Preparation, *In Vitro* and *Ex Vivo* Evaluation of MucoadhesiveBuccal Films of Silibinin

Ahmed A. Hussein[1], Mowafaq M. Ghareeb*[1], Qasim A. Bader[2]

[1]Department of pharmaceutics, College of Pharmacy, Baghdad University, Baghdad, Iraq
[2]Department of pharmaceutics, College of Pharmacy, Kerbala University, Kerbala, Iraq
Corresponding author's E-mail: mopharmacy@yahoo.com

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Abstract

Silibinin is a major biologically active compound present in the Compositae family of plants with promising antinflammatory activity. The purpose of this study was to develop and optimize formulations of mucoadhesivefilms of silibinin to be used for buccal ulcer.Twelve film formulas were prepared by the solvent casting method using several polymers namely: sodium carboxymethylcellulose (SCMC), polyvinylpyrolidone (PVP), polyvinyl alcohol (PVA), carbopol 934, Eudragit E-100, and sodium alginate at various ratios. The prepared films were characterized in terms of film thickness, weight variation, swelling capacity, surface pH,drugcontent uniformity, *ex vivo* adhesion time, bioadhesive strength, folding endurance, *in vitro* drug release, and drug-exicpient compatibility using FTIR. The *in vitro* release studies were conducted for silibininfilms in phosphate buffer-pH-6.6 solution.The films were found to be smooth in texture, uniform in thickness, weight, and drug content with acceptable surfacepH. The film formula (F12) containing combination of two polymers PVP: PVA in ratio of 1:3with 0.3%v/v propylene glycol showed good mucoadhesion properties with maximum release of 95% within 4 hours. The diffusion exponent (n) of KrosmeyerPeppas for best formulation was found to be 0.52 which indicates the mechanism of drug release was anomalous transport. Optimized formulation was checked for stability and was found to be stable with expired date about3.6 years. Thus the selected formula can serve as a good candidate for buccal dosage form of silibinin.

التحضير والتقييم مختبريا وخارج الجسم الحي لشرائح السليبينين الملتصقة ببطانة الفم

أحمد عباس حسين[1] ، موفق محمدغريب*[1]، قاسم علاوي بدر[2]
[1]فرعالصيدلانيات,كليةالصيدلة,جامعةبغداد,بغداد, العراق
[2]فرعالصيدلانيات,كليةالصيدلة,جامعةكربلاء,كربلاء, العراق
*البريدالالكتروني: mopharmacy@yahoo.com

مفتاح البحث : سيليبينين، الشدق شكل جرعات

الملخص

سيليبينين هومنا لمركبات الرئيسية التي لها فعالية بيولوجية من العائلة النباتيةCompositae وله نشاط مضاد للالتهابات واعد. وكان الغرض من هذه الدراسة هو تطوير وتحسين تركيبات من الشرائط اللاصقة بالغشاء المخاطي من سيليبينين لاستخدامها في قرحة الفم. تم إعداد اثني عشرمن صيغ الشرائط حضرت بطريقة الصب مع المذيبات وباستخدام عدة بوليمرات وهي: كربوكسي ميثيل سلولوز الصوديوم (SCMC)، polyvinylpyrolidone (PVP)، بولي فينيل الكحول PVA، carbopol 934، Eudragit E-100، والجينات الصوديوم في نسب مختلفة. تم تقييم الشرائط المعدة عن طريق سمك الفيلم، وتباين الوزن، قدرة الانتفاخ، ودرجة حموضة السطح، تجانس محتوى الدواء، وقتالالتصاق بالجسم الحي ، وقوة الالتصاقbioadhesive، قابيلة للطي ، سرعة تحرر الدواء، وتوافق الدواء مع المواد المضافة باستخدام FTIR. أجريت دراسات في المختبر لتحرر الدواء من الشرائط سيليبينين في محيط ذو حامضيةPH 6.6-الفوسفات. كانت مواصفات الشرائط سلسة في الملمس، وموحدة في السمك والوزن ودرجة الحموضة ومحتوى الدواء مع سطح مقبولة.

وأظهرتالصيغة فيلم (F12) التي تحتوي على مزيج من اثنين من البوليمرات PVP: PVA في نسبة 1:3 مع جليكول البروبيلين بنسبة 0.3٪ V / V خصائص mucoadhesion جيدة مع نسبة تحرر للدواءتصل إلى 95٪ خلال 4 ساعات:. تم تحليل ميكانيكية التحرر حسب موديل PeppasKrosmeyerوحساب اس الطاقة ووجد انه 0،52 مما يدل على آلية تحرر للدواءهي النقل الشاذ. تم فحص ثباتية الاشرطة المحضرة ووجدت مستقرة مع تاريخ انتهاء حوالي 3.6 سنوات. وبالتالي يمكن للصيغة المختارةان تكون مرشح جيد لشكل مستحضرشريطي فموي جيد للفم من السيليبينين.

Introduction

The drug delivery in the oral mucosal cavity can be classified into three categories; sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; buccal delivery, which isdrug administration through mucosal membranes lining the cheeks (buccal mucosa); and local delivery, which is drug delivery into the oral cavity.

Conventional formulations for local oral delivery are principally lozenges, mouthwashes, mouth-paints, oral gels, pastes and suspensions. One of the major limitations associated with buccal route of administration is the lack of dosageform retention at the site of absorption;consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems in the form of adhesive patches [1], adhesive films [2], adhesive tablets [3]and buccalgels[4].

These conventional dosage forms have two major disadvantages which consist of an initial burst of activity followed by a rapid decrease in drug release,[5] and in a limited permanence in situ related to the constant flow of saliva. Buccal films are highly flexible and ensure more accurate dosing of the drug compared to gels and ointments. Moreover, buccal films are suitable for protecting wound surfaces, thus reducing pain and increasing the treatment effectiveness [6].

Silibinin is a major biologically active compound present in the Composite family of plants with abundance in milk thistle (*Silybummarianum*) and artichoke (*Cynarascolymus*). Milk thistle extract is widely used as dietary supplement for hepatoprotective effect, and silymarin, the crude polyphenolic component containing silibinin, is clinically used to treat liver diseases or toxicity including that of amanita poisoning and liver cirrhosis [7].

Previous study showed that topical buccal therapy with silymarin is useful in controlling ulcerative and inflammatory mucosal diseases [8]. This local treatment is based on the concept that a high activity of anti-inflammatory agent can be produced at the site of administration and, at the same time, the degree of systemic side effects can be minimized or avoided.

The main objective of this work is to formulate silibininmuccoadhesive films for topical treatment of oral mucosal inflammatory symptoms to ensure satisfactory silibinin level in the mouth for prolonged duration of time.

Material And Methods

Silibinin (Tolbiac S.R.L., Jose E. Argentina), Sodiumcarboxymethylcellulose (Metsaserla, Sweden), Polyvinyl pyrolidone(Fluka analytical, USA), Polyvinyl alcohol(Riedel-DeHAEN AG Seelze Hannover, Germany), Sodium alginate(BDH (British Drug House) Lab. Chemical division Pool, England.), Carbapol 934P(Cadila Health Care Ltd. India), Eudraget E-100(Evonik GmbH –Germany) , and all other materials used were of analytical grade reagents.

Methods

Preparation of the BuccoadhesiveFilms

The buccoadhesive film formulas (1-12) of silibinin (table 1) were prepared by solvent casting method using different percents of polymers like NaCMC and PVP seperately as the main film forming polymer and in combination with PVA , Sodium alginate, Eudraget E-100 and Carbapol 934 P as mucoadhesive polymers [9]. The calculated amount of polymer was socked in 50 ml of distilled water for 24 hours. then 50 mg of silibinin was incorporated into polymeric solution with continues stirring.

The propylene glycol was added into homogenized drug polymer solution as a plasticizer and as a permeation enhancer and then kept aside for 1 hr at room temperature. The resultant viscous gel

mixture was poured into fabricated glass ring placed on aluminum foil in a petri dish, and then the petri dish was kept aside for drying at room temperature for 24 hours. The dried films were then cut into 2×2 cm pieces, wrapped in aluminum foil and kept in desiccators until evaluation. The amount of drug in the film was calculated using the following equation:

Theoretical amount of drug in each 2×2 cm film = (W/S) X 4

where (S) is the total surface area of the petridish = 63.5 cm^2, and (W) is the total amount of drug added (W) = 50 mg

Drug Polymer Compatibility Study

Drug polymer interactions were studied by FTIR spectroscopy. The drug, physical mixture, and prepared buccal films were analyzedby infrared spectrophotometer(shimadzu FTIR 8000). Samples were compressed withKBrandscanned in range of 400-4400 cm^{-1}.

Evaluation of the Mucoa dhesive Silibinin Buccal Films

Film Weight and Thickness

For evaluation of film weight, three films of every formula were selected randomly and individual 2×2 cm^2 film was weighed. The average weight was calculated similarly, the film thickness was measured using micrometer screw gauge at three different points and the mean value was calculated [10].

Surface pH of the Film

For determination of surface pH three films of each formulation were selected randomly and are allowed to swell for 2 hours on the surface of previously prepared 2% agar plate. The surface pH was measured by using a pH meter probe placed on the surface of swollen film [11].

Folding Endurance

Folding endurance of the 2×2 cm films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties[12] .

Swelling Index

Buccalfilms were weighed initially (X_o) and placed in 2% agar gel plates, incubated at 37±1°C, and examined for any physical changes. After 1 hour, films were removed from the gel plates and excess surface water was removed carefully using the filter paper. The swollen films were then reweighed (X_t) , and the percent of swelling (%S) was calculated using the following formula [13]:

(% S) = (Xt–Xo/Xo) ×100

Drug Content Uniformity

Drug content uniformity was determined by dissolving each 2×2cm films of different batches in 100 ml distilled water. The whole content was then shake continuously 5 hours with the help of rotary shaker and then kept aside for 24 hours. Then the solution was filter with Whatman filter paper (0.45 µm). From the filtrate, 5ml solution was taken and suitably diluted with distilled water and analyzed at the λ max of 327.5 nm using a UV spectrophotometer [14] . The experiments were performed in triplicate.

Determination of Exvivo AdhesionTime

The ex vivo adhesion time was evaluated by assessing the time to detach the film from chicken pouch membrane in a well stirred beaker [15].The chicken pouch membranes were fixed on the side of the beaker with cyanoacrylate glue. The films were attached to the membrane by applying light force with finger tip for 60 seconds. The beaker was then filled with 500 ml phosphate buffer pH 6.6 at 37℃ and magnetically stirred at an approximate rate of 150 rpm[16].

Measurement of Bioadhesive Strength

Bioadhesive strength of the buccal films was measured on modified physical balance followed the method described by Gupta *et al.* [17], using the chicken pouch membranes as shown in figure (1).Force of adhesion and bond strength parameters were calculated from using equations[18].

Force of Adhesion=Bioadhesive strength (g) x980 / 1000

Bond strength (Nm^{-2})= force of adhesion / surface area of film

***In vitro*Release Study**

The drug release was determined using USP dissolution test apparatus II (paddle) thermostated at 37 ± 1°C and stirred at a rate of 50 rpm [19]. Sink condition was maintained throughout the study. Each film with size of 2×2 cm was fixed on glass slide with the help of cyanoacrylate adhesive, so that the drug could be released only from upper face. The slide was immersed in the vessel containing 250 ml of phosphate buffer system with pH 6.6. Aliquots of 5 ml of sample were withdrawn at predetermined time intervals over 4 hrs and each sample was replaced with equal volume of phosphate buffer and analyzedspectrophotometrically atthe λ max 327.5 nm of the drug[20].

Kinetic Analysis of Release

The release kinetics of silibinin from the prepared films was determined by fitting the dissolution data to mathematical Korsmeyer-Peppasmodelusing the following equation.

$Q_t / Q_\infty = kt^n$ *where, Q*t: amount of drug released in time t; *Q*∞: total amount of drug dissolved ;*K*: release rate constants; *n*: release exponent

Stability Study

The study was done to assess the selected formula stability according to Arrhenius method and to determine the expired date. The films were stored at different storage conditions at elevated temperatures of 40, 50, and 60ºC for 4 months.

Results And Discussion

Physical parameters evaluation data are listed in table (2). Theaverage weightsand thickness for all the prepared formulas were uniform and comply with specified values. The surface pH of all films was within the range of salivary pH.The folding endurance was found to be within the recommended values except for F5 and F6 formulas which were lower than minimum accepted value of 250.The average drug content of the films was found to be within the range of (87- 98%) which comply with official specification.

Swelling behavior for all formulas was studied for 60 minute. The results indicate that swelling indexes were proportional to (Na. CMC) concentration andthis may be attributed to its highly hydroxylic content comparing with PVP, PVA polymers [22].Higher swelling values would result in excessively increased surface area which could result in unmanageable faster release of the drug. Also, higher swelling may cause patient discomfort due to occupying of larger space in the oral cavity and chances of dislodgement [23].

The results of*In vitro* residence time indicate that the longest adhesion time was observed for carbopol film F2, while the lowest one was for F1 as shown in table(6).

The swelling state of the polymer in the film was reported to be crucial for its bioadhesivebehaviour. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong.

The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface [24] ; generally all Na.CMC formulations were showed reasonable residence time when used in higher concentration than the other polymers. It was noted that increasing PVA concentration in all formulas leading to a significant decrease ($p< 0.05$) in the residence time of the film.

The data of mucoadhesion strength indicate thatthe increase the amount of PVA in the formula produced a significant ($p<0.005$) decrease in the mucoadhesion strength and force, while the change in the amount of PVA had no significant effect ($p>0.005$) on the mucoadhesion bond strength within the same polymeric blend and this may be attributed to the weak hydrophobic bonds that occur due to interaction of non polar groups when the polymers were dispersed in an aqueous solutions [25]. No correlation was found between the bioadhesion force and the residence time of the polymers. It seems

that highly bioadhesive polymers do not necessarily reside longer on the mucosal surface. Surface charge density and chain flexibility are considered to be prerequisites for bioadhesion, whereas the residence time is primarily dependent on the dissolution rate of the polymer, these results are in good agreement with that observed in study of cetylpyrediniummucoadhesivepatches[26] .

The dissolution study of prepared formulas which have acceptable physical properties (F3,F4,F7, F9, and F12) as shown in figure (2) indicates that F3 containing NaCMC:EudragitE100 in ratio (3:1) eroded in the first hour of test, while F4 containing NaCMC:EudragitE100in ratio (1:2) and F7 containingNaCMC:PVA in ratio (3:1) were swell to unacceptable degree. Also the*in vitro* release studyshowed that the best formula which release maximum percent of drug was formula F12 which consist of PVP and PVA combination in ratio of 1:3 in comparison to formula (F9) which consist of Na.CMC and PVA combination in same ratio, the results indicate that the percent of silibinin released after 90 minute was 75% and 47% for F9 and F12 respectively. Since F9 eroded in the dissolution test at 90 minute, thus F12 remain as the best formula.

The initial burst release of drug that noticed with F9may attributed to rapid dissolve ofNa.CMC leading to the formation of channels inside the matrix of the film which enhance the diffusion of silibininacross such channels followed by the formation of a stable gel layer which in turn, controls the release of drug from the delivery system.

On contrary,the presenceof PVP with PVA increase a barrier like effect causing a decrease in the release of silibinin from the hydrated films andthese results are in good agreement with study results ofAlanazi*et al*. [27]In addition, PVP may increase the solid content of the polymer which consequently reduce the swelling index of the formula and these results are in accordance with published data ofAnantaChoudhury*et al*[28] .

The diffusion exponent (n) of KrosmeyerPeppas for best formulation was found to be 0.52 which indicates the mechanism of drug release was anomalous transport.

The FTIR analysis indicates that there was no chemical incompatibility between drug and polymer since there is no significant change in the characteristic peaks ofdrug after formulation to film.

The accelerated expiration date of the selected formula can be calculated from figure (4) using the following equation since the degradation of the drug follows first order kinetics:

$$t_{90\%} = 0.105 / K_{25}$$

where$t_{90\%}$is the time required for a drug to lose 10% of its potency and it was found to be 3.6 years since K_{25} was equal to 5.6×10^{-4} week $^{-1}$.

Conclusion

The results of this study reveals that the formula consist of combination two polymers PVP and PVA in ratio of 1:3 with 0.3% propylene glycol as a plasticizer have the best physical, mucoadhesion, and release properties thus can be consider a promising formula for optimum buccal drug delivery system.

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Table 1. Components of Various Buccoadhesive Films Formulasof silibinin

Components (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Silibinin	50	50	50	50	50	50	50	50	50	50	50	50
Na CMC	750	333	750	333	750	333	750	500	250	_	_	_
Carbapol	250	667	_	_	_	_	_	_	_	_	_	_
EudragetE-100	_	_	250	667	_	_	_	_	_	_	_	_
Na alginate	_	_	_	_	250	667	_	_	_	_	_	_
PVA	_	_	_	_	_	_	250	500	750	250	500	750
PVP	_	_	_	_	_	_	_	_	_	750	500	250
Propylene glycol (ml)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Ethanol (ml)		_	50	50	_	50						
Distilled water (ml)	50	50	50	50	50	50	50	50	50	50	50	50

Figure 1. Modified balance for *in vitro*mucoadhesion strength measurement.

Table 2. The evaluation parameters of prepared silibininbuccal films

Formula code	Weight. variation (mg)	Thickness (mm)	Surface pH	Drug content uniformity (%)	Folding endurance	Swelling index at 60 min
F1	127± 0.5	0.208±0.008	6.2±0.3	87±2.0	›300	262
F2	83.3± 0.9	0.159±0.006	6.9±0.5	91±1.0	›300	201
F3	40.0± 0.6	0.190±0.005	6.8±0.6	92±2.0	›300	664

F4	160± 2.4	0.206±0.011	6.9±0.3	88±2.0	›300	137
F5	66.3±1.2	0.222±0.002	6.0±0.4	93±1.0	220	612
F6	75.6±2.1	0.188±0.004	6.2±0.1	92±1.7	180	Eroded
F7	60.0±2.2	0.290±0.008	6.8±0.2	92±1.5	›300	450
F8	70.3±2.9	0.171±0.006	6.5±0.6	90±1.0	›300	226
F9	73.0±0.8	0.210±0.018	6.2±0.3	92±1.0	›300	146
F10	93.0± 0.2	0.190±0.010	6.1±0.6	90±2.0	›300	93
F11	81.3±2.5	0.260±0.004	6.6±0.5	89±2.8	›300	48
F12	91.0± 1.4	0.252±0.003	6.7±0.4	98±2.0	›300	53

Table 3 .Mucoadhesion properties of different silibinin films

Formula code	Mucoadhesion strength (g)	Force of adhesion (N)	Bond strength (Nm-2)	Ex-vivo residence time (hr.)
F1	7.12±1.66	6.90	1.74	3.21±0.26
F2	19.0±0.23	18.6	4.66	6.67±0.23
F3	13.8±0.76	13.5	3.37	4.76±0.39
F4	11.4±0.77	11.1	2.79	3.53±0.24
F5	10.9±0.38	10.6	2.67	*6.58±0.37
F6	8.60±0.63	8.40	2.10	*6.47±0.64
F7	13.7±1.37	13.4	3.37	*4.39±0.23
F8	9.04±0.35	8.85	2.20	5.36±0.21
F9	7.68±0.84	7.52	1.88	4.08±0.31
F10	12.6±0.80	12.4	3.10	5.62±0.37
F11	10.7±0.68	10.5	2.63	3.67±0.31
F12	9.70±0.60	9.50	2.37	4.51±0.42

Note: The star* means the film was eroded during test

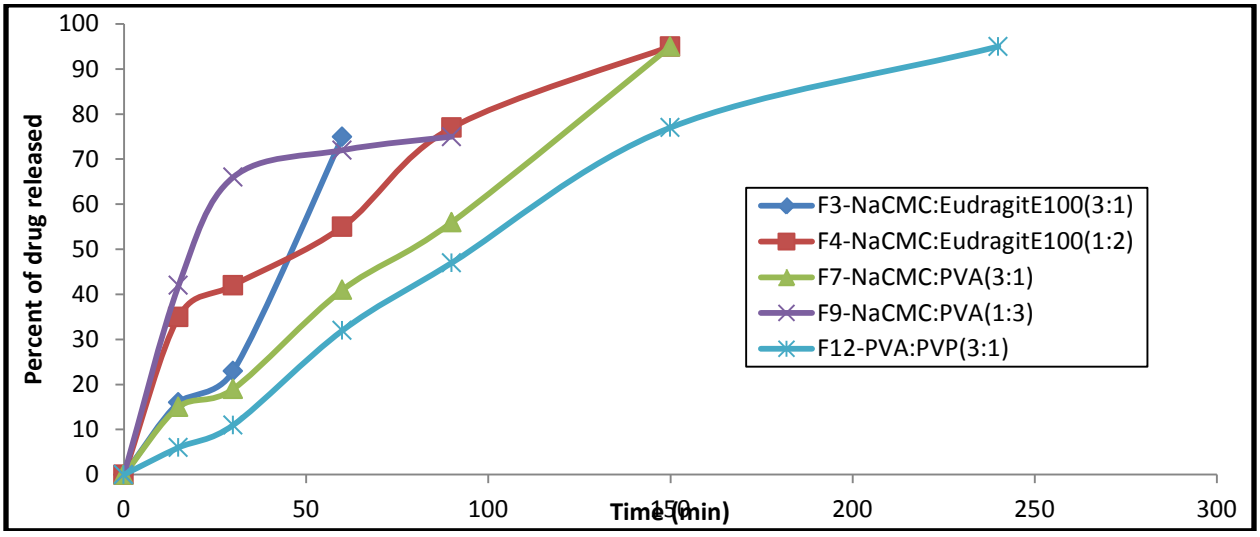

Figure 2. *In vitro* release profile of silibinin from buccoadhesive films at 37°C in phosphatebuffer (pH 6.6)

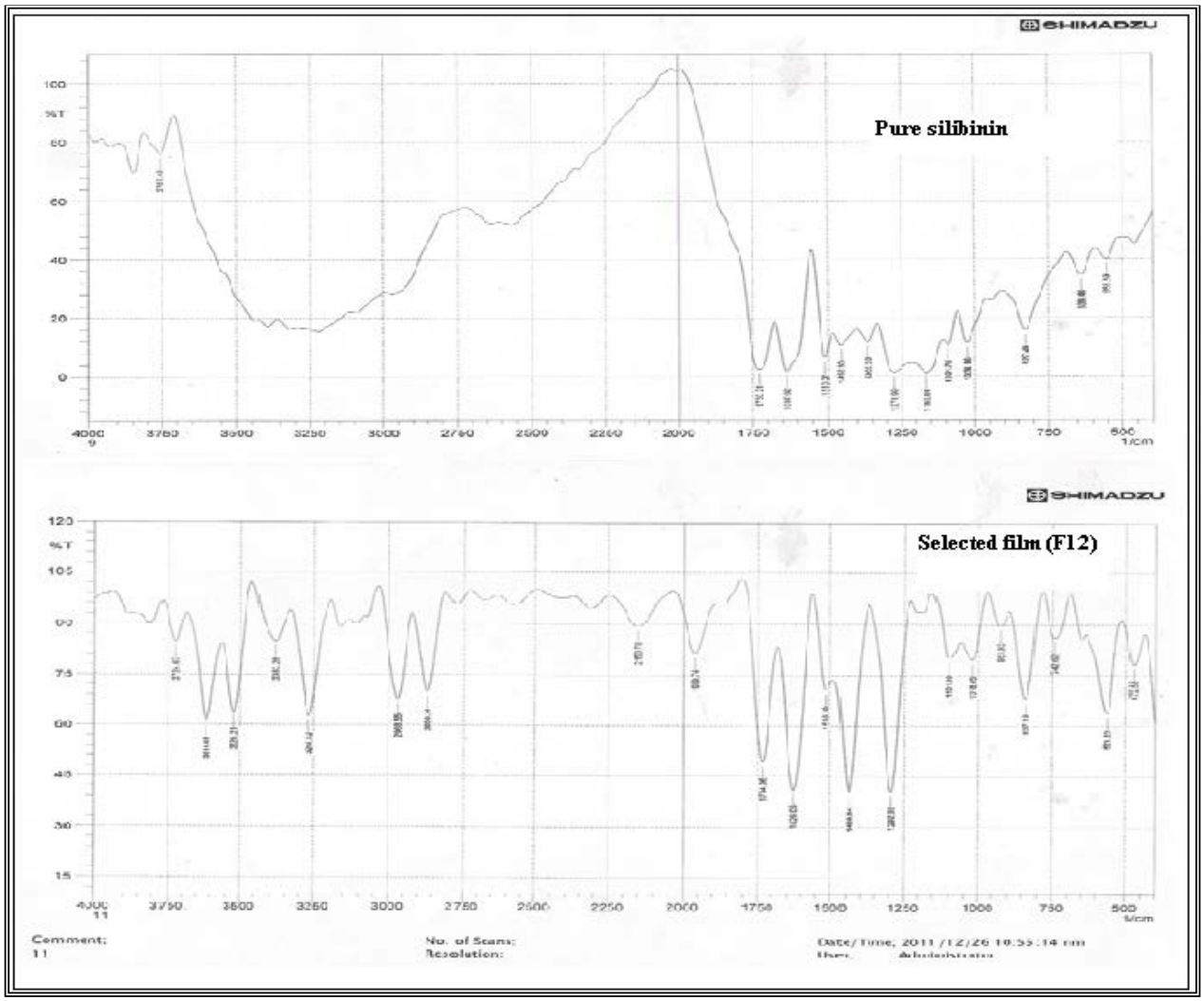

Figure 3. FTIR spectra of pure silibinin and prepared buccal film of selected formula

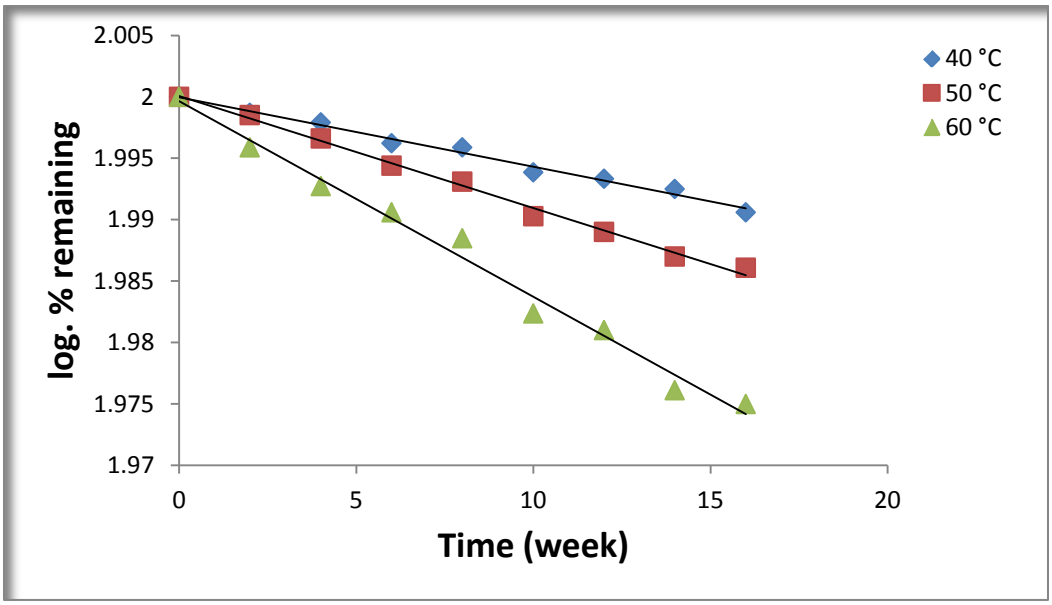

Figure 4. Accelerated degradation profile of silibinin in the selected formula F12