Preparation and Characterization of Montelukast Sodium (SMLT) as a Dual Sustained Release Buccal Strips

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Abstract

An oral bi layer sustained release (SR) strips of Sodium Montelukast SMLT , which is selective leukotriene antagonist , used for patients suffered from mid-night asthma , were prepared successfully ,using different polymers, like guar gum , carrageenan , and xanthan gum , by solvent casting method .

The results obtained by this study revealed ,that best fast dissolving film of SMLT was loaded in carrageenan polymer 57% w\w (30mg.) , with acceptable physical properties, like film thickness , elastic endurance and surface pH .

Besides to that , the disintegration time , and cumulative 80% drug release were estimated 22 seconds and 3.7 minutes , respectively .On the other hand , the sustained release film (FSR6-7) as a second layer , appear to be the most promised layer of SMLT loaded in 50 % w\w (15mg.) PVP K17 , with respect to its film thickness, elastic endurance and , surface pH .

Moreover the , the disintegration time of the second layer film was 21seconds , and the time for 50% drug release was 15 minutes extended for 4hours of 100% drug release .

Meanwhile , the investigation of possible interference between the drug , and, polymers used revealed no evidence of this effect ,using FTIR , and SEM technique . In an attempt to evaluate the extended release effect of the selected formula , Singulair® plain tablet as a marketed product was used , the result gave more than 4 hours of selected formula , compared with 30 minutes to marketed product Singulair® .

The overall results candidates the selected FSR6-7 formula as a promised bi layer buccal fast , as compliance and extended therapy for asthmatic mid- night patients.

Keywords: Montelukast sodium, Dual buccal strips, Guar gum, Xanthan gum, Carrageenan.

تحضيروتشخيص المونتيلوكاست صوديوم كشرائح فموية مزدوجة بطيئة التحرر

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الخلاصة

الشرائح الفموية المزدوجة بطيئة التحرر للمونتيلوكاست والذي يعتبر المضاد والمختص لليكوترابنين, والمستعمل لمرضى الربو الليلي قد حضر بنجاح بأستعمال بوليمرات مختلفة كصمغة الكوار,والكارجينان والزانثين. بأستعمال طريقة القشط المذيب .

أن النتائج المستخلصة في هذه الدراسة أظهرت بشكل افضل شريحة سريعة الذوبان للمونتيلوكاست محملة في بوليمر الكارجينان ٥٧% (وزن\وزن)٣٠ملغم. بصفات فيزياوية مقبولة,مثل سمك الشريحة , مطاطية التحمل والاس الهيدروجيني السطحي . أضافة الى ذالك فأن وقت أنحلال وتحرر ٨٠% من العقار قد بلغت ٢٢ثانية ,٧.٧ دقيقة على التوالي .

ومن الناحية الاخرى فأن الشريحة بطيئة التحرر ف س ر ٦-٧ كطبقة ثانية ،ظهرت الاكثر واعدة للمونتيلوكاست بتحميلها ٥٠% (وزن\وزن) ١٥ملغم. في بوليمر البولي فنيل بايروليدون نسبة الى سمك الشريحة , مطاطية التحمل والأس الهيدروجيني السطحي .

علاوة على ذالك فأن وقت انحلال الطبقة الثانية قد بلغ ٢١ ثانية, ووقت تحرر العقار ل ٥٠% منه في ١٥ دقيقة ولفترة زمنية أمتد ت الى ٤ ساعات لنسبة تحرر ١٠٠% .كما أن أمكانية التداخل بين البوليمر المستخدم والعقار , لم يظهر اي أشارة الى هذا التأثير بأستعمال تكنلوجيا مطياف الأشعة تحت الحمراء , وتكنلوجيا المسح الالكتروني . وفي محاولة لتقييم تأثير التحرر الطويل للتركيبة المختارة, فأن مستحضر السنكولير الجنيس قد أستخدم للمقارنة, حيث أظهرت النتائج تحرر العقار على أمتداد ٤ ساعات بفترة ٣٠ دقيقة لمستحضر السنكولير الجنيس .

أن النتائج الكلية تظهر التركيبة ف س ر ٦-٧ كتركيبة واعدة لشرائح فموية مزدوجة وملائمة لعلاج مرضى الربو الليلي .

الكلمات المفتاحية : المونتيلوكاست صوديوم ، شرائح فموية مزدوجة ، ، صمغة الكوار، صمغة الزانثين ،الكارجينان .

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Introduction

Now a days the synchronized of asthmatic attach at night , became one of the worsening condition of respiratory system [(1)] , Most of the patient suffering from this disease occurred during the mid-night hours and dusty bad weather , mainly for children and elderly [(2)] .

So according to these findings , the drug therapy should be prescribed in a manner to result therapeutic steady state concentration at specific period [(3)] .

Consequently , the administration of the therapy prepared in two types of drug in a loading dose , and maintenance dose at bed time with a programmed drug release in early a hours of next day morning give a best effective therapy than the ordinary controlled delivery system [(4)].

Montelukast sodium SMLT is selective leukotriene antagonist used for the management and treatment of acute asthma and alveoli constriction in preparations formulated as a tablets, oral dispersible tablets in equivalent weight of 10 mg. per dose montelucast MLT as equivalent base of SMLT salt derivative [(5)] .

Fast disintegrating buccal film is the most developed recent product of oro-buccal dosage form due to acceptability by the formulators. They can improve the activity of the medicines by dissolving within seconds in oral cavity by means of saliva presence without chewing and no need of water for administration. So it gives fast absorption and higher bioavailability of drugs due to local high blood flow in the buccal cavity

Materials and Methods

Materials

Montelucast Sodium (Gift from Stada Drug Industry , Vietnam), Guar gum, Xanthan gum, Carrageenan and are obtained by Provizer Pharma Co. India, Dimethyl phthalate , glycerin, ribose sugar obtained by Sigma-Aldrich Co. USA, Fructose , Lactic acid ,Polyvinypyrrolidone K17 , Eudragit RS are given as a gift by Al-sharq Al-Owset ,and orange flavor is from (Merck Labs. ,Germany) ,the other remaining reagents and materials were of analytical grade , obtained by BDH Chemicals Ltd poole, England, GCC Analytical reagents, UK, and Fluka Chemi AG, Switzerland .

Methods

Preparation of rapidly dissolving layer

Table (1), illustrates that eighteen formulas as fast release layer were prepared using a modified solvent casting method [(6)]; with each circular film surface area approximately 7.07 cm^2 is loaded with equivalent weight 5mg MLT.The amounts of polymers were weighed and dissolved in a beaker containing 10ml of distilled water maintained at 40°C overnight to ensure a uniform dispersion of different (w/v)% solutions. Meanwhile the SMLT and other excipients were dissolved in 10ml of distilled water in another beaker. The drug solution was added to the polymer solution and mixed using magnetic stirrer for two hour. The resulting solution was left for 30 minutes to remove all air bubbles entrapped, the resultant solution was cast onto 12 cm – diameter petri dish and dried in the oven at 40^oC for 24 hours. The film was slowly and carefully removed from the petri dish, and checked for any imperfections, cut into 3cm diameter circular films to gain the equivalent dose per strip (5mg.).

Preparation of sustained release layer

Six formulas as sustained release strips (FSR1-FSR2) were prepared alone using spray technique , as a second layer on the surface of the optimized fast dissolving layer (F7), It was prepared by dissolving the SMLT and polymers with other excipients in 10ml of ethanol 95 v\v % , then , and sprayed the solution via nozzle on to other side of the dried optimized formula of the fast dissolving layer in petri dish in a uniform distribution to permit fast drying without deterioration of the fast dissolving layer , then allowed to dry at a room temperature for 24 hours to ensure complete evaporation of all solvent traces [(7)] , The dried bi-layer films (FSR-F7) for each FSR were carefully removed from the petri dish and cut into 3 cm in diameter circular films. Samples were packed in an amber glass container until further analysis. each sample strip contain SMLT 10.38mg , equivalent to 5 mg. MLT in each layer, and total weight 46 mg. (22mg. F7 and 24mg. FSR) .

Physical cracterization

A- ***Visual inspection***
Properties such as homogeneity, color, transparency and surface of films were evaluated for all prepared oral films.[(8)]

B- ***Weight variation***
The 7.07cm^2 strip of **SMLT** was divided into equal four pieces in the cast film. and each film was taken and then differences in weight was observed. [(10)]

C- ***Thickness measurements***
The thickness of each film was determined at eight different locations (two from each four corners) using Vernier caliper micrometer.

Table (1): Composition of the sodium montelukast fast and sustained dissolving layers

Content (mg) / Form.	Sodium Montlucast (SMLT)	Xanthan gum	Guar Gum	Carra-geenan	Dimethyl-Phthalate Glycerin (1:1)	Lactic Acid	Ribose-Fructose (1: 1)	Eudragit RS	PVP 17K	Orange Flavor
F1	5	30			6	2	5			4
F2	5	35			6	2	5			4
F3	5	40			6	2	5			4
F4	5		30		6	2	5			4
F5	5		35		6	2	5			4
F6	5		40		6	2	5			4
F7	5			30	6	2	5			4
F8	5			35	6	2	5			4
F9	5			40	6	2	5			4
F10	5			30	6	2	5			4
F11	5			30	9	2	5			4
F12	5			30	12	2	5			4
F13	5			30	6	4	5			4
F14	5			30	6	6	5			4
FSR1-F7	5				6			5		4
FSR2-F7	5				6			10		4
FSR3-F7	5				6			15		4
FSR4-F7	5				6				5	4
FSR5-F7	5				6				10	4
FSR6-F7	5				6				15	4

Mechanical characterization

To indicate a good elasticity , film strength of the cast was examined by measuring many parameters like modulus, strain, percent of elongation and the folding endurance .The films used for investigating the tensile properties were cut around a standard template (dumbbell) according to American Society for Testing and Materials International Test Method for Thin Plastic Sheeting.[9]

The tensile properties of the films were evaluated by stretching the dumbbell-shaped sections to break using a universal testing machine. The breaking load in Newton [N] and elongation percent were measured [11].

A- Tensile strength (TS)

Evaluation of this type of oral strip films ,tensile strength is used, which is defined as a the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in equation below and was expressed in force per unit area: mega pascal (MPa) [12].

B- Elongation at break (E)

Elongation was estimated by dividing the extension at the moment of rapture of the specimen by the initial gage length of specimen which represents hundred percent according to equation (1) below:

$$\%E = [(L_s - L_0) / L_0] \times 100 \quad \text{… equation 1}$$

C- Elastic modulus (EM)

This parameter is the measure of stiffness of the strip it was calculated as the slope of the linear portion of the stress – strain curve. The result was expressed in force per unit area (MPa) [12].

$$F/A = EM\,[(L_s - L_0) / L_0] \quad \text{… equation 2}$$

Where:

F =breaking load (N)

A = cross-sectional area of the sample

EM = is the modulus of elasticity.

L_0 = is the initial gage length of the specimen

L_s = is the length of the film after elongation.

D- Strain

Strain has been used as an indicator of the overall mechanical quality of the film [12]

$$\text{Strain} = \frac{Tensile\ strength}{Elastic\ of\ modulus} \quad \text{... equation 3}$$

E- Folding endurance

The endurance of each fold was measured manually for the prepared films. A strip ($7.07cm^2$) area of a film was cut and repeatedly folded at the same place till it broke; the number of times of the film could be folded at the same place without breaking gives the value of folding endurance. Folding endurance more than 300 indicating that the formulation good tough and flexible [13].

Drug content uniformity

Four circular strips (3cm in diameter) are placed in 100ml phosphate buffer pH 6.8 solution and kept on magnetic stirrer for 1hr

for first fast dissolving layer and 24hrs for the strips of two layers (fast dissolving layer with sustained release layer). Solution was suitability diluted then the UV absorbance of the solution was measured at SMLT λmax, and the drug content was determined [14].

Measurement of surface pH

The surface pH of the films was determined in order to investigate the possible irritation of buccal mucosa, The strip to be tested was moistened with 0.5ml of distilled water and kept for 1hr. the pH probe electrode must be in contact with the surface of formulation and allowing equilibrating for 1 minute and the average of triplicate measurements for each was indicted and reported [15].

Disintegration test[16]

In-vitro disintegration time

1- Drop method

In this method one drop of distilled water was dropped by a pipette onto the oral films. Therefore the films were placed on a glass slide and placed planar on a Petri dish. The time until the film dissolved and caused a hole within film was measured.

2- Petri dish method

Two milliliters of distilled water was placed in petridish and one film was added on the surface of the water and the time required until the oral film was dissolved completely was measured.

In-vitro drug release

The profile of the SMLT dissolution was performed according to determine the dissolution release profile of the prepared SMLT oral strips . Dissolution medium was 900ml of phosphate buffer pH 6.8 and(0.1 N) HCl at 37 ± 0.5°C with a rotation speed of (50) r.p.m.

Beside to that , the release profile of the Singulair ® . tablet (as references) was also determined using 900ml of the same test environments. (10 ml) of samples were taken at time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 and 30 minutes) for dissolution of fast dissolving layer while continue in sampling every 30 minutes reach to 4 hours for the strips contain the two layers (fast dissolving layer and sustained release layer) at 50 rpm with 900 ml volume of fresh 0.1 N HCl. Both(0.1N) HCl and phosphate buffer pH 6.8 were replenished after each sampling. Samples were filtered through 0.5 µm membrane filter and the concentration of the dissolved SMLT was determined using spectrophotometric technique at SMLT λmax (340nm) , the percent release of SMLT from film was measured. The obtained results represent the mean of three findings .

Meanwhile the drug released period ($T_{80\%}$) and percentage drug dissolve in two minutes (D_{2min}) were used for the first fast dissolving layer of the strip while the sustained and uniform releasing for the second sustained release layer. [17]

Compatibility studies

A- Spectroscopy of the formula (FTIR)

Samples are grinded and mixed with potassium bromide. The spectrum was obtained (for all formulas) between the wave number 4000-400 cm^{-1}.

B-Scanning electron microscope

Scanning electron microscope of the selected formula for both fast dissolving layer and sustained layer were confirmed by direct deposition of the film on double-side carbon tape and coated with gold, the sample visualized using scanning electron microscope operated with a secondary detector at different acceleration voltage and at different magnification. [17].

Statistical analysis

The ANOVA statistical analysis were used, as (probability >0.05) insignificant results, and (probability < 0.05) ,as a significant results .

Results and Discussions

All the prepared fast dissolving films appeared homogenous, transparent, with faint light off white color , and smooth surface properties which they contain (Guar gum, Xanthan gum, and Carrgeenan polymers). The bi-layered formulas are smooth, show homogeneous, cloudy off white with formulas prepared by Eudraget RS® and white with formulas prepared by PVP. [18]

Effect of different types of polymers

Formulas (F1-F9) in (table 1) were used to study the effect of polymer type (Xanthan gum, Guar gum and Carrgeenan) and their weights (30 , 35 , and 40mg.) as the physical and mechanical properties of the prepared SMLT fast dissolving layer.

Results showed in table (2) that the lowest disintegration time of the film forming polymer is gave by Carrgeenan polymer F7 which have disintegration time (22sec.) and with good mechanical properties (folding endurance more than 300) and surface pH with in normal physiological mouth pH (6.6) range of oral cavity .

Films of Guar gum (F4) and (F5) showed in-vitro disintegration time 29 seconds and 31 seconds respectively but these polymers give brittle films with weak folding endurance (1 fold) , which is in a consistent

with results obtained by Harsha *et.al* for tramadol [19]. While films of Xanthan gum (F1-F3) have good mechanical properties with good peeling off and good appearance , but with a long disintegration time (100- 127 seconds) , which may be attributed to the interaction of drug with dimethyl phthalate molecules which is enriched with multi hydroxyl groups that formed hard ester bonds, and the long disintegration time of this polymer due to the swelling property of this polymer which make a gel like layer on the surface of the film upon contact with aqueous media lead to prevent penetration of water to the film, this swelling property increased with increasing of the polymer concentration., which is similar to the dicyclomine drug[20].

Also , the results in table (2) revealed different thickness of flake films depending, on the type and concentration of the,, film forming polymer used where the thickness of the film increased as the polymer concentration increased. At the same time for each polymer type where the thickness of film increased lead to delay the time required for, disintegration. A very low standard deviation value indicates the uniform thickness of the films. Surface pH was found to be in the range (6.6 – 7.1) which close to salivary pH, which indicates that the films have less potential to irritate the oral mucosa, so they are comfortable films.

Table (2): Physical and mechanical properties of the prepared SMLT oral fast dissolving layer formula F1-F9 / values are presented as mean ± SD (n=3).

Formulation code		Film* thickness (mm)	*In-vitro* DT (sec)	Folding endurance	Surface pH	Drug content (%)
Xanthan Gum	F1	0.077±0.0001	100±0.032	300	6.9±0.001	99.4±0.55
	F2	0.092±0.0001	110±0.043	300	6.8±0.002	94.6±0.54
	F3	0.99±0.0001	127±0.041	300	6.8±0.002	94.4±0.53
Guar Gum	F4	0.035±0.0001	29±0.035	1	7.1±0.001	99.1±0.52
	F5	0.043±0.0001	31±0.039	1	6.8±0.003	94.8±0.51
	F6	0.048±0.0001	55±0.058	1	6.5±0.001	98.8±0.54
Carrgeen anGum	F7	0.039±0.0001	22±0.031	300	6.6±0.002	98.7±0.54
	F8	0.042±0.0001	43±0.034	300	6.8±0.001	93.5±0.52
	F9	0.046±0.0001	69±0.030	300	6.9±0.002	91.1±0.52

Effect of different concentrations of carrageenan polymer

According to the physical and mechanical properties, Carrageenan gum was selected as an optimized suitable polymer for prepare fast dissolving SMLT layer with respect to its disintegration time , pH and mechanical strength .On the other hand , formulas (F8, and F9) of different Carrageenan concentrations were further evaluated to get an optimum suitable polymer concentration by study their dissolution profile parameters.Table (3) shows that the formula (F7) has the highest $D_{2\ min}$ percent (39.24%) and the lowest $T_{80\%}$ (3.7min) compared with formulas F8 and F9 , indicating that Carrgeenan at this concentration gave lowest interaction between with SMLT **,** allowing higher solubility to the drug , and the higher dissolution rate appear[21] as shown in figure (1).

Table (3): Effect of carrageenan concentration on the *In-vitro* dissolution parameters of fast dissolving SMLT layers in phosphate buffer pH 6.8. at 37 °C.

Formula No.	$T_{80\%}$ (min)	$D_{2\ min}$ (%)
F7	3.7	39.24
F8	8.1	20.66
F9	9.7	13.76

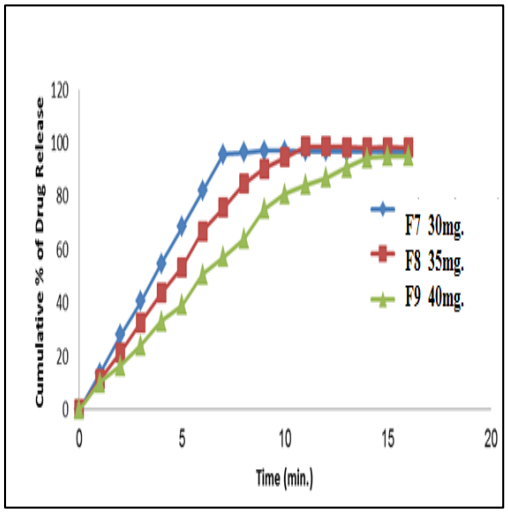


Figure (1): Effect of carrageenan polymer on the dissolution profile of the prepared SMLT fast dissolving layer in pH 6.8 phosphate buffer at 37°C. (results are expressed as mean, n=3).

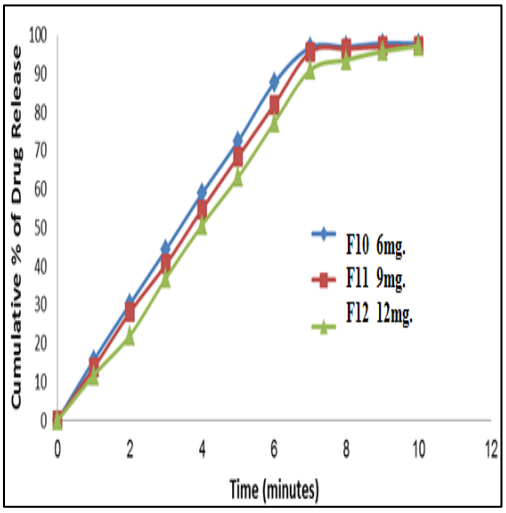


Figure (2): The. Effect of glycerinated dimethylphthalate concentration ,on the release profile of fast dissolving layer of SMLT in pH 6.8 phosphate buffer at 37°C (Results are expressed as mean, n=3).

Effect of combined plasticizers ratios

Table (4) shows the effect of changing the concentration of a dual combined dimethylpthalate – glycerin (1:1) ratio . Results revealed that there is no significant difference (P<0.05) in the disintegration time of SMLT fast dissolving layer upon changing the concentration of dimethylpthalate – glycerin (1:1) ratio . Mean while Figure (2) revealed also that thee is no significant difference in the release profile of SMLT , which may be attributed to to the effect of both plasticizers alone, the same result was obtained when Losartan fast dissolving oral strip film formulated with the combined glycerinated resins as plasticizers , which they show little enhance in dissolution rate [18] .

Table (4): Effect of glycerinated dimethyl-phthalate concentration on the *In-vitro* dissolution parameters in phosphate buffer pH 6.8. at 37°C

Formula No.	$T_{80\%}$ (min)	$D_{2\ min}$ (%)
F10	3.9	38.7
F11	3.1	39.5
F12	3.4	40.2

Effect of lactic acid as a saliva stimulant

The formulas F13 and F 14 were prepared using different concentrations of lactic acid as a stimulant , Table 5 , revealed that no effect of film thickness differences occurred . Meanwhile the surface pH decrease significantly (P< 0.05) for both F13 and F14,this may be attributed to the acidic nature of lactic acid , while the disintegration time decrease to 15 and 11 seconds for both F13 and F14 compared with 22 second for F7.This result also reported by Shweta Kalyanand et al, where get an enhancement in the dissolution of atenolol fast dissolving film by using weak acid stimulants.[22]

On the other hand adding lactic acid to the prepared SMLT fast dissolving layer showed an enhancement in the dissolution release profile compared with (F7) as discussed in table (5) which represented by figure (3).

This result also reported by Deep AK et al. were they got an increase in disintegration and enhance in dissolution release profile of cinnarizine fast dissolving films by increasing the amount of citric acid from 2% to 4% w/w[23].

Table (5): Physical properties of the prepared SMLT fast dissolving layer F13 and F14 / values are

Formulation code		Film* thickness (mm)	*In-vitro* DT (sec)	Surface pH	Drug content (%)
Lactic Acid 4mg.	F13	0.070±0.001	15±0.034	6.1±0.001	97.92±0.56
Lactic Acid 6mg.	F14	0.068±0.001	11±0.015	5.5±0.001	98.61±0.51

presented as mean±SD (n=3), (n*=5).

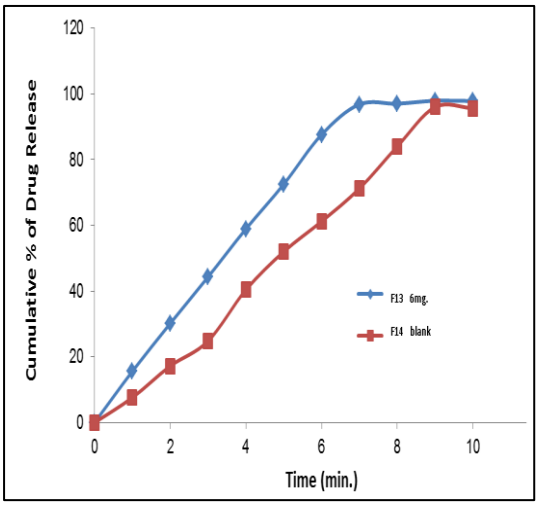


Figure (3): The effect of lactic acid stimulant on the dissolution profile of the prepared SMLT fast dissolving layer in pH 6.8 phosphate buffer at 37°C. (results are expressed as mean, n=3).

Sustained release layer

Formulas (FSR1-7 to-FSR6-7) , were utilized to study the effect of polymer type (Eudraget® RS100, and PVP K17), with different concentrations on the physical properties of the prepared **SMLT** bilayer strip.

The results showed in table (6) for formulas prepared by using Eudraget® RS100 and PVP K17 in different ratios (FSR1-7 to-FSR3-7) show decease in disintegration time as the Eudraget® RS100 concentration increased ; this is due to the swelling property of the hydrophilic polymer (Eudraget® RS100) which form gel like layer cause reduction of water permeation and disintegration this swelling property increased with increasing hydrophilic polymer concentration, this result is in a consistent with the result obtained by Shalini Mishra *et al.*,[24].

While for formulas prepared by PVP K17 in different concentrations (FSR4-7 to-FSR6-7) shows also a reduction in the disintegration time with increase addition of PVP K17, which may be attributed to the higher solubility of PVP K17 [24].

The dose of SMLT used is (10mg) divided as (5mg) for each layer (Fast release layer and sustained release layer), so the dissolution profile evaluated in a manner that 50% of the drug (5mg) must release fast with in short duration of time (as its fast release layer) while the rest 50% must be released in a sustained manner in a comparison with fast dissolving layer .

On the other hand , the other formulas , do not show any significant variations, concerned with film thickness , surface pH , and drug content percentages.

According to the these results, the formula (FSR6-7) which is subjected into bi phasic sustained layer composed from PVP K17 only selected as an optimized formula with low disintegration time (21 seconds), besides to first 50% of drug released with (15 minutes) and the remaining drug released in a sustained stable manner reach (4 hours) , as shown in table (7) .

Table (6): Physical properties of the prepared SMLT sustained release layer values are presented as mean ±SD (n=3)

Formulation code		Film* thickness (mm)	*In-vitro* DT (sec)	Surface pH	Drug content (%)
Eudraget ®	FSR1-7	0.108±0.001	95±0.011	6.1±0.001	99.97±0.56
	FSR2-7	0.144±0.001	90±0.014	5.8±0.002	99.53±0.51
	FSR3-7	0.131±0.001	82±0.013	6.4±0.001	98.36±0.55
PVP K17	FSR4-7	0.124±0.001	46±0.018	6.2±0.001	98.95±0.50
	FSR5-7	0.104±0.001	42±0.032	6.0±0.002	99.54±0.50
	FSR6-7	0.086±0.001	21±0.014	5.9±0.001	99.67±0.53

Table (7): *In-vitro* dissolution parameters of different formulas in 0.1N HCl. and 37°C Temp.

Formula No.	$T_{50\%}$ of drug released (min.)	$T_{100\%}$ of drug released (min.)
FSR1-7	22	225
FSR2-7	27	240
FSR3-7	25	230
FSR4-7	26	240
FSR5-7	20	270
FSR6-7	15	240

Compatibility of SMLT and polymers

FTIR of the prepared fast dissolving film F7 and sustained release film FRS6-7 were utilized to investigate the interaction of the drug and polymers used , It was seen that there was no significant shift with FTIR spectra by comparing with the spectra of SMLT powder , and polymer used as a physical mixture of SMLT with polymer as shown in figures 4, 5 and 6 that indicated lack of the possibility of interaction between SMLT and polymers used in the preparation of bi layer films.

On the other hand ,Figure (7) shows the morphology of both layers , the fast dissolving layer (7a) and sustained release layer (7b) of the prepared SMLT bi layer oral strip. The fast dissolving layer (Carrageenan layer) show clear, smooth surface without pores.

While the sustained release layer (PVP K17 layer) showed clear porous surface , which may be referred to the rapid diffusion and evaporation of solvent which easily occurred with low polymer concentration, this result , also reported by YM Jagtap et al [24] which revealed that porous structure is useful to enhance the disintegration of the sustained release layer. In a comparison of the dissolution release profile of the selected fast release layer formula (F7) with the release profile of the marketed SMLT oral tablet (Singulair ®), the result indicated no significant difference ($p>0.05$) in cumulative percent of SMLT release from prepared formula (F7) and the marketed oral plain tablet (Singulair®) as shown in figure (7).

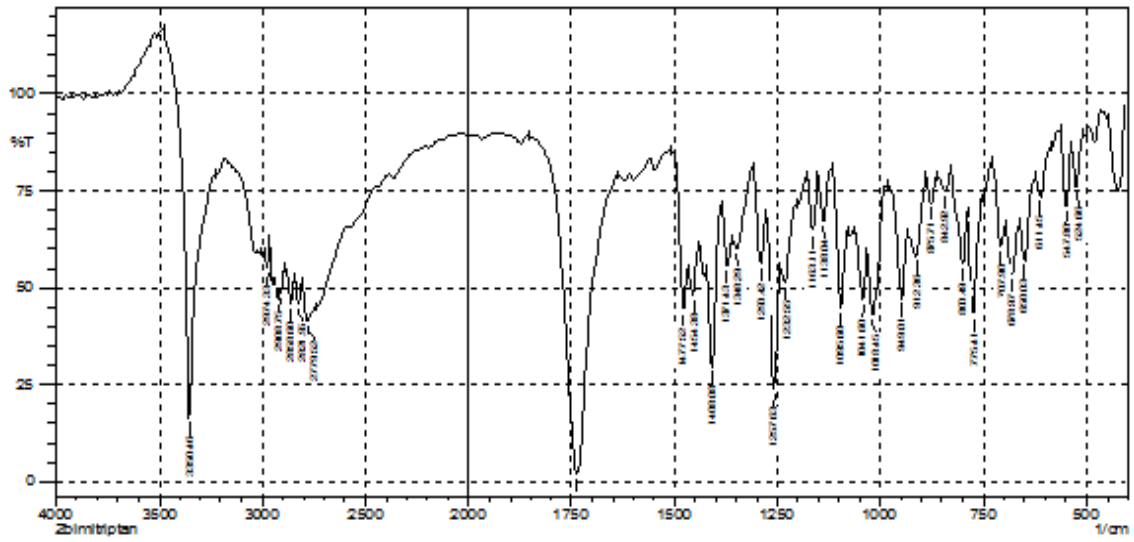


Figure (4): FTIR spectrum of SMLT pure powder

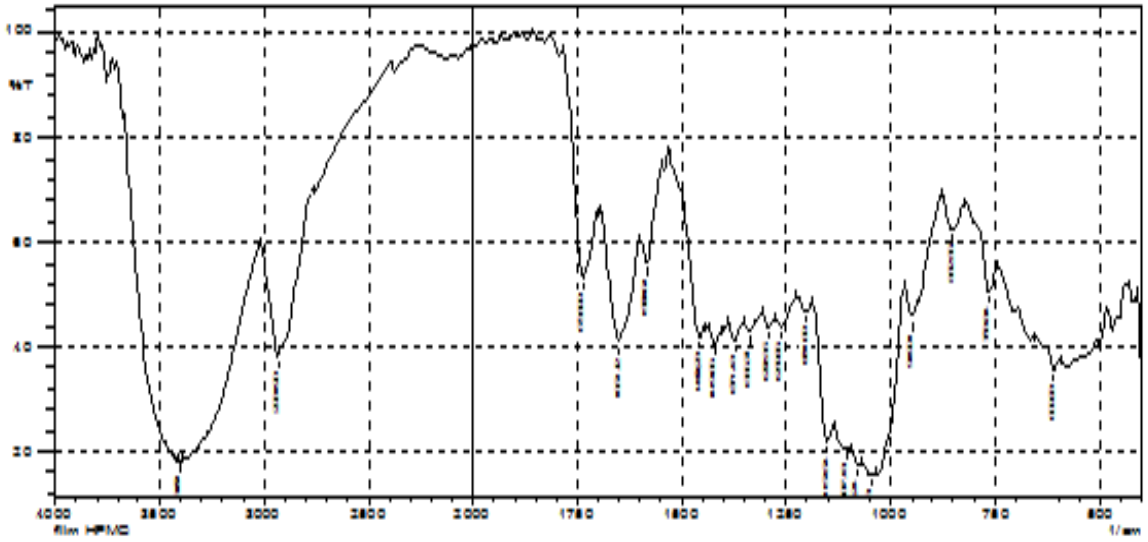


Figure (5): FTIR spectrum of Formula 7 SMLT fast dissolving film

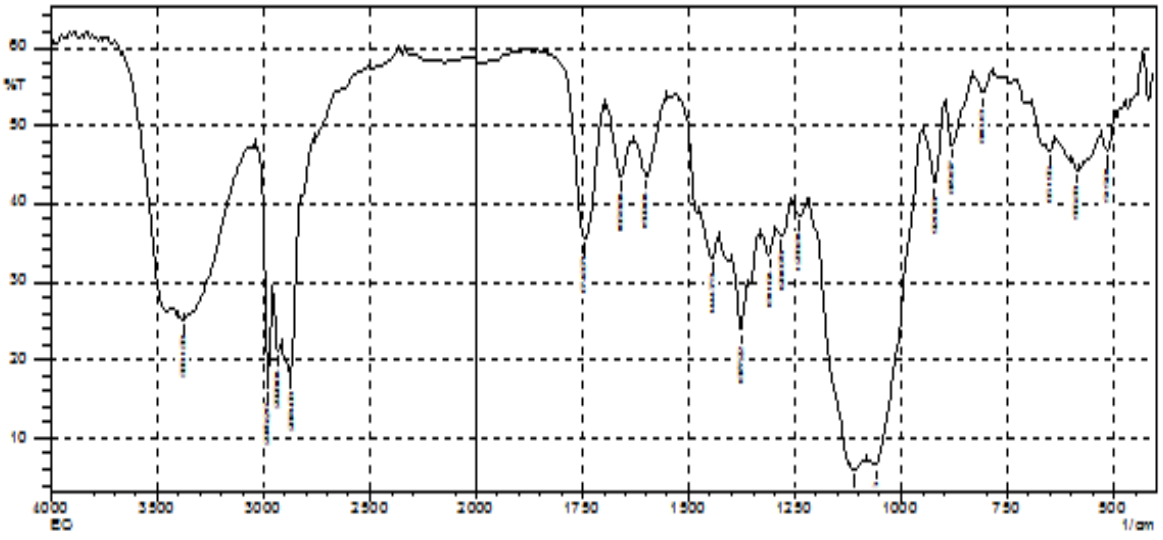
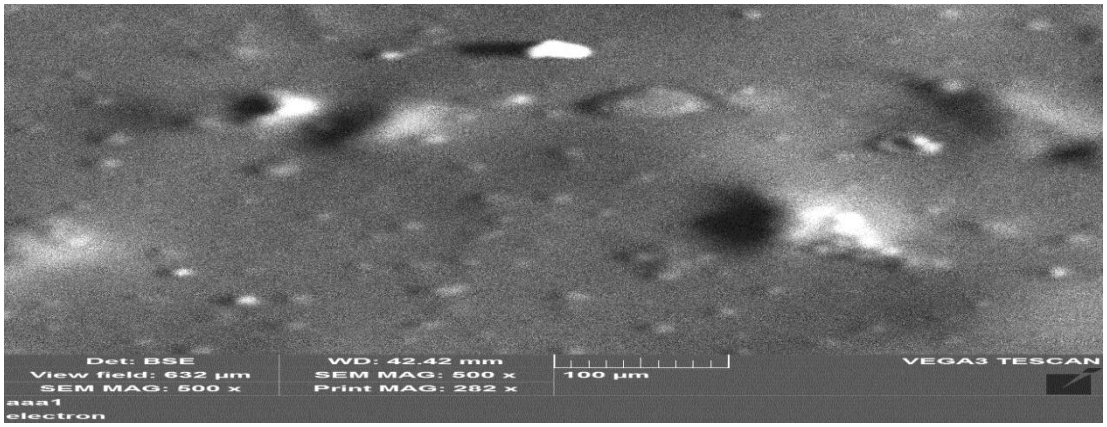
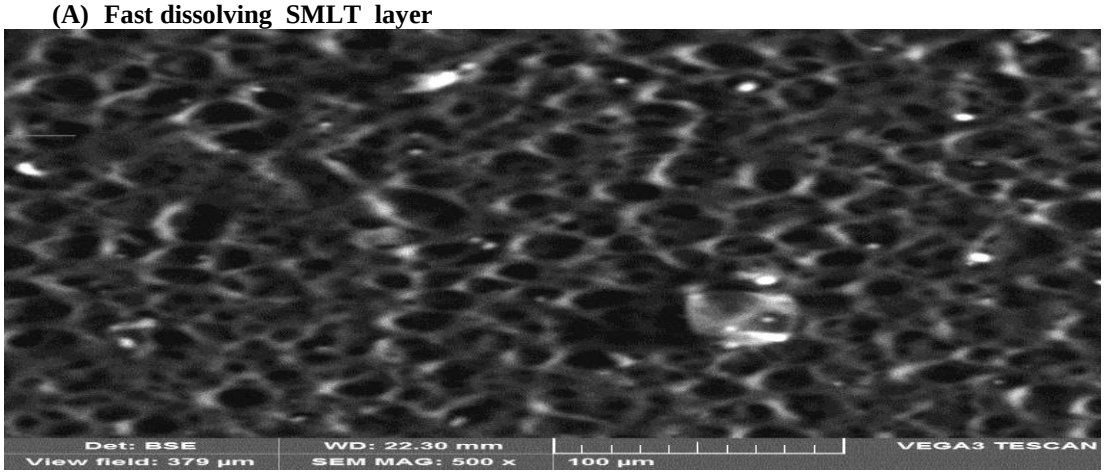


Figure (6): FTIR spectrum of FSR7-6 SMLT sustained release layer



(A) Fast dissolving SMLT layer



(B) Sustained release SMLT layer

Figure (7) SEM of FSR6-7 bi layer SMLT buccal strip

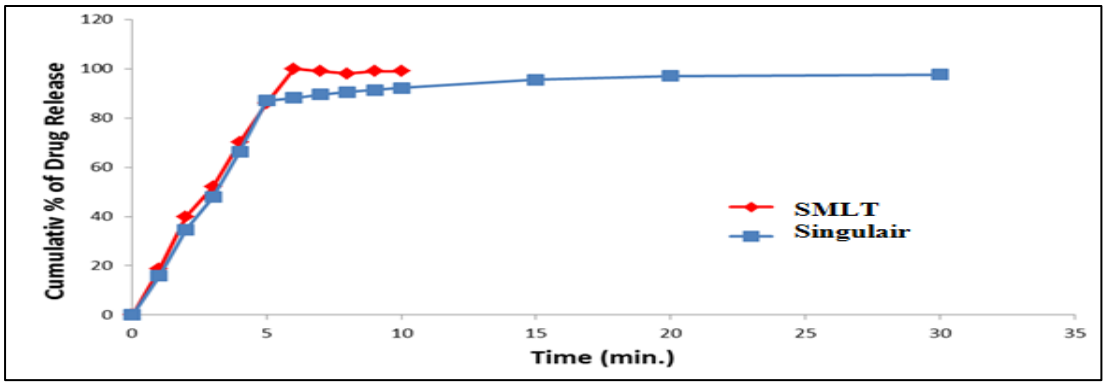


Figure (5): A comparison of cumulative dissolution profile of the prepared SMLT fast dissolving film and marketed SMLT oral plain tablet (Singulair®) in pH 6.8 phosphate buffer at 37°C.

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