

1 **Preparation and Characterization of**
2 **Mucoadhesive Buccal Film for Delivery of**
3 **Meloxicam**

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8 **ABSTRACT**

9 **Aims:** preparation of mucoadhesive buccal films able to deliver the meloxicam drug to the site
10 of application through oral mucosal tissues. This dosage form is advantageous due to
11 absence the problems of the ordinary dosage forms.

11 **Study Design:** in this research, it was prepared a lot of formulations from different polymers
12 and plasticizers to select the best one which has the optimum and required characteristics.

12 **Place and Duration of Study:** Department of Pharmaceutics, Faculty of Pharmacy, Suez
13 Canal University and Misr International University, Egypt, between July 2009 and July 2012.

13 **Methodology:** there are different polymers used in preparation of the films which are
14 hydroxypropylmethyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, pectin
15 and polyvinyl alcohol. Also, the plasticizers used are glycerin, propylene glycol and
16 polyethylene glycol. The film was prepared by solvent casting technique. Firstly, the calibration
17 curve of meloxicam was carried out. Then, the properties of the formulations were examined
18 through some experiments which are determination of drug content, study of efficacy of
19 mucoadhesion, *in-vitro* drug release studies and differential scanning calorimetry.

19 **Results:** it was found that the formula containing polyvinyl alcohol 2% (w/w) and propylene
20 glycol 20% from the weight of the polymer has ideal characteristics. Results showed that this
21 formula has optimum drug content, acceptable mucoadhesion and fast drug release with
22 compatibility between drug and excipients.

23 *Keywords: Meloxicam; Mucoadhesion; in-vitro release; differential scanning calorimetry.*

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24 **1. INTRODUCTION**

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

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

51 Ordinary dosage forms of meloxicam are suspension 7.5mg/5ml and tablet 7.5 mg and 15 mg.
52 These formulations are called Mobic [6]. But, these old formulations were suffering from many
53 side effects which related to the oral administration of the drug. Firstly, slow onset time of oral
54 meloxicam dosage forms in comparison with mucoadhesive buccal films. For instance, the time
55 needed to reach maximum plasma concentration after administration of meloxicam dose (Mobic)
56 is approximately 4-5 hours in the fasted state and 5-6 hours in the fed state [7]. Secondly,
57 difficulty of swallowing of the oral dosage forms for geriatrics. This is an important point because
58 this drug treats osteoarthritis and rheumatoid arthritis, these diseases are related mostly to
59 geriatrics. So, the aim in this study is to prepare new dosage form fulfilling the patient's
60 circumstances and interest with least percent of side effects. This aim can be developed by
61 formulating meloxicam in mucoadhesive buccal film which is a new route that will develop a
62 revolution in drug industry.

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

75 of drug from the film was accepted in a high degree. It was found that the drug in this dosage
76 form was protected from first pass metabolism which is required [10].

77 2. MATERIALS AND METHODS

78 2.1 Materials

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

85 2.2 Methods

86 2.2.1 Preparation of buccal films

87 Polymeric film vehicle was carried out by calculating the desired amount of polymer, plasticizer
88 and drug. The weight of the polymer (HPMC, HEC, SCMC, PVA or pectin) incorporated in the film
89 was 2% (w/w). Each polymer has a different method of preparation. SCMC and HEC were
90 dispersed in 3/4 the volume of distilled water at 25 °C. Then, the rest 1/4 of volume distilled water
91 was added [12]. HPMC was dispersed in 1/3 the volume of the distilled water at 90 °C. Then, the
92 2/3 volume of the distilled water at 5 °C was added [13]. Pectin was dispersed in dilute solution of
93 0.1N HCL at pH 3. Then, calcium chloride 0.1% (w/v) was added and the solution was heated at
94 50 °C [14]. PVA was dispersed in hot distilled water at 80-100 °C [15]. Then, plasticizer 20% from
95 the weight of the polymer (PEG 400, glycerin or PG) and drug 0.5% (w/w) were blended to the
96 polymeric solution. The medicated gel was kept overnight at room temperature to obtain clear
97 and bubble free gel [16]. After that, this gel will be poured to the glass Petri dishes to be dried in
98 oven at 60-70 °C [17]. Finally, the films were cut into the required dimensions, enveloped in
99 aluminum foil and stored in glass container to be ready for any experiment [18]. Table 1 shows
100 the composition of each buccal film.

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

Formulation	Polymer					Plasticizer		
	HEC	HPMC	SCMC	PVA	Pectin	PEG 400	Glycerin	PG
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(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

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114 **2.2.2 Construction of meloxicam calibration curve.**

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

123 **2.2.3 Physicochemical evaluation of polymeric matrix films**

124 **2.2.3.1 Determination of drug content**

125 Uniformity of drug content was determined according to the following procedure. Three randomly
126 selected films of each batch were weighed accurately and dissolved at room temperature in 50 ml
127 methanol and stirred continuously for one hour on a magnetic stirrer. The volume was made up to
128 100 ml with phosphate buffer at pH 6.8. Then, 1 ml was transferred to 10 ml volumetric flask and
129 the volume was adjusted with phosphate buffer at pH 6.8 and methanol. Concentration of drug
130 contained in each film was measured spectrophotometrically at λ max 361 nm [21].

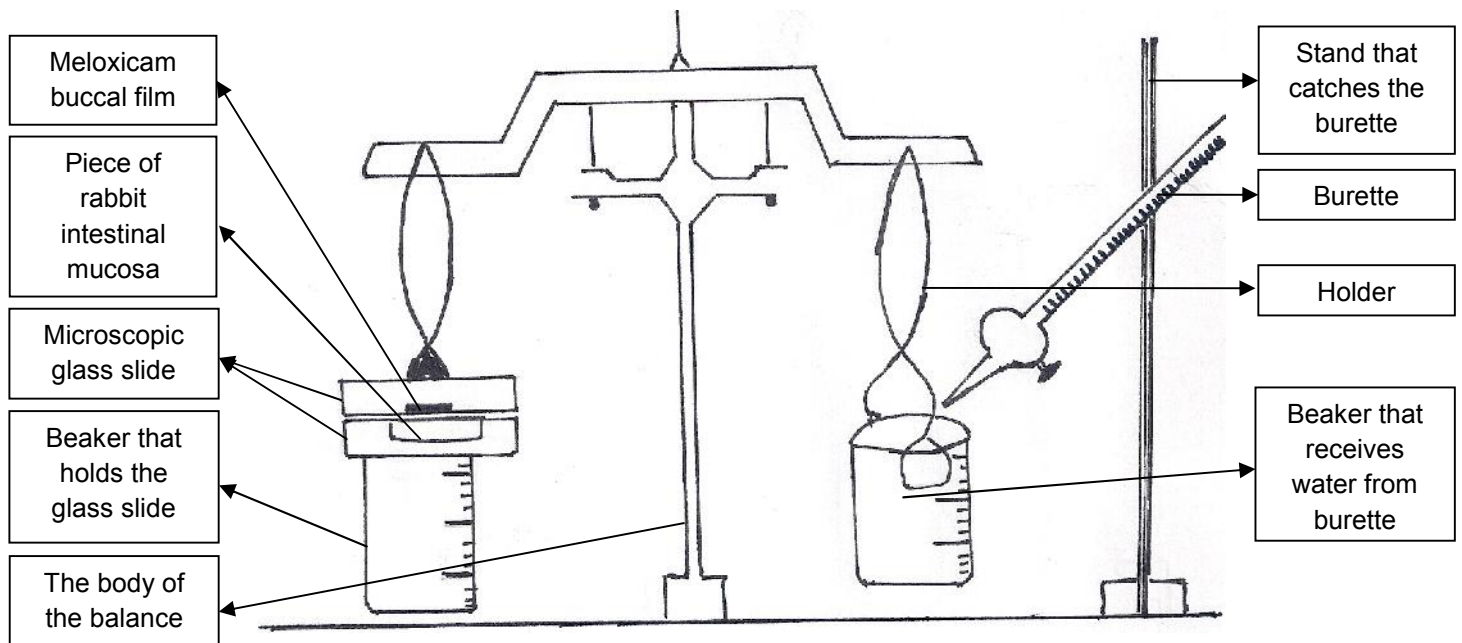
131 **2.2.3.2 Study of efficacy of mucoadhesion.**

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

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Fig. 1. The main parts of the mucoadhesion instrument

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173 2.2.3.3 *In-vitro* drug release studies

174 Three samples from each formula were utilized to examine their drug release profile [12]. The size of the
175 sample was 2.5 cm² and the dose of meloxicam in it was 9.824 mg. This test gives information about
176 release rate of the drug from the formula and also the amount of the drug released during that time.
177 Varian VK 7000/7010 Dissolution apparatus was used to perform this study. The dissolution medium that
178 is equivalent to saliva is phosphate buffer at pH 6.8. Volume in the vessel of the dissolution apparatus
179 (Varian VK7000 Dissolution apparatus, USA) is 900 ml [22]. Temperature should be adjusted at 37±0.5
180 °C. There are two parameters related to the paddle should be taken into consideration. Speed of the
181 paddle should be 50 RPM [21]. This is because the normal mouth motion of the body approximately
182 within this speed. Also, the height of paddle from the bottom of the vessel should be fixed for all
183 formulations at 2.5 cm [23]. The film can be attached to the paddle directly [21]. This attachment can be
184 done by using a thread. At each time interval (5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150 and 180 minute)
185 [24], 10 ml will be withdrawn from the vessel to be analyzed and replaced by buffer to maintain sink
186 condition. It is important to filtrate the 10 ml before analyzing them by using 0.45 µm Millipore filter
187 because the solution may contain some particles not dissolved such as the polymer, plasticizer or the
188 drug itself [21]. The filtrate will be analyzed spectrophotometrically at λ max 361. There are many release
189 parameters used to differentiate between different formulations present such as % of cumulative amount
190 of drug released after 3 hours (%Q₃) and time for 100% release (T₁₀₀) [25].

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

$$192 RE = \left(\int_0^t Y \cdot dt \right) / Y_{100 \cdot t} \quad (1) [26].$$

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

196 Zero-order model

$$197 M_t = M_0 + K_0 t \quad (2)$$

198 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
199 release constant [27].

200 First order model

$$201 \text{Log}M_t = \text{Log}M_0 - kt / 2.303 \quad (3)$$

202 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
203 constant [28].

204 Higuchi model

$$205 M_t = M_0 + K_H t^{0.5} \quad (4)$$

206 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
207 rate constant [27].

208 Korsmeyer-Peppas model

$$209 M_t / M_\infty = k (t)^n \quad (5)$$

210 M_t / M_∞ is the fraction of drug release at time t , k is the release rate constant, and n is the release
211 exponent indicative of the mechanism of release [27].

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

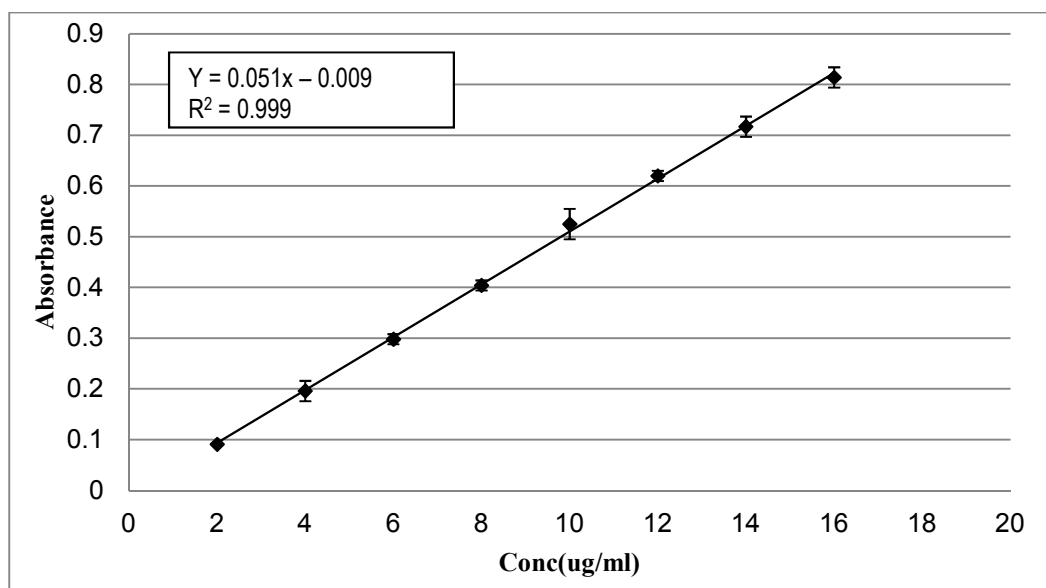
216 2.2.3.4 Differential scanning calorimetry (DSC) analysis

217 Compatibility of meloxicam and different polymers to be used for the development of film formulations
218 was studied using a differential scanning calorimeter (DSC 60, Shimadzu, Japan) at a nitrogen flow of 30
219 mL min⁻¹ [30]. Thin films are easily prepared for encapsulation. Typically, a cork borer or a clean paper
220 punch is used to punch several sample specimen disks from the larger thin film sheet. Other tools that
221 can be used for thin film preparation are scissors or razor blades [31]. Samples (1-8 mg) were sealed in
222 aluminum pans and heated at a scanning rate of 10 °C min⁻¹ [32]. Range of the heating temperature is
223 35-270°C.

224 3 Results and discussion

225 3.1 Construction of meloxicam calibration curve

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



229

230 **Fig. 2 Meloxicam calibration curve.**

231 3.2 Physicochemical evaluation of polymeric matrix films

232 3.2.1 Determination of drug content

233 Homogenous uniform drug distribution is very important aspect that must be verified during the
234 preparation of the film [33]. If the drug is not dispersed and distributed well in the preparation, each film
235 will contain a different amount from the drug. Also, the drug in the film itself in this case will not be
236 homogeneously distributed. As mentioned in table 2, drug content in most formulations was found to be not
237 less than 90% which is accepted. It was showed that drug content in most formulations used in their
238 research was 91-98% [34]. This means that the drug is uniformly distributed in the preparation and inside
239 the film itself. B10 and B12 films contain an extra drug content more than 120 % which is not accepted.
240 Venkatalakshmi et al, stated that the highest drug content for the prepared films was 109%. This percent
241 was found in the film prepared from SCMC and PG [21]. Also, there were some values below 90% as B8
242 which is not accepted. Prasanth et al, explained that drug content was 66-97%, so there were
243 formulations containing very low amount of drug [35]. Thus, drug will not perform its action perfectly. This

244 is due to heterogeneity between meloxicam and different types of polymers. So, B2, B3, B5 and B17
245 formulations have the optimum drug content.

246 **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

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

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

249 **3.2.2 Study of efficacy of mucoadhesion.**

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

254 According to table 2, Pectin polymer did not give promising results for mucoadhesion. These inadequate
255 mucoadhesion properties were noted whether by the addition of glycerin or PEG400. Researches
256 explained that mucoadhesion of pectin is not high either the buccal tissues were hydrated enough or not
257 [37]. This can be explained from the nature and structure of pectin. Pectin is a polysaccharide polymer
258 and consists of partially methoxylated polygalacturonic acid [38]. So, this polymer will not adhere well to
259 buccal cavity which is not preferred.

260 From table 2 showed that, PVA has low mucoadhesive properties in the prepared buccal patches.
261 Addition of glycerin to the polymer is better than propylene glycol or PEG400. Mishra et al, stated that
262 PVA patches that were used in their research gave the lowest values for mucoadhesion than HPMC and
263 SCMC patches [39]. The reduced mucoadhesion of PVA is due to its high aqueous solubility [40]. It was
264 proved that with the increase of polymer to drug ratio, the % of mucoadhesion in the film will increase
265 [41]. This can also give a reason for low bioadhesive results of PVA polymer, where concentration of the
266 polymer was 2%.

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

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

283 **3.2.3 In-vitro drug release studies**

284 Release studies for specific dosage form are considered the most important studies have to be examined.
285 If the selected drug is not released from the formulation in the exact time by its expected concentration,
286 there will be no need for the patient to take it. So, it is important in this study to evaluate the ability of the
287 formulation to release the whole dose of the drug in its expected time. In the fast dissolving buccal films,
288 the dose of the drug should be released within minutes. Thus, the factor of time is substantial. There are
289 some parameters should be calculated to make sure the release of the drug from the film. $Q_3\%$ is the first
290 parameter and can be defined as cumulative drug amount released after 3 hours [25]. The second
291 parameter is release or dissolution efficiency. It is defined as the area under the dissolution curve up to a
292 certain time 't', expressed as a percentage of the area under the rectangle described by 100% dissolution
293 in the same time. This parameter can assume a range of values depending on the time intervals chosen
294 for interpretation [26]. The last parameter is T_{100} which is defined as the expected time to achieve 100%
295 drug release [47].

296 Kinetics of drug release from the mucoadhesive film can be calculated using some mathematical
297 modelings. The models used are zero order, first order, Higuchi order, and Korsmeyer-Peppas model.

298 Kinetics of meloxicam can be determined by detecting the best fitting release data to the mathematical
299 models used [25].

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

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

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

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

326 Release of meloxicam from HPMC is considered slower than release from PVA, SCMC and HEC. Figure
327 3 showed that most of the formulations prepared using HPMC polymer have a decreased release
328 properties. It was proved that the presence of HPMC in the formulation retards the release rate of the
329 drug from the film. This is explained by the fact that HPMC has high swelling properties. So, the thickness
330 of the swollen gel layer in HPMC containing films would be high which result in an increase in the
331 diffusion pathway for the drug molecule. As a result, the increased diffusion pathway slowed the
332 meloxicam release from the HPMC incorporated matrix [49]. Statistical analysis of HPMC films explained
333 that there were significant differences between B4, B5, B6 and B7 at 0.05 level.

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

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

347 during the preparation of film containing more than one polymer, the release will be enhanced [50]. B18,
348 B19, B20, B21 and B22 films yielded significant difference in ANOVA test at the 0.05 level.

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

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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

$$B22 \quad y = 1.014x - 0.079 \quad 0.984 \quad y = 0.028x + 0.679 \quad 0.956 \quad y = 7.781x - 13.73 \quad 0.956 \quad y = 0.933x + 0.085 \quad 0.954 \quad 0.933$$

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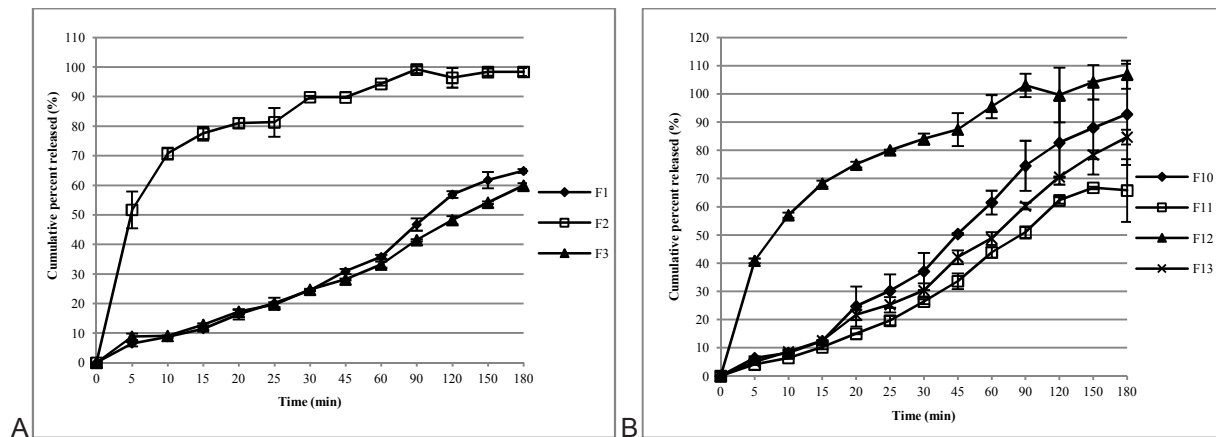
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Table 4. Release properties of meloxicam from different mucoadhesive films

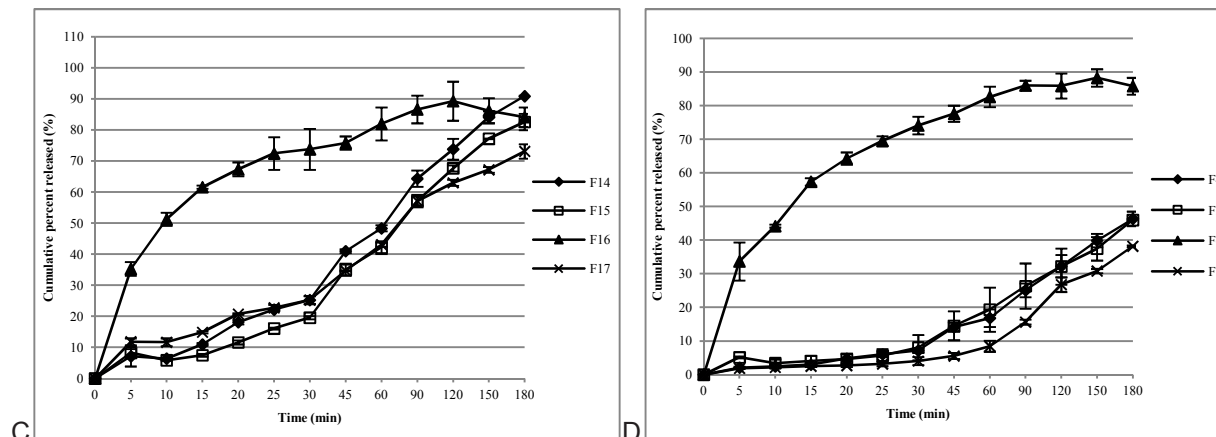
Film	Q ₃ %	RE %	T ₁₀₀
B1	64.90 ± 0.67	58.54 ± 0.66	296.33 ± 2.52
B2	98.41 ± 1.33	78.97 ± 0.09	N/A
B3	59.94 ± 0.81	58.20 ± 0.34	342.17 ± 9.75
B4	46.35 ± 2.16	50.85 ± 1.06	394.67 ± 8.39
B5	45.99 ± 0.18	53.44 ± 4.93	460.67 ± 86.38
B6	85.80 ± 2.50	68.19 ± 1.48	N/A
B7	38.20 ± 0.27	47.21 ± 0.60	424.83 ± 10.77
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

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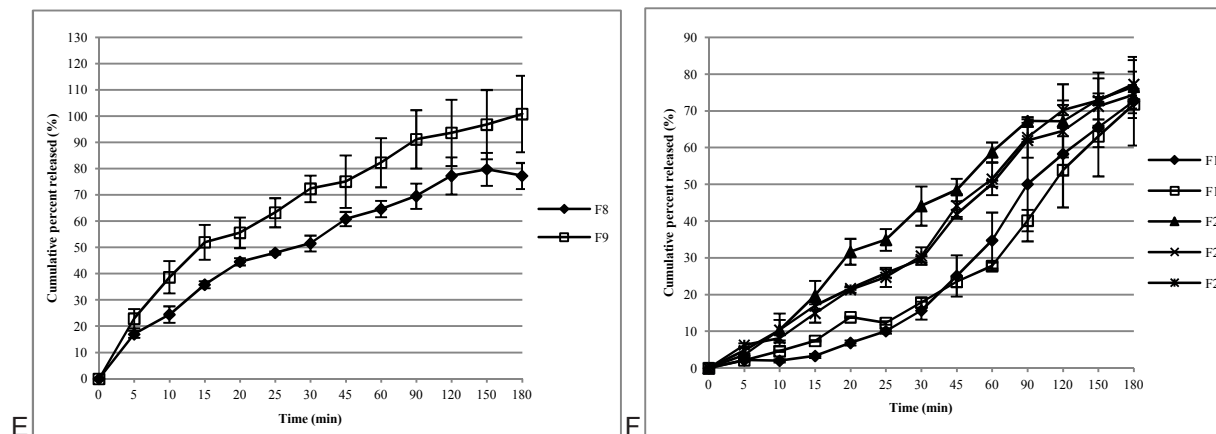
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387 **Figure 3. Release of Meloxicam from different PVA (A), HEC (B), SCMC (C), HPMC (D) and pectin**
388 **(E) monolithic matrix films and release of Meloxicam from monolithic matrix films with a binary**
389 **polymeric mixture (F).**

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391 3.2.4 Differential scanning calorimetry (DSC) analysis

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

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

413 In figure 5, pectin endothermic peak was represented at 100 °C and after preparing its plain film, a shift
414 occurred in the temperature to be at 118 °C. It was showed that endothermic peak of pectin representing
415 its melting point was 91 °C [58]. The pectin peak is corresponding to the glass transition temperature and
416 also associated to the elimination of bound water in the pectin sample [59]. By measuring the DSC of the
417 physical mixture, polymer and drug appeared with a small shift in the temperature of the peak. The
418 medicated film of pectin (B9) indicated the presence of meloxicam. This is due to appearance of
419 exothermic peak at 245 °C. The shift in the temperature of the meloxicam peak was due to presence of
420 PEG 400 in the film in the molten state, which decreases the melting point of the drug [32]. This is
421 attributed to dissolution effect of PEG 400 on meloxicam [60]. The heat of fusion of the polymer in the A,
422 B, D, and E approximately was similar to each other. But the heat of fusion of meloxicam reduced in the
423 physical mixture (-305.77 mJ) especially in the medicated film (-2.45 mJ). This is due to partial or
424 complete loss of crystallinity as a result of amorphization and complexation of the drug within the matrix
425 [61]. The exothermic peak appeared in thermogram E at 245 °C was due to crystallization of water
426 present in the film [62].

427 Figure 6 showed the effect of combining SCMC and pectin on meloxicam (B22). Drug endothermic peak
428 appeared in both the physical mixture and also the medicated film at 250 °C. By comparing the heat of
429 fusion which are related to the polymer whether pure polymer or in the form of matrix, it was found that
430 there were no changes. The physical mixture showed a reduction in the heat of fusion of meloxcam from
431 -636.31 mJ to -95.32 mJ. In addition, heat of fusion of drug in the medicated film was -8.96 mJ. This was
432 due to formation of amorphous aggregates, where it is impossible to differentiate the two components,
433 also, due to a major interaction between the drug and the matrix [61].

434 Figure 7 represented the DSC of HEC. HEC powder endothermic peak appeared at 80 °C. Also, there
435 was a research paper proved that melting point of HEC occurred at 80 °C [63]. The plain film containing
436 HEC and PG gave endothermic peak at 70 °C. The drug appeared in the physical mixture with an
437 endothermic peak at 250 °C. The heat of fusion of drug in the physical mixture was altered from -636.31
438 mJ to -76.83 mJ. DSC thermogram of the medicated film (B12) showed that meloxicam peak was not

439 seen. This is due to presence of the solvent which decreases the melting point. As a result, the
440 crystallinity of the drug will decrease [64].

441 Figure 8 showed that HPMC has an endothermic peak at 80 °C. DSC peak of this polymer was found to
442 be at 95 °C [65]. By preparing the plain film containing HEC and PG, it was found that HEC peak
443 appeared at 70 °C. Analysis of physical mixture proved that HPMC and meloxicam endothermic peak
444 were present at 80 and 225 °C respectively. The medicated film (B6) showed a peak for meloxicam at
445 230 °C. Almost, there were no changes in the heat of fusion of the polymer in thermograms A,B,D and E.
446 The heat of fusion of meloxicam reduced a lot in the physical mixture and the medicated drug to be
447 -63.82 mJ and -2.47 mJ respectively. This means that the intensity of the drug peak was decreased due
448 to reduction of drug crystallinity. This was attributed to the increase in the dissolution rate. Since PG
449 enhances the solubility of meloxicam [51]. Thus, it is common for drug peak to disappear.

450 Figure 9 showed two endothermic peaks for PVA at 90 and 190°C. PVA first peak appeared at 100 - 120
451 °C corresponding to the evaporation of residual water content present in the film. The second sharp peak
452 showed at 190 - 220 °C corresponding to the melting point of PVA [66]. By preparing the plain film
453 containing PVA and PG, the previously mentioned peaks were appeared. Physical mixture has three
454 peaks indicating the two peaks of PVA and a peak for Meloxicam at 250 °C. Moreover, it was found that
455 DSC thermogram of the medicated film (B2) showed the same peaks of the physical mixture. By
456 comparing the heat of fusion of meloxicam in the physical mixture (73.61 -mJ) and the medicated film (-
457 20.90 mJ) to that of the pure drug (-636.31 mJ), it was mentioned that the drug transformed into the
458 amorphous form due to the effect of PG which acts as a solvent as mentioned before.

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489 **Fig. 4. DSC thermograms of: A) SMC powder, B) SMC + PG film C) Meloxicam powder, D) SMC**

490 **+ Meloxicam PM and E) SMC + PG + Meloxicam film [displaced for better visualization].**

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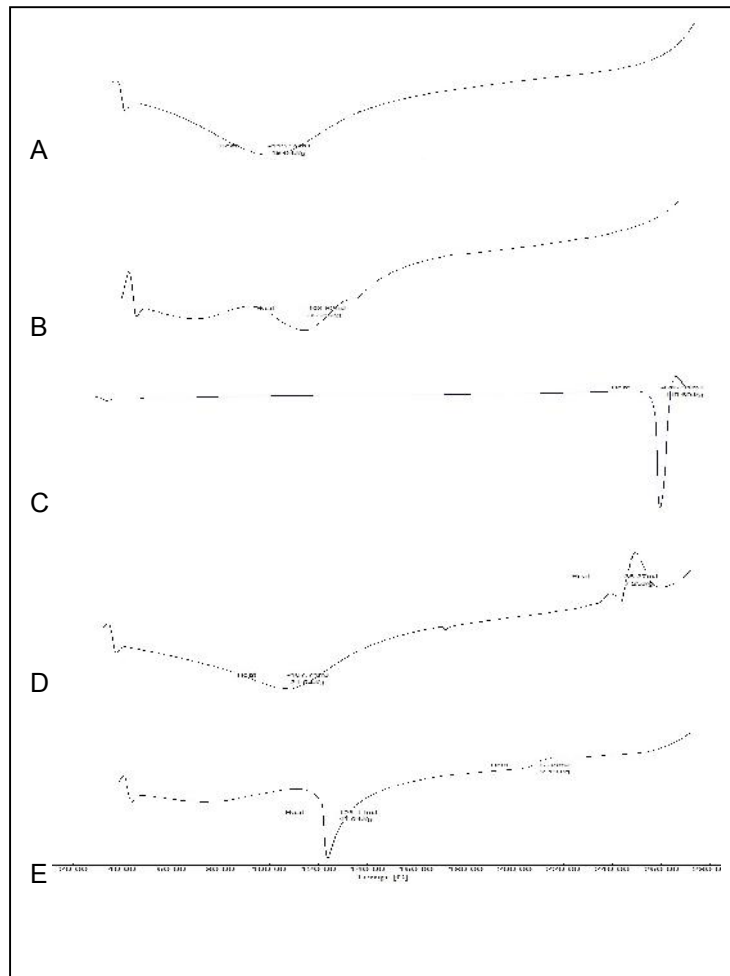
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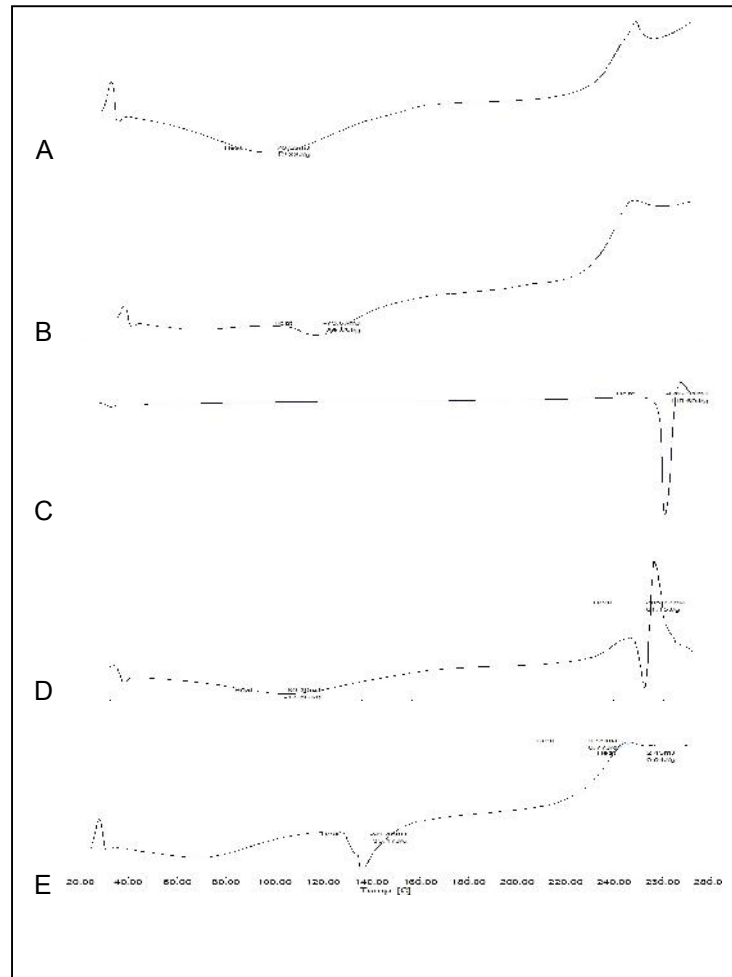
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517 **Fig. 5. DSC thermograms of: A) Pectin powder, B) Pectin + PEG film, C) Meloxicam powder, D)**
518 **Pectin + Meloxicam PM and E) Pectin + PEG400 + Meloxicam film [displaced for better**
519 **visualization].**

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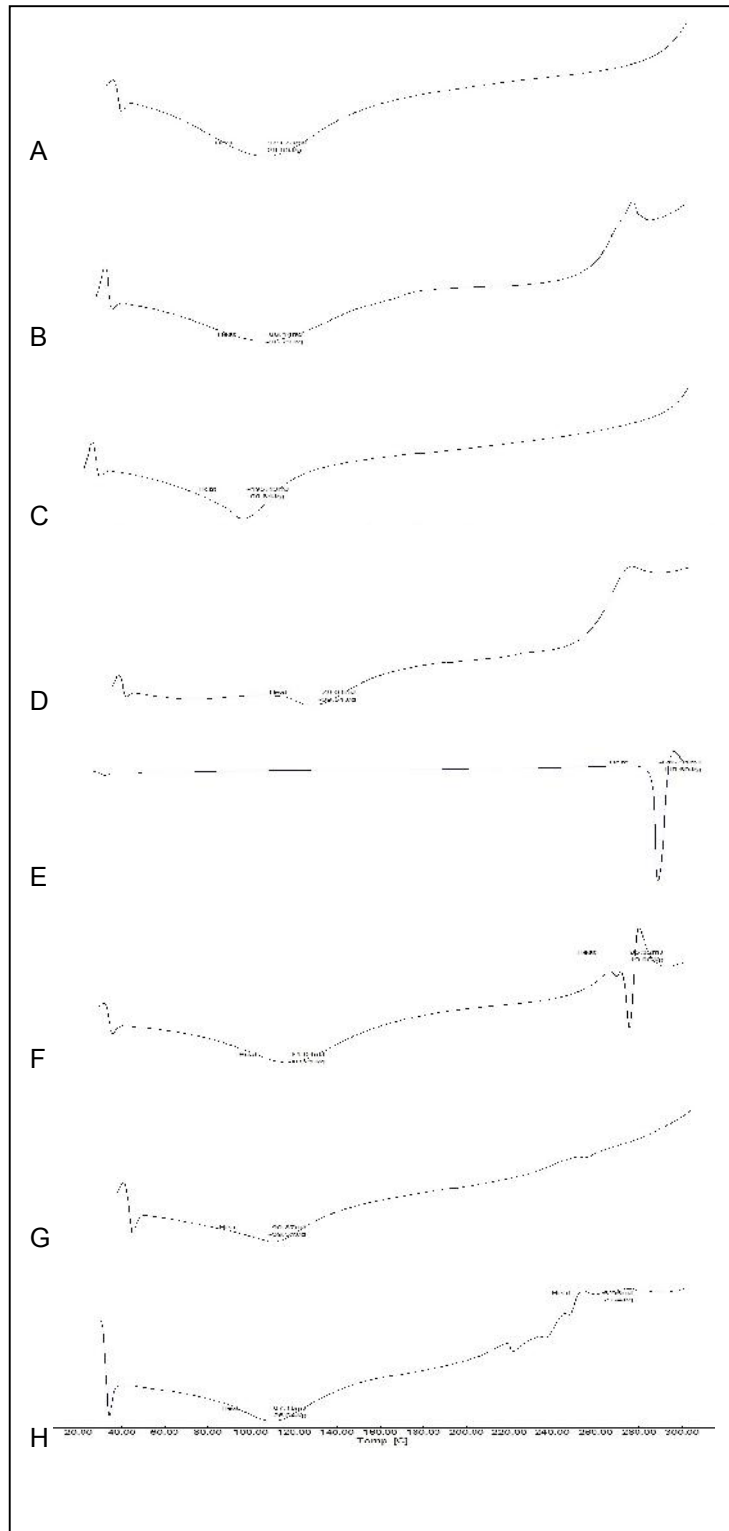
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551 **Fig. 6. DSC thermograms of: A) SCMC powder, B) Pectin powder, C) SCMC film, D) Pectin +**
552 **PEG400 film, E) Meloxicam powder, F) SCMC + Pectin + Meloxicam PM, G) SCMC + Pectin film and**
553 **H) SCMC + Pectin + Meloxicam film [displaced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

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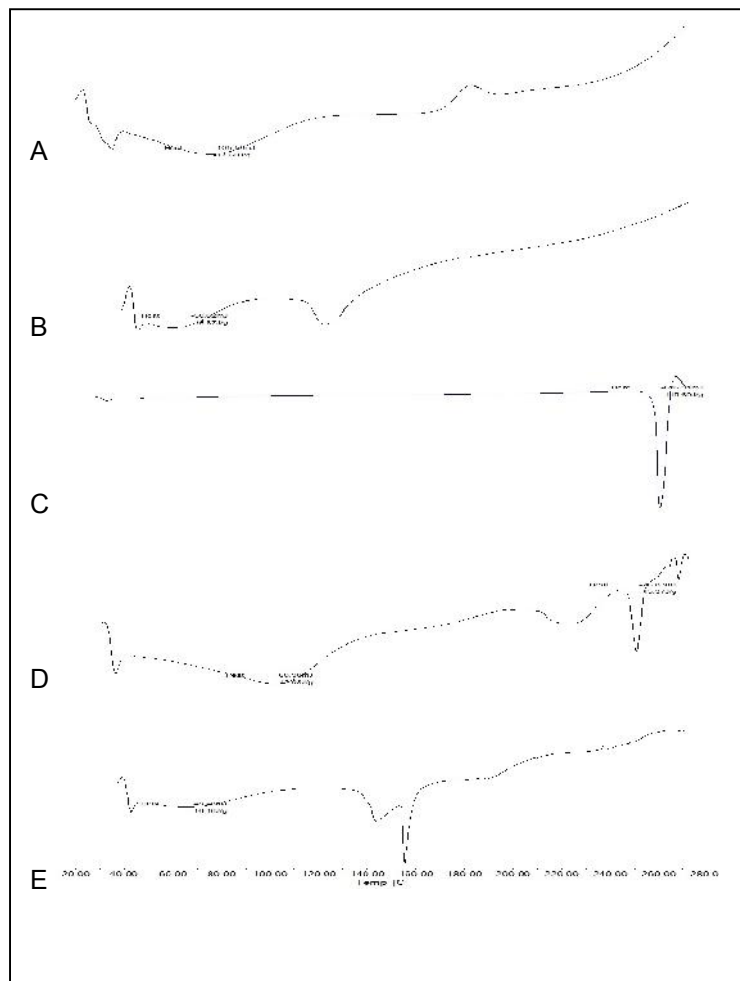


Fig. 7. DSC thermograms of: A) HEC powder, B) HEC + PG film, C) Meloxicam powder, D) HEC + Meloxicam PM and E) HEC + PG + Meloxicam film [displaced for better visualization].

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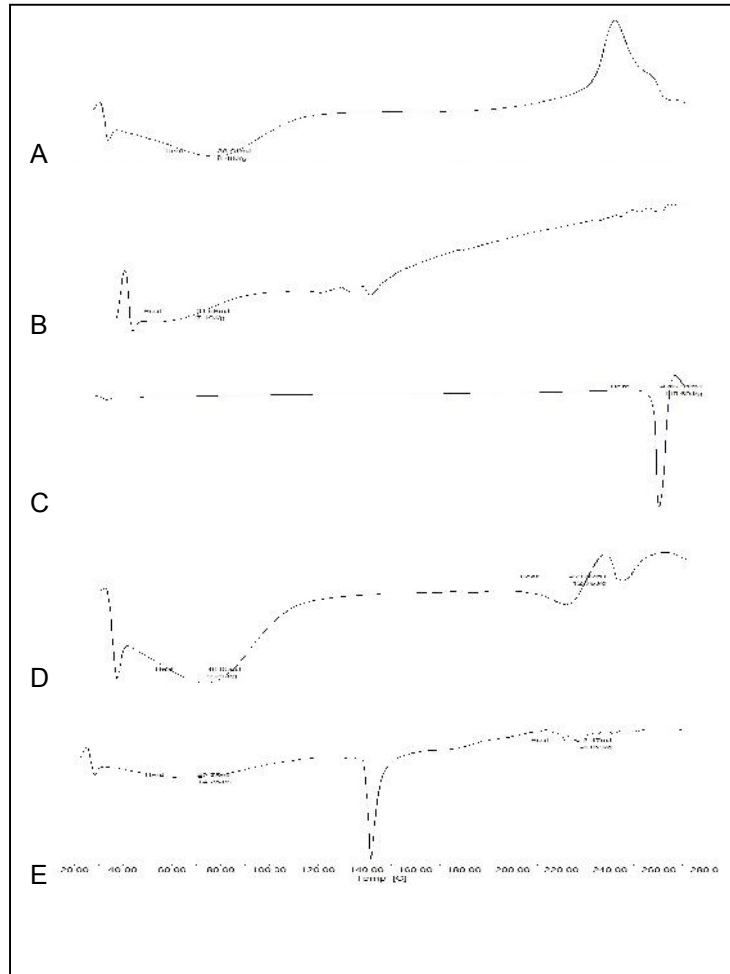


Fig. 8. DSC thermograms of: A) HPMC powder, B) HPMC + PG film, C) Meloxicam powder, D) HPMC + Meloxicam PM and E) HPMC + PG + Meloxicam film [displaced for better visualization].

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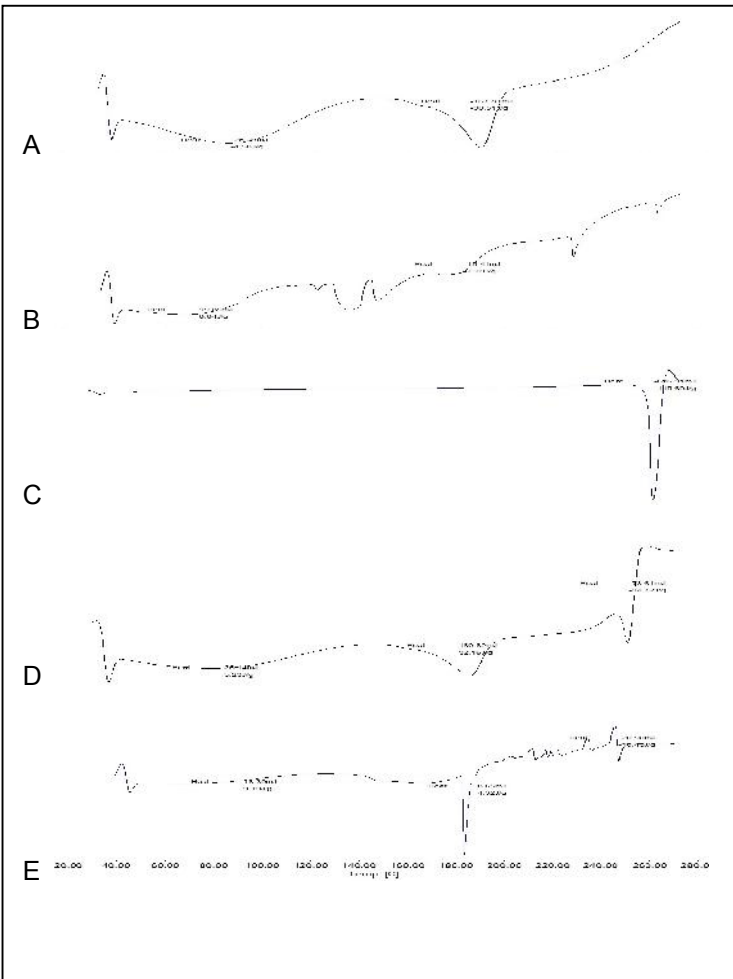


Fig. 9. DSC thermograms of: A) PVA powder, B) PVA + PG film, C) Meloxicam powder, D) PVA + Meloxicam PM and E) PVA + PG + Meloxicam film [displaced for better visualization].

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639 **CONCLUSION**

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

644 **CONSENT**

645 Not applicable.

646

647 **ETHICAL APPROVAL**

648 Not applicable.

649

650 **ACKNOWLEDGEMENTS**

651 Thanks to department and team of pharmaceuticals, faculty of Pharmacy, Suez Canal University who gave
652 us the right to work on DSC instrument which belongs to them and provided us with valuable information
653 during the experiment. My acknowledgements to all people who helped us to carry out and finish this
654 work.

655

656 **COMPETING INTERESTS**

657 Authors have declared that no competing interests exist.

658

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