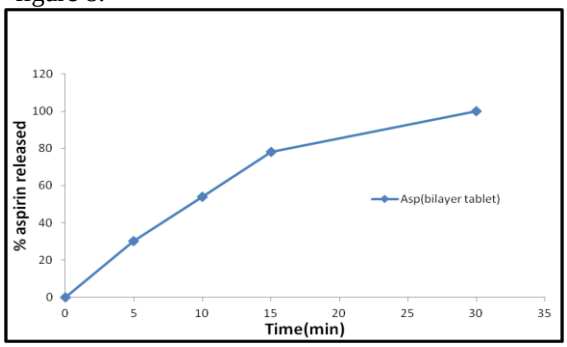

Figure7:Dissolution profile of selected aspirin formula from bilayer tablet in 0.1N HCl and 37˚C.

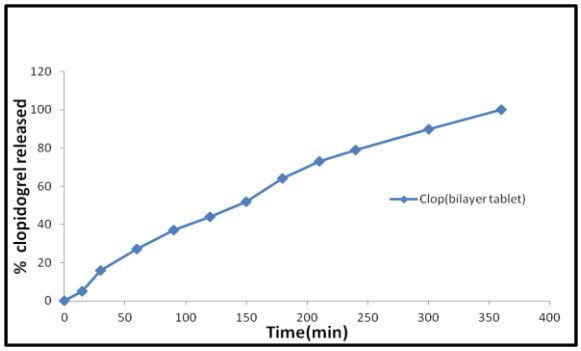

Figure8:Dissolution profile of selected clopidogrel formula from bilayer tablet in 0.1N HCl and37˚C

Kinetic study

The stability of of aspirin and clopidogrel bilayer tablets were studied at three different temperatures;40˚C,50˚Cand 60˚C.The degradation of aspirin and clopidogrel followed first order kinetics because straight lines were obtained when logarithm of percent remaining of both drugs were plotted versus time .figure 9and10 show the degradation curves of aspirin and clopidogrel at 40˚C,50˚Cand 60˚C.

The slopes of these lines were determined and from them we can calculate rate constant (k) .Arrhenius plot was constructed as shown in figure 11and 12 by utilizing Arrhenius plot we can determine rate of degradation at lower temperature. The shelf life can be calculated at 25˚Cand it was about 3 years for aspirin and was about 2.8 years for clopidogrel.

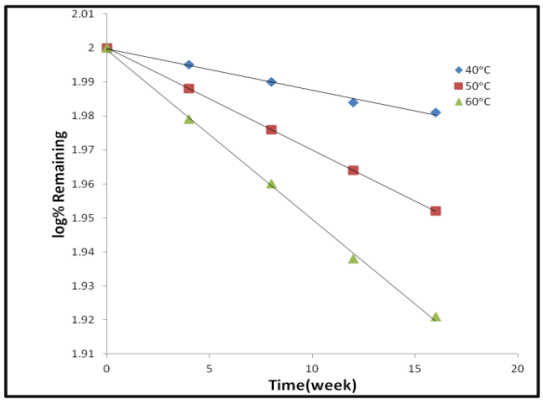

Figure9: First order plot for the degradation of aspirin in bilayer tablet at different temperature

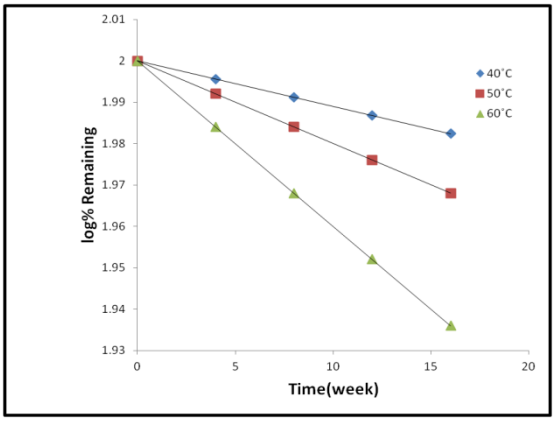

Figure10:First order plot for the degradation of clopidogrel in bilayer tablet at different temperature.

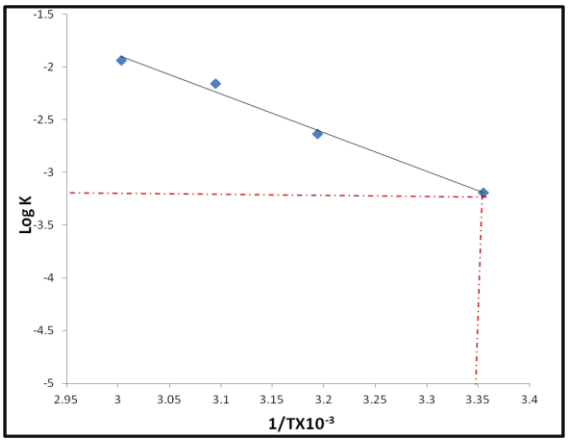

Figure11: Arrhenius plot of aspirin for estimation of shelf life

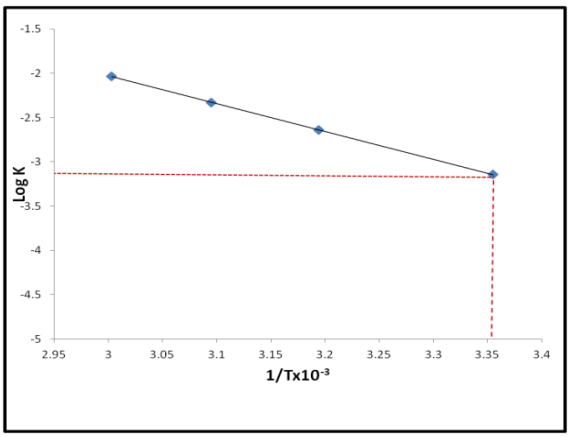

Figure12: Arrhenius plot of clopidogrel for estimation of shelf life

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