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Preparation and Characterization of Mucoadhesive Buccal Film for Delivery of Meloxicam

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Authors' contributions

This work was carried out in collaboration between all authors. Author ARG managed the literature searches and reviewed the differential scanning calorimetry analysis and in-vitro drug release studies. Authors MMG and SSB designed the study, wrote the protocol and managed the analysis of the study. Author RBG carried out the experimental work, performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Preparation of mucoadhesive buccal films able to deliver the meloxicam drug to the site of application through oral mucosal tissues. This dosage form is advantageous due to absence the problems of the ordinary dosage forms.
Study Design: In this research, it was prepared a lot of formulations from different polymers and plasticizers to select the best one which has the optimum and required characteristics.
Place and Duration of Study: Department of Pharmaceutics, Faculty of Pharmacy, Suez Canal University and Misr International University, Egypt, between July 2009 and July 2012.
Methodology: There are different polymers used in preparation of the films which are hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, pectin and polyvinyl alcohol. Also, the plasticizers used are glycerin, propylene glycol and polyethylene glycol. The film was prepared by solvent casting technique. Firstly, the calibration curve of meloxicam was carried out. Then, the properties of the formulations

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were examined through some experiments which are determination of drug content, study of efficacy of mucoadhesion, *in-vitro* drug release studies and differential scanning calorimetry.
Results: It was found that the formula containing polyvinyl alcohol 2% (w/w) and propylene glycol 20% from the weight of the polymer has ideal characteristics. Results showed that this formula has optimum drug content, acceptable mucoadhesion and fast drug release with compatibility between drug and excipents.

Keywords: Meloxicam; mucoadhesion; in-vitro release; differential scanning calorimetry.

1. INTRODUCTION

In the last decades, joint diseases have become spread a lot between people. Rheumatoid arthritis and osteoarthritis are considered among these diseases. Rheumatoid arthritis is the most common systemic inflammatory disease characterized by symmetrical joint inflammation. It processes extraarticular involvement which includes rheumatoid nodules, vasculitis, eye inflammation, neurologic dysfunction, cardiopulmonary disease, lymphadenopathy, and splenomegaly. The most popular symptoms are joint and muscle pain, stiffness, fatigue and weakness. The common signs are tenderness with warmth and swelling in the affected joints [1]. Osteoarthritis (OA) is a disease of cartilage that results in failure of the chondrocyte to maintain proper balance between cartilage formation and destruction. This causes loss of cartilage in the joint, local inflammation, pathologic changes in underlying bone, and further damage to cartilage triggered by the affected bone. OA disease is induced from both mechanical and biologic events. Joints pain and stiffness are the most common symptoms of the disease. OA signs are probability of joint enlargement, crackling sound during motion and limited range of motion [2]. So, the need for anti-inflammatory and analgesic drug as non-steroidal anti-inflammatory drugs is the first line treatment in the management of osteoarthritis and rheumatoid arthritis.

Meloxicam which is non-steroidal anti-inflammatory drug can be considered a good treatment for joint disorders due to its mechanism of action. Actions of meloxicam occurred through Inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) from plasma concentration. It has inhibitory effects on cyclooxygenase-2 more than cyclooxygenase-1 which is required [3]. Meloxicam has high anti-inflammatory potency, where it induces analgesic effect on inflammatory pain with excellent tolerability. This is due to its preferentially inhibition of COX-2 than COX-1 isozyme. In arthritis, meloxicam inhibits paw swelling, bone cartilage destruction and systemic signs of disease [4]. This drug performs its actions as a result of presence of excellent properties. It has a high rate of joint penetration due to high synovial uptake. So, meloxicam is very beneficial in joint arthritis diseases. Moreover, meloxicam can reduce fever by decreasing plasma cortisol and interlukin-6 [5].

Ordinary dosage forms of meloxicam are suspension 7.5mg/5ml and tablet 7.5 mg and 15 mg. These formulations are called Mobic [6]. But, these old formulations were suffering from many side effects which related to the oral administration of the drug. Firstly, slow onset time of oral meloxicam dosage forms in comparison with mucoadhesive buccal films. For instance, the time needed to reach maximum plasma concentration after administration of meloxicam dose (Mobic) is approximately 4-5 hours in the fasted state and 5-6 hours in the fed state [7]. Secondly, difficulty of swallowing of the oral dosage forms for geriatrics. This is

an important point because this drug treats osteoarthritis and rheumatoid arthritis, these diseases are related mostly to geriatrics. So, the aim in this study is to prepare new dosage form fulfilling the patient's circumstances and interest with least percent of side effects. This aim can be developed by formulating meloxicam in mucoadehesive buccal film which is a new route that will develop a revolution in drug industry.

This dosage form has many advantages. The film can be defined as a dosage form that employs a water dissolving polymer which allows the dosage form to quickly hydrate, adhere, and dissolve when placed on the tongue or in the oral cavity which results in systemic drug delivery [8]. There is a property which accelerates absorption is this dosage form which is large surface area of the film in comparison with tablets. This allows quick wetting of the film [9]. Buccal mucosa is rich with blood supply which acts as a perfect and fast site for absorption of drug [10]. So, it is advantageous to put a drug treating pain and inflammation like meloxicam in the form of thin buccal film, because patient in these cases needs a rapid solution for his/her symptoms. Since, the drug is not swallowed; it will not be affected by the first pass metabolism [11]. Some researchers stated that they prepared atenolol buccal films using many polymers as sodium carboxymethyl cellulose (SCMC), polyvinyl alcohol (PVA) and hydroxypropylmethyl cellulose (HPMC). Films showed satisfactory physicochemical and mucoadhesive properties. Also, release of drug from the film was accepted in a high degree. It was found that the drug in this dosage form was protected from first pass metabolism which is required [10].

2. MATERIALS AND METHODS

2.1 Materials

Meloxicam, HPMC and hydroxyethyl cellulose (HEC) were acquired as a gift from Medical Union Pharmaceuticals (MUP), (Abou Sultan, Ismailia, Egypt). PVA was bought from Arabic Laboratory Equipment Co. (ALEC), (Egypt). SCMC high viscosity was bought from El Nasr Pharmaceutical Chemicals Co. (ADWIC), (Qaliubiya, Egypt). Polyethylene glycol 400 (PEG 400) was bought from Alpha Chemika (Mumbai, India). Pectin was purchased from Sigma-Aldrich (Germany). All other chemicals are of analytical grade.

2.2 Methods

2.2.1 Preparation of buccal films

Polymeric film vehicle was carried out by calculating the desired amount of polymer, plasticizer and drug. The weight of the polymer (HPMC, HEC, SCMC, PVA or pectin) incorporated in the film was 2% (w/w). Each polymer has a different method of preparation. SCMC and HEC were dispersed in 3/4 the volume of distilled water at 25 ºC. Then, the rest 1/4 of volume distilled water was added [12]. HPMC was dispersed in 1/3 the volume of the distilled water at 90 ºC. Then, the 2/3 volume of the distilled water at 5 ºC was added [13]. Pectin was dispersed in dilute solution of 0.1N HCL at pH 3. Then, calcium chloride 0.1% (w/v) was added and the solution was heated at 50ºC [14]. PVA was dispersed in hot distilled water at 80-100 ºC [15]. Then, plasticizer 20% from the weight of the polymer (PEG 400, glycerin or PG) and drug 0.5% (w/w) were blended to the polymeric solution. The medicated gel was kept overnight at room temperature to obtain clear and bubble free gel [16]. After that, this gel will be poured to the glass Petri dishes to be dried in oven at 60-70ºC [17]. Finally, the films were cut into the required dimensions, enveloped in aluminum foil and

stored in glass container to be ready for any experiment [18]. Table 1 shows the composition of each buccal film.

Table1. Composition of buccal meloxicam film including type and concentration of polymer and plasticizer

Formulation	Polymer					Plasticizer		
	HEC (MG)	HPMC (MG)	SCMC (MG)	PVA (MG)	Pectin (MG)	PEG 400 (MG)	Glycerin (MG)	PG (MG)
B1	0.0	0.0	0.0	2000	0.0	0.0	400	0.0
B2	0.0	0.0	0.0	2000	0.0	0.0	0.0	400
B3	0.0	0.0	0.0	2000	0.0	400	0.0	0.0
B4	0.0	2000	0.0	0.0	0.0	0.0	0.0	0.0
B5	0.0	2000	0.0	0.0	0.0	0.0	400	0.0
B6	0.0	2000	0.0	0.0	0.0	0.0	0.0	400
B7	0.0	2000	0.0	0.0	0.0	400	0.0	0.0
B8	0.0	0.0	0.0	0.0	2000	0.0	400	0.0
B9	0.0	0.0	0.0	0.0	2000	400	0.0	0.0
B10	2000	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B11	2000	0.0	0.0	0.0	0.0	0.0	400	0.0
B12	2000	0.0	0.0	0.0	0.0	0.0	0.0	400
B13	2000	0.0	0.0	0.0	0.0	400	0.0	0.0
B14	0.0	0.0	2000	0.0	0.0	0.0	0.0	0.0
B15	0.0	0.0	2000	0.0	0.0	0.0	400	0.0
B16	0.0	0.0	2000	0.0	0.0	0.0	0.0	400
B17	0.0	0.0	2000	0.0	0.0	400	0.0	0.0
B18	0.0	1000	0.0	0.0	1000	0.0	0.0	0.0
B19	0.0	1000	0.0	1000	0.0	0.0	0.0	0.0
B20	1000	1000	0.0	0.0	0.0	0.0	0.0	0.0
B21	1000	0.0	0.0	0.0	1000	0.0	0.0	0.0
B22	0.0	0.0	1000	0.0	1000	0.0	0.0	0.0

2.2.2 Construction of meloxicam calibration curve

An accurately weighted quantity of meloxicam (25 mg) was transferred in 50 ml volumetric flask to be dissolved in sufficient quantity of methanol and phosphate buffer pH 6.8 (50%:50%). Phosphate buffer pH was adjusted by using pH meter (3510, Jenway, UK). The concentration in the flask was 500 ug/ml. A 1 ml of this solution was diluted with the same reagents, methanol and phosphate buffer in 50 ml volumetric flask. The final concentration became 10 ug/ml. The standard solution of meloxicam was scanned spectrophotmetrically by using UV spectrophotometer, UV-1800 (Shimadzu, Japan). The measuring range was 200-400 nm against blank solution. The overlain spectrum of drug was recorded [19-20].

2.2.3 Physicochemical evaluation of polymeric matrix films

2.2.3.1 Determination of drug content

Uniformity of drug content was determined according to the following procedure. Three randomly selected films of each batch were weighed accurately and dissolved at room temperature in 50 ml methanol and stirred continuously for one hour on a magnetic stirrer. The volume was made up to 100 ml with phosphate buffer at pH 6.8. Then, 1 ml was

transferred to 10 ml volumetric flask and the volume was adjusted with phosphate buffer at pH 6.8 and methanol. Concentration of drug contained in each film was measured spectrophotometrically at λ max 361 nm [21].

2.2.3.2 Study of efficacy of mucoadhesion

The force required to detach the bioadhesive films from the mucosal surface was used as a measure of bioadhesion performance. The instrument used is composed of a modified two arm physical balance. The right pan of the balance had been replaced by a formulation holding microscopic glass slide (2.5 × 7.5 cm) and counter balanced by a water collecting beaker suspended to the left arm. Films were fixed on the center of the formulation holding glass slide with an adhesive. The beaker received water from 100 ml burette, which was kept at a high place in such a way that enables it to be above the water collecting beaker. A metal beaker holder was used to suspend the water collecting beaker to the balance and another one was used to suspend the formulation holding microscopic glass slide to the other side of the balance. Another glass beaker was filled with phosphate buffer (pH 6.8) to simulate in-vivo saliva conditions. A magnetic stirrer provided with temperature control was used to maintain the temperature of phosphate buffer (pH 6.8) at 37±0.5 *ºC*. A piece of rabbit intestinal mucosa, 3 cm long, was slightly secured on another microscopic slide by using two paper clips and then the glass slide was fixed in such a way to be under the other glass slide holding the film. The exposed film surface was moistened with phosphate buffer (pH 6.8) and left for 30 seconds for initial hydration and swelling. Then glass slide holding the film was kept on the glass slide holding the mucosal tissue in such a way that film completely remained in contact with mucosa. The whole assembly was kept undisturbed for 3 min (preload time) to establish the adhesion between the film and mucosal tissue. After the preload time, water collecting pan was suspended to the left arm and water was added in it, until detachment of the film from mucosal surface took place. A piece of carton or rubber was kept under the water collecting beaker to avoid breakdown of it at the time of detachment. Weight of water collected in the beaker at the time of detachment which is considered a force was measured. The experiment was performed in triplicate [18]. Fig. 1 explains the main parts of the mucoadhesion instrument in details.

2.2.3.3 In-vitro drug release studies

Three samples from each formula were utilized to examine their drug release profile [12]. The size of the sample was 2.5 cm^2 and the dose of meloxicam in it was 9.824 mg.This test give information about release rate of the drug from the formula and also the amount of the drug released during that time. Varian VK 7000/7010 Dissolution apparatus was used to perform this study. The dissolution medium that is equivalent to saliva is phosphate buffer at pH 6.8. Volume in the vessel of the dissolution apparatus (Varian VK7000 Dissolution apparatus, USA) is 900 ml [22]. Temperature should be adjusted at 37±0.5º*C*. There are two parameters related to the paddle should be taken into consideration. Speed of the paddle should be 50 RPM [21]. This is because the normal mouth motion of the body approximately within this speed. Also, the height of paddle from the bottom of the vessel should be fixed for all formulations at 2.5 cm [23]. The film can be attached to the paddle directly [21]. This attachment can be done by using a thread. At each time interval (5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150 and 180 minute) [24], 10 ml will be withdrawn from the vessel to be analyzed and replaced by buffer to maintain sink condition. It is important to filtrate the 10 ml before analyzing them be using 0.45 um Millipore filter because the solution may contain some particles not dissolved such as the polymer, plasticizer or the drug itself [21]. The filtrate will be analyzed spectrophotometrically at λ max 361. There are many release

parameters used to differentiate between different formulations present such as % of cumulative amount of drug released after 3 hours ($\%Q_3$) and time for 100% release (T_{100}) [25].

Also, it is important to calculate release efficiency (RE)

$$RE = ({}_0\int^t Y.dt) / Y_{100}.t \quad (1)$$ [26].

Mechanism of drug release and variations in release profile among formulations can be explained by plotting drug released versus time. Kinetic models such as zero order, first order, Higuchi square root, and Korsmeyer-Peppas are very important to investigate release. Zero-order model

$$M_t = M_0 + K_0t \quad (2)$$

where M_t is the amount of drug dissolved at time t, M_0 is the initial amount of drug and K_0 is the zero order release constant [27].

First order model

$$LogM_t = LogM_0 - kt / 2.303 \quad (3)$$

where M_t is the amount of drug dissolved at time t, M_0 is the initial amount of drug and K is first order constant [28].

Higuchi model

$$M_t = M_0 + K_H t^{0.5} \quad (4)$$

where M_t is the amount of drug dissolved at time t, M_0 is the initial amount of drug and K_H is the Higuchi rate constant [27].

Korsmeyer-Peppas model

$$M_t /M\infty = k (t)^n \quad (5)$$

$M_t/M\infty$ is the fraction of drug release at time t, k is the release rate constant, and n is the release exponent indicative of the mechanism of release [27].

To reinforce our results, data can be analyzed by using one way analysis of variance which called ANOVA. Spss statistical program (version 16, 2007, SPSS Inc, Chicago, IL) was used. The statistical differences that produce $P \leq .05$ can be considered significant [29]. Also, LSD post hoc test was used during the analysis.

2.2.3.4 Differential scanning calorimetry (DSC) analysis

Compatibility of meloxicam and different polymers to be used for the development of film formulations was studied using a differential scanning calorimeter (DSC 60, Shimadzu, Japan) at a nitrogen flow of 30 mL min^{-1} [30]. Thin films are easily prepared for encapsulation. Typically, a cork borer or a clean paper punch is used to punch several sample specimen disks from the larger thin film sheet. Other tools that can be used for thin film preparation are scissors or razor blades [31]. Samples (1-8 mg) were sealed in

aluminum pans and heated at a scanning rate of 10 ºC min^{-1} [32]. Range of the heating temperature is 35-270ºC.

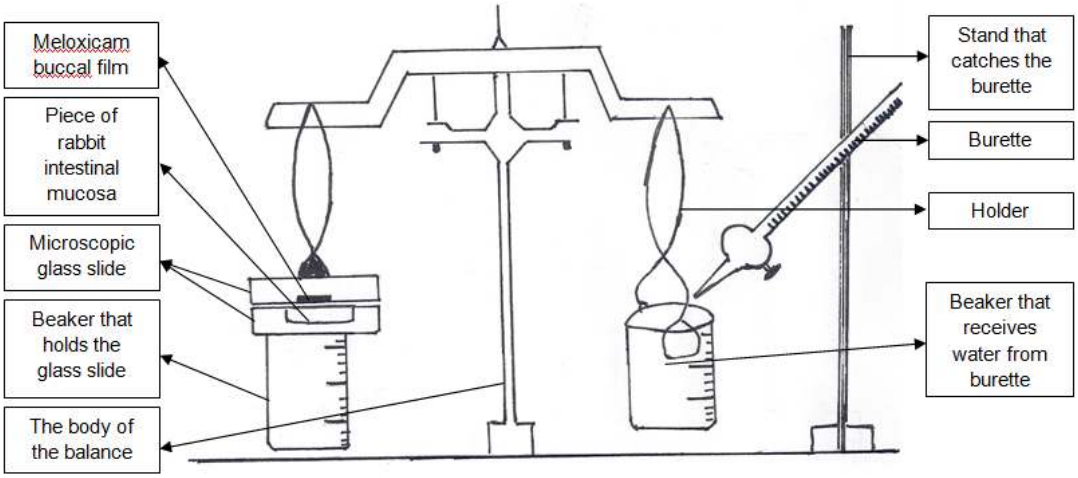

Fig. 1. The main parts of the mucoadhesion instrument

3. RESULTS AND DISCUSSION

3.1 Construction of Meloxicam Calibration Curve

By scanning of meloxicam solution in the UV spectrophotometer, it was found that maximum wavelength was 361 nm. This complies with Khan et al [20]. The data of each absorbance and concentration are graphically represented in Fig. 2.

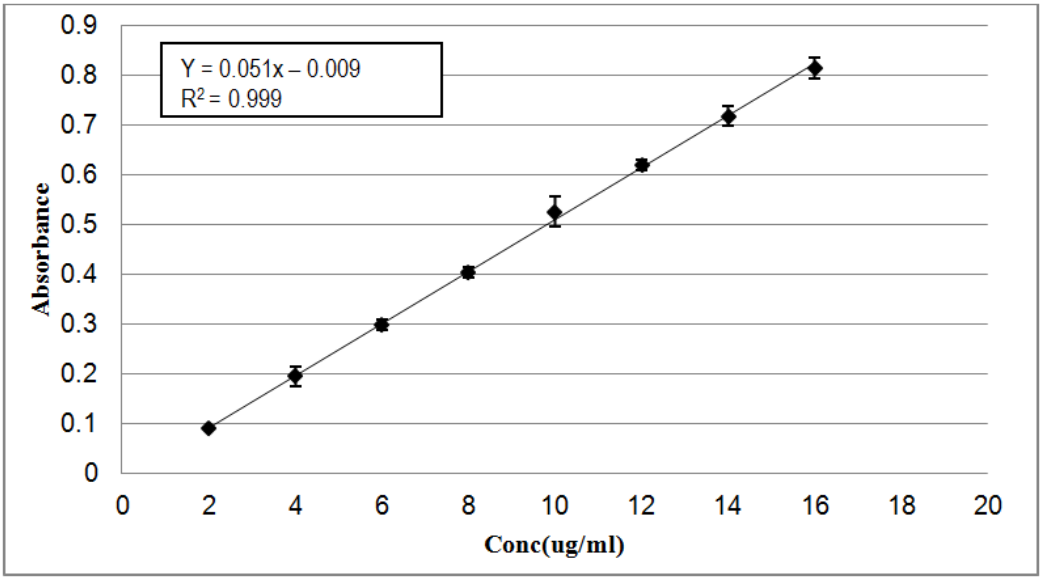

Fig. 2. Meloxicam calibration curve

3.2 Physicochemical Evaluation of Polymeric Matrix Films

3.2.1 Determination of drug content

Homogenous uniform drug distribution is very important aspect that must be verified during the preparation of the film [33]. If the drug is not dispersed and distributed well in the preparation, each film will contain a different amount from the drug. Also, the drug in the film itself in this case will not be homogenously distributed. As mentioned in Table 2, drug content in most formulations was found to be not less than 90% which is accepted. It was showed that drug content in most formulations used in their research was 91-98% [34]. This means that the drug is uniformly distributed in the preparation and inside the film itself. B10 and B12 films contain an extra drug content more than 120 % which is not accepted. Venkatalakshmi et al, stated that the highest drug content for the prepared films was 109%. This percent was found in the film prepared from SCMC and PG [21]. Also, there were some values below 90% as B8 which is not accepted. Prasanth et al, explained that drug content was 66-97%, so there were formulations containing very low amount of drug [35]. Thus, drug will not perform its action perfectly. This is due to heterogeneity between meloxicam and different types of polymers. So, B2, B3, B5 and B17 formulations have the optimum drug content.

Table 2. Drug content and mucoadhesion of the films

Film	Drug content %	Mucoadhesion (G)*
B1	94.01 ± 6.60	18.70 ± 0.44
B2	98.23 ± 5.83	15.63 ± 1.40
B3	100.79 ± 4.18	11.83 ± 0.95
B4	106.98 ± 9.95	54.07 ± 0.93
B5	101.32 ± 3.00	36.30 ± 3.34
B6	82.63 ± 15.75	31.17 ± 2.40
B7	113.43 ± 3.07	25.10 ± 4.00
B8	59.88 ± 14.53	20.80 ±0.26
B9	72.85 ± 3.70	12.03 ± 1.12
B10	121.22 ± 15.83	33.53 ± 1.23
B11	80.97 ± 1.15	68.67 ± 2.40
B12	122.81 ± 3.89	23.37 ± 0.93
B13	109.57 ± 5.89	23.83 ± 3.49
B14	92.88 ± 4.15	17.40 ± 1.41
B15	104.16 ± 6.94	24.73 ± 0.60
B16	88.55 ± 1.55	33.83 ± 12.00
B17	101.06 ± 7.20	39.63 ± 1.46
B18	105.03 ± 4.17	17.77 ± 0.25
B19	89.28 ± 1.17	24.80 ± 4.75
B20	94.41 ± 8.01	18.97 ± 0.98
B21	96.80 ± 14.87	22.37 ± 0.84
B22	89.95 ± 4.92	23.63 ± 0.51

Each value represents the ± SD (n = 3).

** Weight of grams of water required to detach films from mucous membrane.*

3.2.2 Study of efficacy of mucoadhesion

It is important for the mucoadhesive films to be adhered to mucus membrane in the buccal cavity to allow release of the drug. Mechanism of polymer-mucus interaction can be explained by intimate contact between the bioadhesive polymer and biological tissue. After that, chemical bonds play its role during the hydration process to enhance bioadhesion [36].

According to Table 2, Pectin polymer did not give promising results for mucoadhesion. These inadequate mucoadhesion properties were noted whether by the addition of glycerin or PEG400. Researches explained that mucoadhesion of pectin is not high either the buccal tissues were hydrated enough or not [37]. This can be explained from the nature and structure of pectin. Pectin is a polysaccharide polymer and consists of partially methoxylated polygalacturonic acid [38]. So, this polymer will not adhere well to buccal cavity which is not preferred.

From Table 2 showed that, PVA has low mucoadhesive properties in the prepared buccal patches. Addition of glycerin to the polymer is better than propylene glycol or PEG400. Mishra et al, stated that PVA patches that were used in their research gave the lowest values for mucoadhesion than HPMC and SCMC patches [39]. The reduced mucoadhesion of PVA is due to its high aqueous solubility [40]. It was proved that with the increase of polymer to drug ratio, the % of mucoadhesion in the film will increase [41]. This can also give a reason for low bioadhesive results of PVA polymer, where concentration of the polymer was 2%.

In addition, Table 2 showed that SCMC films whether plasticized or not have decreased mucoadhesive strength. This is due to its degree of solubility in water and its low viscosity [42-43]. B4 patch containing HPMC exhibited a strong mucoadhesion. This polymer is a long chain nonionic polymer and so its mucoadhesion is attributable to formation of physical bonds with the mucus components. It possesses a large number of hydroxyl groups that are responsible for adhesion. Formation of hydrogen bonds between the hydrophilic functional groups of mucoadhesive polymers and the mucus layer is a prerequisite for extensive and longer mucoadhesion. Also, the increase in the concentration of the HPMC polymer can enhance the mucoadhesion properties [44]. The highest mucuadhesion properties were observed for B11 films plasticized with glycerin. Jones et al, prepared a gel containing glycerin as plasticizer. They found that this formula gave the highest mucoadhesion [45]. Glycerin increases the viscosity of the formulation and thereby enhances the residence time of the film [46].

Combining two polymers with each others did not give promising results. Data in the Table 2 explained that B19 mixed formula has the highest mucoadhesion strength among all formulations that contain more than one polymer. This is due to presence of HPMC. As mentioned before, this polymer contains hydroxyl groups that help in hydrogen bond formation. So, the ability of mucoadhesion is high. Thus, the best formula which exhibited high mucoadhesion strength was B11.

3.2.3 *In-vitro* drug release studies

Release studies for specific dosage form are considered the most important studies have to be examined. If the selected drug is not released from the formulation in the exact time by its expected concentration, there will be no need for the patient to take it. So, it is important in this study to evaluate the ability of the formulation to release the whole dose of the drug in its

expected time. In the fast dissolving buccal films, the dose of the drug should be released within minutes. Thus, the factor of time is substantial. There are some parameters should be calculated to make sure the release of the drug from the film. Q_3% is the first parameter and can be defined as cumulative drug amount released after 3 hours [25]. The second parameter is release or dissolution efficiency. It is defined as the area under the dissolution curve up to a certain time 't', expressed as a percentage of the area under the rectangle described by 100% dissolution in the same time. This parameter can assume a range of values depending on the time intervals chosen for interpretation [26]. The last parameter is T_{100} which is defined as the expected time to achieve 100% drug release [47].

Kinetics of drug release from the mucoadhesive film can be calculated using some mathematical modelings. The models used are zero order, first order, Higuchi order, and Korsmeyer-Peppas model. Kinetics of meloxicam can be determined by detecting the best fitting release data to the mathematetical models used [25].

Table 3 showed that by applying the release of the different formulations to different release models, it was found that B5, B13, B14, B15, B17 and B22 obeyed zero order equation. The most fitting release rate for B1, B3, B4, B7, B10, B11 and B18 was first order kinetic. B9 and B21 followed Higuchi order kinetics. B2, B6, B8, B12, B16, B19 and B20 obeyed Korsmeyer-Peppas order kinetics.

It is remarkable in the data present in Fig. 3 and Table 4 that formulations which contain propylene glycol as a plasticizer have high release and dissolution properties than others. This is because in-vitro release studies of drug depend on the nature of plasticizer. Meloxicam as any other NSAIDs is very difficult to include it in the formulation. This is due to its low solubility. It was explained that solubility of NSAIDs can be enhanced through the addition of propylene glycol. In other words, incorporation of propylene glycol in the preparation helps the solution to be more hydrophilic. In addition, propylene glycol can increase the partition coefficient. This helpful property can increase the diffusion of meloxicam through different mechanisms of action [48].

Release of meloxicam from PVA films was explained through a specific mechanism. The PVA films swell very fast, the water flow weakens the network integrity of the polymer. So, erosion of the film takes place. This can be discussed by the viscosity of the polymer solution and solubility of PVA in water. If concentration of PVA is less than 5% w/v, the solution will be less viscous [40]. ANOVA test for PVA formulations showed that the statistical differences between B1, B2 and B3 were significant at the 0.05 level.

HEC and SCMC showed similar drug release mechanism. But, HEC is more hydrophobic and decreases the drug release than SCMC. According to swelling, these polymers exhibited high swelling; the film weight increased from the original. Although the marked increase in surface area during swelling can promote drug release, the increase in diffusional pathlength of the drug may paradoxically delay the release. Also, the thick gel layer formed on the swollen film surface is capable of preventing matrix disintegration and controlling additional water penetration [12]. ANOVA results for HEC films B10, B11, B12 and B13 were found to be significantly different at the level 0.05. Also, there is significant difference in statistics of B14, B15, B16 and B17 SCMC films at 0.05 level.

Table 3. Release kinetics of meloxicam from buccal films

Film	Zero order		First order		Higuchi order		Korsmeyer-peppas model		
	Equation	R^2	Equation	R^2	Equation	R^2	EQUATION	R^2	N
B1	Y = 0.738X + 1.694	0.985	Y = 0.023X + 0.706	0.990	Y = 5.622X - 8.081	0.943	Y = 0.753X + 0.234	0.955	0.753
B2	Y = 1.290X + 52.80	0.845	Y = 0.008X + 1.731	0.793	Y = 10.42X + 33.30	0.910	Y = 0.282X + 1.538	0.937	0.282
B3	Y = 0.661X + 3.828	0.965	Y = 0.019X + 0.818	0.971	Y = 5.007X - 4.806	0.912	Y = 0.598X + 0.453	0.884	0.598
B4	Y = 0.217X + 0.457	0.956	Y = 0.023X + 0.178	0.974	Y = 1.640X - 2.361	0.900	Y = 0.718X - 0.259	0.886	0.718
B5	Y = 0.125X + 2.969	0.518	Y = 0.009X + 0.527	0.493	Y = 0.857X + 1.709	0.398	Y = 0.226X + 0.430	0.254	0.226
B6	Y = 1.628X + 28.70	0.959	Y = 0.013X + 1.506	0.914	Y = 12.86X + 5.261	0.989	Y = 0.454X + 1.207	0.991	0.454
B7	Y = 0.081X + 1.316	0.931	Y = 0.012X + 0.200	0.975	Y = 0.615X + 0.260	0.874	Y = 0.395X - 0.039	0.882	0.395
B8	Y = 1.440X + 11.71	0.957	Y = 0.019X + 1.198	0.905	Y = 11.35X - 8.896	0.981	Y = 0.654X + 0.766	0.984	0.654
B9	Y = 1.855X + 18.36	0.959	Y = 0.018X + 1.361	0.877	Y = 14.64X - 8.275	0.986	Y = 0.622X + 0.946	0.984	0.622
B10	Y = 1.324X - 3.344	0.958	Y = 0.033X + 0.628	0.965	Y = 10.04X - 20.69	0.910	Y = 1.051X - 0.026	0.917	1.051
B11	Y = 0.890X - 1.936	0.976	Y = 0.032X + 0.489	0.988	Y = 6.746X - 13.59	0.926	Y = 1.040X - 0.168	0.972	1.040
B12	Y = 1.676X + 37.90	0.942	Y = 0.011X + 1.609	0.887	Y = 13.34X + 13.38	0.985	Y = 0.404X + 1.340	0.991	0.404
B13	Y = 1.062X - 1.319	0.982	Y = 0.031X + 0.605	0.957	Y = 8.156X - 15.65	0.955	Y = 1.042X - 0.064	0.979	1.042
B14	Y = 0.829X + 0.501	0.943	Y = 0.026X + 0.659	0.919	Y = 6.279X - 10.33	0.894	Y = 0.807X + 0.168	0.828	0.807
B15	Y = 0.522X + 2.341	0.824	Y = 0.019X + 0.682	0.792	Y = 3.810X - 3.898	0.724	Y = 0.536X + 0.389	0.579	0.536
B16	Y = 1.495X + 34.12	0.899	Y = 0.011X + 1.558	0.838	Y = 12.02X + 11.75	0.960	Y = 0.418X + 1.275	0.974	0.418
B17	Y = 0.606X + 7.257	0.945	Y = 0.015X + 0.966	0.937	Y = 4.616X - 0.762	0.904	Y = 0.469X + 0.680	0.846	0.469
B18	Y = 0.542X - 2.790	0.887	Y = 0.038X + 0.038	0.948	Y = 4.008X - 9.474	0.799	Y = 1.139X - 0.635	0.807	1.139
B19	Y = 0.617X - 1.092	0.933	Y = 0.035X + 0.277	0.903	Y = 4.774X - 9.558	0.922	Y = 1.186X - 0.501	0.974	1.186
B20	Y = 1.646X - 4.717	0.986	Y = 0.041X + 0.538	0.886	Y = 12.75X - 27.40	0.977	Y = 1.416X - 0.404	0.989	1.416
B21	Y = 0.999X + 0.732	0.989	Y = 0.029X + 0.668	0.892	Y = 7.806X - 13.28	0.996	Y = 1.025X - 0.013	0.993	1.025
B22	Y = 1.014X - 0.079	0.984	Y = 0.028X + 0.679	0.956	Y = 7.781X - 13.73	0.956	Y = 0.933X + 0.085	0.954	0.933

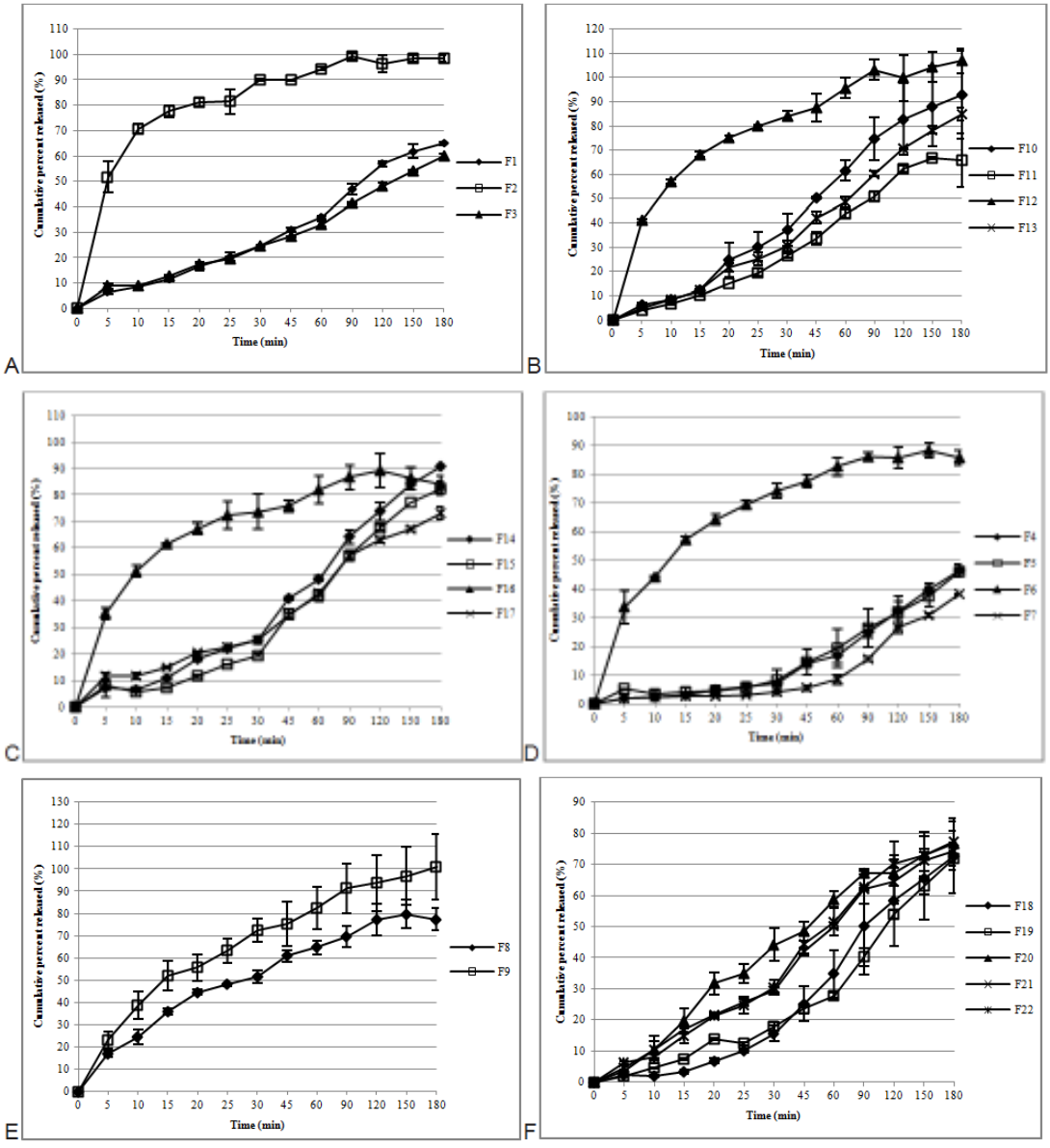

Fig. 3. Release of Meloxicam from different PVA (A), HEC (B), SCMC (C), HPMC (D) and pectin (E) monolithic matrix films and release of Meloxicam from monolithic matrix films with a binary polymeric mixture (F)

Table 4. Release properties of meloxicam from different mucoadhesive films

Film	Q_3 %	RE %	T_{100}
B1	64.90 ± 0.67	58.54 ± 0.66	296.33 ± 2.52
B2	98.41 ± 1.33	78.97 ± 0.09	N/A
B3	59.94 ± 0.81	58.20 ± 0.34	342.17 ± 9.75
B4	46.35 ± 2.16	50.85 ± 1.06	394.67 ± 8.39
B5	45.99 ± 0.18	53.44 ± 4.93	460.67 ± 86.38
B6	85.80 ± 2.50	68.19 ± 1.48	N/A
B7	38.20 ± 0.27	47.21 ± 0.60	424.83 ± 10.77
B8	77.29 ± 4.95	75.04 ± 0.57	323.17 ± 72.49
B9	100.85 ± 14.55	81.31 ± 2.06	201.00 ± 105.59
B10	92.82 ± 17.96	68.07 ± 4.85	235.83 ± 112.33
B11	65.82 ± 11.08	59.85 ± 4.74	282.00 ± 20.66
B12	106.89 ± 5.02	84.18 ± 2.47	112.50 ± 49.53
B13	84.73 ± 2.61	62.23 ± 2.34	223.27 ± 16.77
B14	90.89 ± 0.20	62.17 ± 1.52	207.00 ± 1.50
B15	82.57 ± 2.61	60.19 ± 3.12	234.83 ± 21.25
B16	84.12 ± 3.15	68.56 ± 3.04	N/A
B17	73.11 ± 2.34	66.48 ± 0.30	336.67 ± 19.01
B18	72.69 ± 12.06	58.43 ± 6.03	281.00 ± 36.81
B19	77.28 ± 6.59	48.63 ± 5.80	310.67 ± 35.35
B20	74.41 ± 6.31	72.32 ± 1.45	317.17 ± 70.91
B21	76.62 ± 0.48	66.90 ± 1.80	346.67 ± 10.02
B22	71.83 ± 2.42	74.08 ± 10.39	226.90 ± 35.55

Release of meloxicam from HPMC is considered slower than release from PVA, SCMC and HEC. Fig. 3 showed that most of the formulations prepared using HPMC polymer have a decreased release properties. It was proved that the presence of HPMC in the formulation retards the release rate of the drug from the film. This is explained by the fact that HPMC has high swelling properties. So, the thickness of the swollen gel layer in HPMC containing films would be high which result in an increase in the diffusion pathway for the drug molecule. As a result, the increased diffusion pathway slowed the meloxicam release from the HPMC incorporated matrix [49]. Statistical analysis of HPMC films explained that there were significant differences between B4, B5, B6 and B7 at 0.05 level.

Also, Fig. 3 showed the release of meloxicam from pectin film. Films containing pectin have a good drug release if compared with others. This resulted from the swelling nature of pectin which causes the drug to diffuse rapidly from the film. It was found that the higher the pectin concentration in the film, the higher the drug release rate [50]. Also, pectin films containing PEG 400 have high release properties than films containing glycerin. This is due to structure of PEG 400. It has large nonpolar part and various hydroxyl groups that responsible for improvement of solubility of meloxicam [51]. Statistics data of pectin polymer stated that the differences between B8 and B9 were significant at the 0.05 level.

According to Fig. 3 which contained results of polymer combination films combining two polymers with each others. These films did not give promising results. It was found that presence of HPMC whether alone or in combination decreases or slows the release of drug from the film. So, by combining HPMC with any other polymer, the release of meloxicam will be affected negatively [49]. This point gave a reason for decreased release from B18, B19 and B20 films. On the other hand, incorporation of pectin in B21 and B22 formulations

enhanced the release. It was explained that by increasing the ratio of pectin during the preparation of film containing more than one polymer, the release will be enhanced [50]. B18, B19, B20, B21 and B22 films yielded significant difference in ANOVA test at the 0.05 level.

The fastest release was marked in F2 formula where 51.57% from the drug was released within 5 minutes which was a prerequisite for this dosage form. It was stated that the most significant advantage in mucoadhesive film is that it can be loaded with drug dose lower than dose used in the conventional dosage forms [42].

3.2.4 Differential scanning calorimetry (DSC) analysis

The aim of Drug-excipient compatibility studies is to select an ideal composition for mucoadhesive films. Any type of incompatibility between meloxicam and film-forming polymer affects the effectiveness of the formula to a high extent [30]. Results of meloxicam-excipents compatibilities studies performed by DSC are shown in Figs. (4-9).

As mentioned in DSC thermogram of Fig. 4, meloxicam powder showed a sharp endothermic peak representing its melting point. The peak of the drug was at 260 ºC [32,52]. SCMC endothermic peak appeared at 100 ºC. It was found that the melting point of this polymer appeared at 125 ºC [53]. This difference may be due to instrument. By preparing the SCMC plain film containing SCMC and PG, the peak was shifted to be at 115 ºC. In the physical mixture, both SCMC and meloxicam appeared in the thermogram. After preparing the medicated film (B16), it was found that the peak of meloxicam disappeared. Pure drug showed intensive peak as a result of the crystalline nature of the meloxicam [54]. This peak was reduced in solid complexes due to conversion of drug into the amorphous form as a result of addition of PG. Since PG can be used as a cosolvent to enhance solubility of meloxicam and improve dissolution properties in the vehicle [55]. So, it normal for meloxicam peak to disappear. The heat of fusion of the polymer in A, B, D and E thermograms was not altered which reflects absence of any change in the polymer. But the heat of fusion of the drug (-636.31 mJ) was decreased a lot in physical mixture (-36.27 mJ) due to reduction in the crystallinity and transformation into the amorphous form [56]. The exdothermic peak appeared at melting point 220 ºC was due to presence of PG. This was due to appearance of the peak in thermogram E only not in the rest of thermograms. By addition of PG to meloxicam as a solvent, intermolecular interactions and hydrogen bond will occur which result in dissolution of drug [57].

In Fig. 5, pectin endothermic peak was represented at 100 ºC and after preparing its plain film, a shift occurred in the temperature to be at 118 ºC. It was showed that endothermic peak of pectin representing its melting point was 91 ºC [58]. The pectin peak is corresponding to the glass transition temperature and also associated to the elimination of bound water in the pectin sample [59]. By measuring the DSC of the physical mixture, polymer and drug appeared with a small shift in the temperature of the peak. The medicated film of pectin (B9) indicated the presence of meloxicam. This is due to appearance of exothermic peak at 245 ºC. The shift in the temperature of the meloxicam peak was due to presence of PEG 400 in the film in the molten state, which decreases the melting point of the drug [32]. This is attributed to dissolution effect of PEG 400 on meloxicam [60]. The heat of fusion of the polymer in the A, B, D, and E approximately was similar to each other. But the heat of fusion of meloxicam reduced in the physical mixture (-305.77 mJ) especially in the medicated film (-2.45 mJ). This is due to partial or complete loss of crystallinity as a result of amorphization and complexation of the drug within the matrix [61]. The exothermic peak

appeared in thermogram E at 245 ºC was due to crystallization of water present in the film [62].

Fig. 6 showed the effect of combining SCMC and pectin on meloxicam (B22). Drug endothermic peak appeared in both the physical mixture and also the medicated film at 250 ºC. By comparing the heat of fusion which are related to the polymer whether pure polymer or in the form of matrix, it was found that there were no changes. The physical mixture showed a reduction in the heat of fusion of meloxcam from -636.31 mJ to -95.32 mJ. In addition, heat of fusion of drug in the medicated film was -8.96 mJ. This was due to formation of amorphous aggregates, where it is impossible to differentiate the two components, also, due to a major interaction between the drug and the matrix [61].

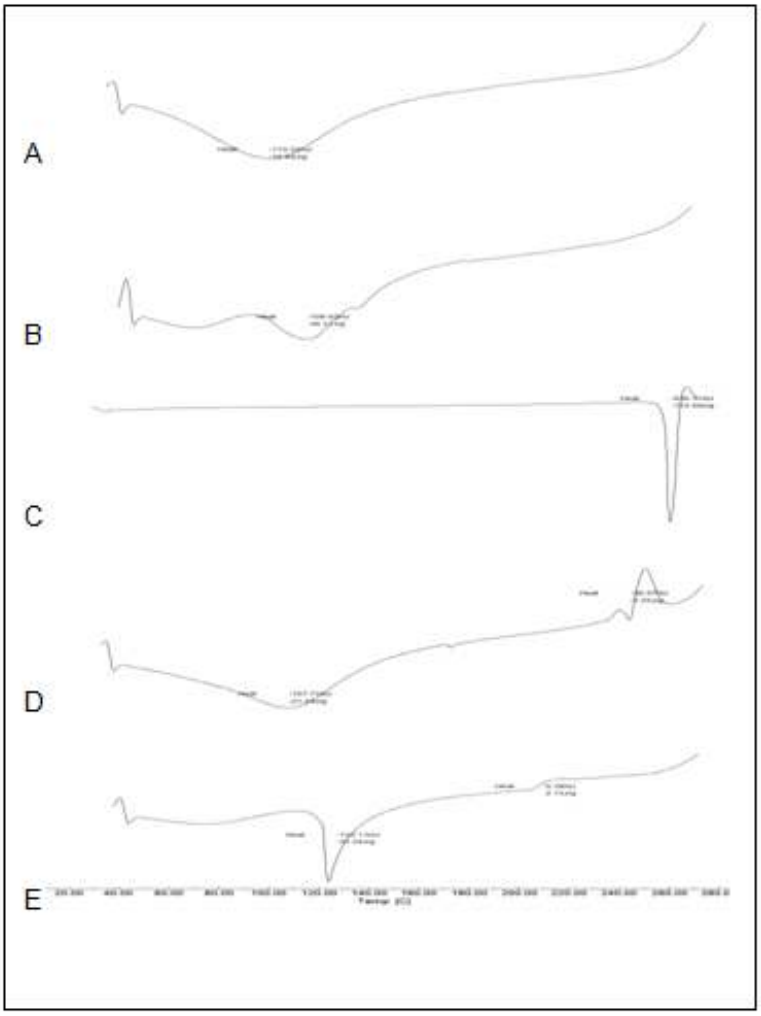

Fig. 4. DSC thermograms of: A) SCMC powder, B) SCMC + PG film C) Meloxicam powder, D) SCMC + Meloxicam PM and E) SCMC + PG + Meloxicam film [displaced for better visualization]

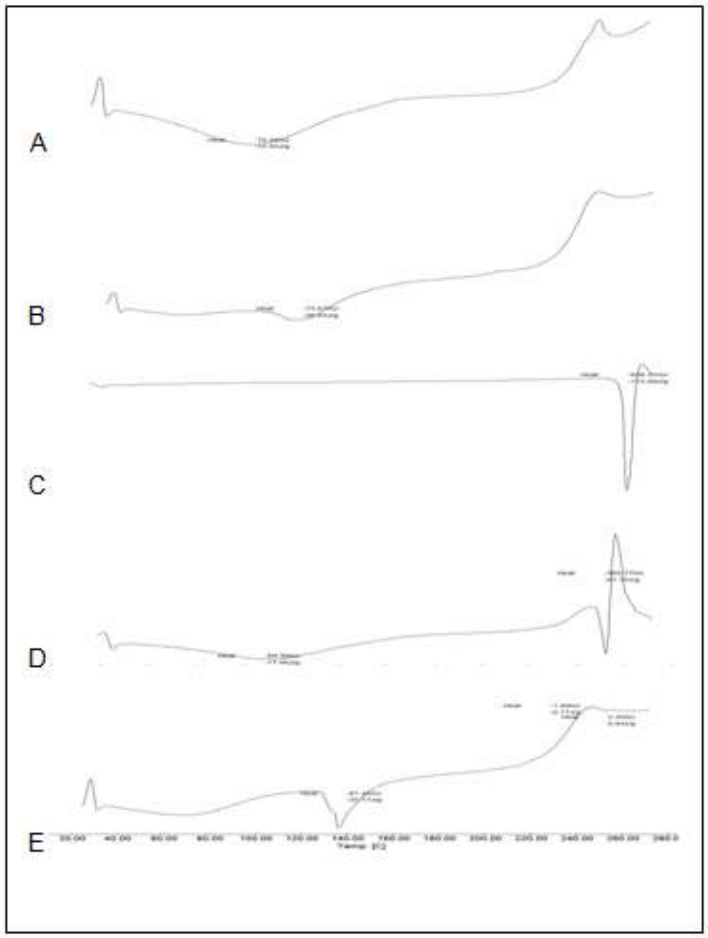

Fig. 5. DSC thermograms of: A) Pectin powder, B) Pectin + PEG film, C) Meloxicam powder, D) Pectin + Meloxicam PM and E) Pectin + PEG400 + Meloxicam film [displaced for better visualization]

Fig. 7 represented the DSC of HEC. HEC powder endothermic peak appeared at 80 ºC. Also, there was a research paper proved that melting point of HEC occurred at 80 ºC [63]. The plain film containing HEC and PG gave endothermic peak at 70 ºC. The drug appeared in the physical mixture with an endothermic peak at 250 ºC. The heat of fusion of drug in the physical mixture was altered from -636.31 mJ to -76.83 mJ. DSC thermogram of the medicated film (B12) showed that meloxicam peak was not seen. This is due to presence of the solvent which decreases the melting point. As a result, the crystallinity of the drug will decrease [64].

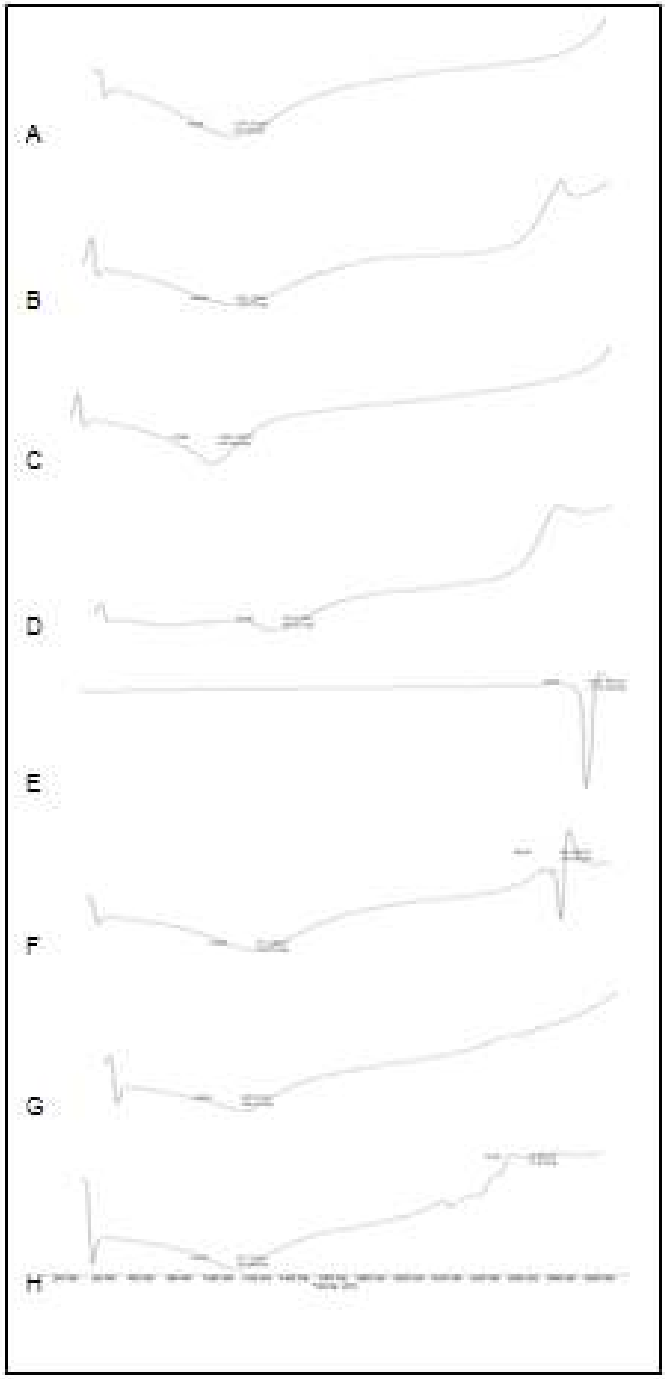

Fig. 6. DSC thermograms of: A) SCMC powder, B) Pectin powder, C) SCMC film, D) Pectin + PEG400 film, E) Meloxicam powder, F) SCMC + Pectin + Meloxicam PM, G) SCMC + Pectin film and H) SCMC + Pectin + Meloxicam film [displaced for better visualization]

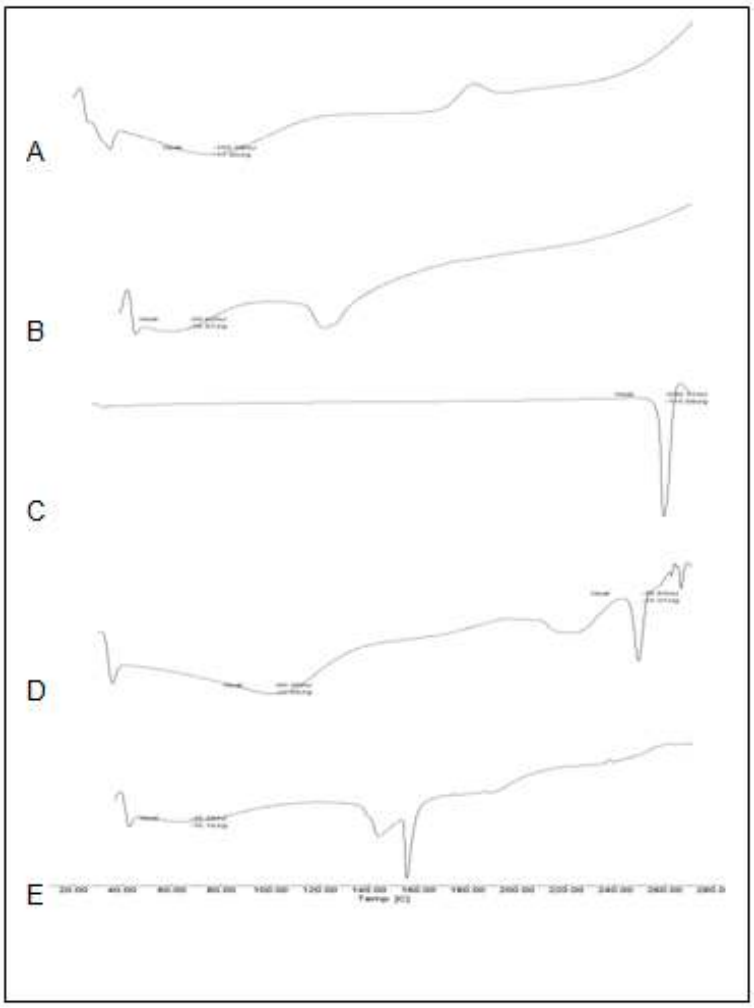

Fig. 7. DSC thermograms of: A) HEC powder, B) HEC + PG film, C) Meloxicam powder, D) HEC + Meloxicam PM and E) HEC + PG + Meloxicam film [displaced for better visualization]

Fig. 8 showed that HPMC has an endothermic peak at 80 ºC. DSC peak of this polymer was found to be at 95 ºC [65]. By preparing the plain film containing HEC and PG, it was found that HEC peak appeared at 70 ºC. Analysis of physical mixture proved that HPMC and meloxicam endothermic peak were present at 80 and 225 ºC respectively. The medicated film (B6) showed a peak for meloxicam at 230 ºC. Almost, there were no changes in the heat of fusion of the polymer in thermograms A,B,D and E. The heat of fusion of meloxicam reduced a lot in the physical mixture and the medicated drug to be -63.82 mJ and -2.47 mJ respectively. This means that the intensity of the drug peak was decreased due to reduction of drug crystallinity. This was attributed to the increase in the dissolution rate. Since PG enhances the solubility of meloxicam [51]. Thus, it is common for drug peak to disappear.

Fig. 9 showed two endothermic peaks for PVA at 90 and 190ºC. PVA first peak appeared at 100 - 120 ºC corresponding to the evaporation of residual water content present in the film. The second sharp peak showed at 190 - 220 ºC corresponding to the melting point of PVA [66]. By preparing the plain film containing PVA and PG, the previously mentioned peaks were appeared. Physical mixture has three peaks indicating the two peaks of PVA and a peak for Meloxicam at 250 ºC. Moreover, it was found that DSC thermogram of the medicated film (B2) showed the same peaks of the physical mixture. By comparing the heat of fusion of meloxicam in the physical mixture (73.61 –mJ) and the medicated film (-20.90 mJ) to that of the pure drug (-636.31 mJ), it was mentioned that the drug transformed into the amorphous form due to the effect of PG which acts as a solvent as mentioned before.

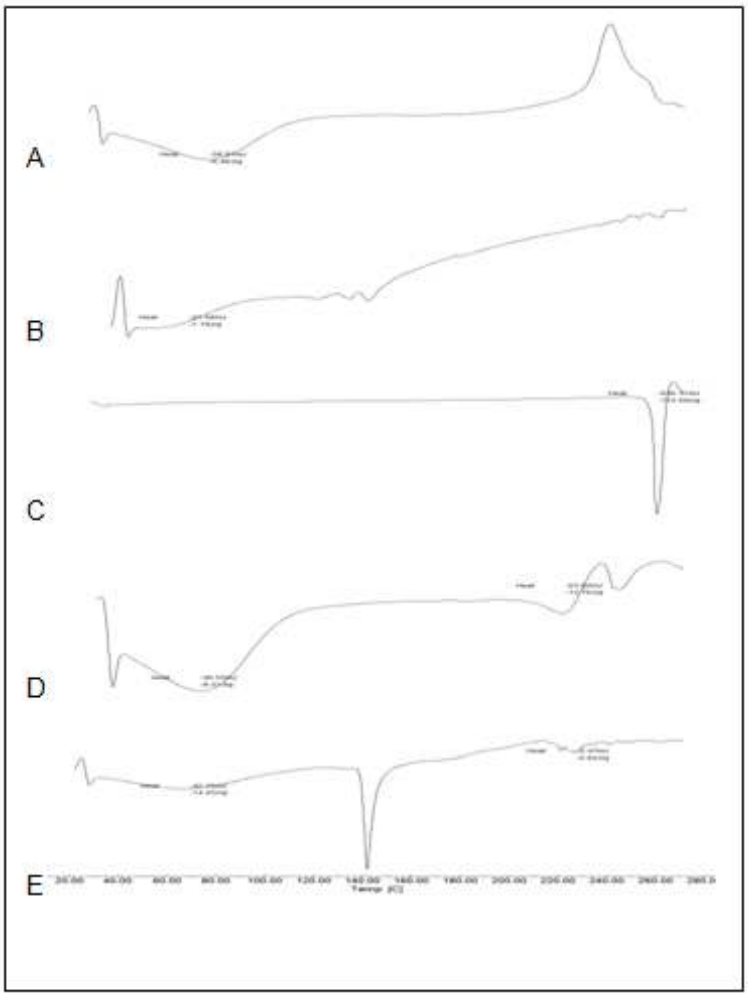

Fig. 8. DSC thermograms of: A) HPMC powder, B) HPMC + PG film, C) Meloxicam powder, D) HPMC + Meloxicam PM and E) HPMC + PG + Meloxicam film [displaced for better visualization]

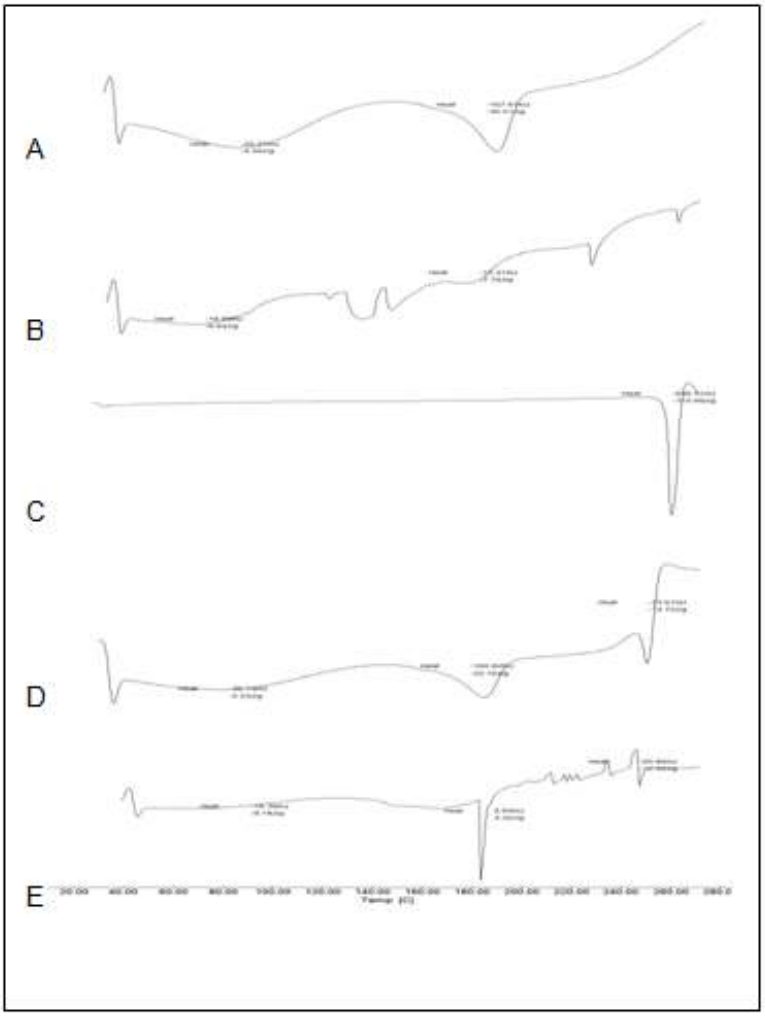

Fig. 9. DSC thermograms of: A) PVA powder, B) PVA + PG film, C) Meloxicam powder, D) PVA + Meloxicam PM and E) PVA + PG + Meloxicam film [displaced for better visualization]

4. CONCLUSION

The aim of this research was to select the best formula which has ideal properties to be suitable for mucoadhesive delivery of meloxicam. It was concluded that B2 formula has the required characteristics. It contained the optimum drug content with acceptable mucoadhesion. Also, drug release from this was very fast. In addition, there was no any incompatibility between meloxicam and the other excipents.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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