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Preparation and Characterization of Polymeric Mucoadhesive Film for Buccal Administration

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MMG and SSB designed the study, wrote the protocol and managed the analysis of the study. Authors ARG and HMG managed the literature searches and revision of the paper. Author RBG carried out the experimental work performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Objectives: Buccal films consist mainly of polymer that has a good mucoadhesive profile and plasticizer. A lot of polymers and plasticizers can be used to configure the mucoadhesive films as hydroxyethyl cellulose and glycerin respectively.
Material and Methods: Films prepared by dispersing the polymer, mixing it with plasticizer and pouring it in Petri dishes to be dried and cut finally. Physicochemical tests were used to evaluate the films. These tests are organoleptic evaluation and polymer and plasticizer selection, determination of rheological properties of polymers, film thickness, and determination of moisture content, determination of moisture uptake and evaluation of mechanical properties.
Results and Conclusions: It was found that films prepared from polyvinyl alcohol 2% (w/w) especially with the addition of propylene glycol 20% from the weight of the polymer have excellent characteristics. This formula has promising organoleptic and mechanical properties and its solution is Non-Newtonian pseudoplastic. Moreover, this formula is very thin and has moderate percent of moisture content and moisture uptake. Also, it has high elongation with moderate tensile strength. As a result, it is better to prepare the film by

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these ingredients to obtain an ideal mucoadhesive formula.

Keywords: Organoleptic evaluation; rheological properties; mechanical properties; propylene glycol; mucoadhesive film.

1. INTRODUCTION

Recent years have seen a growing interest in the development of novel buccalbioadhesive dosage forms. This new route is useful for both for systemic delivery of drugs and local targeting of drugs to a specific region in the body [1]. Mouth dissolving films is new drug delivery system for the oral delivery of the drugs. The delivery system composed of a very thin oral strip. This strip is simply placed on the patient's tongue or any oral mucosal tissue. Then, it is immediately wet by saliva. The film rapidly hydrates and adheres onto the site of application. After that, it rapidly disintegrates and dissolves to release the medication for or mucosal absorption [2].These films have specific characteristics. They are generally thin, flexible and dissolve rapidly within few minutes [3]. Buccal films also should contain optimum moisture content and be suitable for labeling, packing, handling and application [4]. Moreover this dosage form should not be large a lot the convenience of the patient and have enough strength and elongation [5].

Mucoadhesive film consists mainly of two components which are polymer and plasticizer. There are many polymers can be used such as polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and hydroxypropylmethyl cellulose (HPMC) [6]. Also, carbopol, polycarbophil, chitosan and xanthan gum are considered important mucoadhesive polymers that can be used in preparation of buccal films. These polymers gave a reasonable drug release and residence time [1]. Plasticizers used in the preparations were glycerin, propylene glycol (PG) and polyethylene glycol 400 (PEG 400) [7]. Polymers used in this dosage form should show a good mucoadhesive profile. High molecular weight (up to 100,000), high viscosity (up to an optimum), long chain polymers, optimum concentration of polymeric adhesive, flexibility of polymer chain, optimum cross-linked density of polymer, optimum medium PH, optimum hydration of the polymer, high applied strength and high initial contact time must be taken into consideration to avoid any problem can be initiated during the application of the dosage form [8]. Also, polymers must be nontoxic, form strong noncovalent bond with the mucin epithelial cell surfaces, allow good incorporation of drug without hindrance to its release and adhere quickly to most tissues [9,10].

This unique route of administration has many benefits and advantages. Difficulties caused from swallowing tablets are circumvented. Thus, these strips or films are especially advantageous for children and geriatric patients, or in diseases with nausea and vomiting. Buccal filmis lacking the risk of inaccurate dosing of drops and syrup dosage forms. Rapid films combine the advantages of tablets which are precise dosage and easy application with the advantages of liquid dosage forms which are easy swallowing and rapid bioavailability. Rapid films combine the advantages of tablets which are precise dosage and easy application with the advantages of liquid dosage forms which are easy swallowing and rapid bioavailability. Also, children can't spit the film out because it adheres to the upper gum after wetting with mucus [2].

On the other hand, there are problems facing mucoadhesive film. Physiological factors are considered one of these problems due to its effect on mucoadhesion. For example, mucus

can be changed by the effect of some diseases as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of female reproductive tract and inflammatory conditions of the eye [11]. The aim of this work is preparation of mucoadhesive films for buccal administration. These films should possess acceptable physicochemical properties to be intended for that use.

2. MATERIALS AND METHODS

2.1 Materials

Hydroxypropyl methyl cellulose Pharmacoat 615 with viscosity 15 (mPa.s) and hydroxyethyl cellulose were obtained as a gift from Medical Union Pharmaceuticals (MUP), (Abou Sultan, Ismailia, Egypt). Sodium carboxymethyl cellulose high viscosity (SCMC) was obtained from El Nasr Pharmaceutical Chemicals Co. (ADWIC),(Qaliubiya, Egypt). Polyethylene glycol 400 was obtained from Alpha Chemika (Mumbai, India). Pectin was obtained from Sigma-Aldrich (Germany). Polyvinyl alcohol is A,R 99.9% assay was obtained from Arabic Laboratory Equipment Co. (ALEC), (Egypt). All other chemicals are of analytical grade.

2.2 Methods

2.2.1 Preparation of polymeric mucoadhesive film

Polymeric matrix system was prepared by weighing the required amount of polymer by using a sensitive balance (BL210S, Sartoruis, Germany). The amount of polymer (HPMC, HEC, SCMC, pectin and PVA) used was 2% (w/w). Then, dissolve the polymer powder in its specific medium (mainly water) to get a polymeric solution or dispersion. This can be done by using mechanical stirrer (Jenway 1000, UK). After that, plasticizer 20% from the weight of the polymer (glycerin, PG or PEG 400) and drug 0.5% (w/w) were added and mixed. The medicated gel was left overnight at room temperature to allow air bubble to get out from the preparation [12]. The preparation was poured in a glass Petri dish and dried at 70°C for 2-3 hours [13]. Finally, the dried films were cut at the required dimensions. The films were packed in aluminum foil and stored in an air tight glass container to maintain the integrity and elasticity of them [14]. Table 1 shows the composition of each formula with its code.

Table 1. Composition of mucoadhesive film with their codes

Formulation	HPMC (g)	HEC (g)	SCMC (g)	Pectin (g)	PVA (g)	Glycerin (g)	PG (g)	PEG 400 (g)
F1	--	--	--	--	2	0.4	--	--
F2	--	--	--	--	2	--	0.4	--
F3	--	--	--	--	2	--	--	0.4
F4	2	--	--	--	--	--	--	--
F5	2	--	--	--	--	0.4	--	--
F6	2	--	--	--	--	--	0.4	--
F7	2	--	--	--	--	--	--	0.4
F8	--	--	--	2	--	0.4	--	--
F9	--	--	--	2	--	--	--	0.4
F10	--	2	--	--	--	--	--	--
F11	--	2	--	--	--	0.4	--	--
F12	--	2	--	--	--	--	0.4	--
F13	--	2	--	--	--	--	--	0.4
F14	--	--	2	--	--	--	--	--
F15	--	--	2	--	--	0.4	--	--
F16	--	--	2	--	--	--	0.4	--
F17	--	--	2	--	--	--	--	0.4
F18	1	--	--	1	--	--	--	--
F19	1	--	--	--	1	--	--	--
F20	1	1	--	--	--	--	--	--
F21	--	1	--	1	--	--	--	--
F22	--	--	1	1	--	--	--	--

2.2.2 Physicochemical evaluation of polymeric matrix films

2.2.2.1 Organoleptic evaluation and polymer and plasticizer selection

There are many physical characteristics should be studied such as color, transparency, gloss, flexibility, elasticity, integrity, strength, smoothness and homogeneity. These parameters or characteristics help in selecting the proper formulations for mucoadhesive purpose by choosing the best polymer with its plasticizer. Plasticizers used during study were glycerin, propylene glycol and polyethylene glycol 400. A rating score system has been constructed in the test in which the positive characteristics take (+), (++) or (+++), on the other hand the negative characteristics take (-), (--) or (---). (+++) and (---) are the most positive and negative characteristics respectively [15].

2.2.2.2 Determination of rheological properties of the polymers

Shear stress, viscosity and area of hysteresis loop or thixotropic loop are important parameters to be measured by using Anton Pear, physica 301, Austria, device at 27±0.1ºC. Shear rate in the experiment was adjusted gradually from 0.5 to 60 sec^{-1} in up and down cycles. By constructing rheograms, we can measure the rheological properties of the polymeric solutions. By plotting the shear stress versus shear rate, the flow curve can obtained. And by plotting the viscosity versus shear rate, the viscosity curve can be obtained. Area of hysteresis loop was calculated from the area between upward and downward curves [16].

The aim of this test is to scan the rheological properties of the entire polymers and some combination only. This is to make sure that these polymers can be used and give reliable flow characteristics or not. So, rheological measurements were done for selected formulations only.

2.2.2.3 Film thickness

Three films of each formulation were taken and the film thickness was measured using micrometer (150 mm Digital Operate Caliper Vernier Gauge Micrometer, China). Film thickness was determined from three different places and the mean value was calculated [17].

2.2.2.4 Determination of moisture content

This test can be done by using moisture analyzer (Ohaus, MB23, USA). Drying temperature for this test was 105ºC. Sample was put in the equipment and then dried until constant weight obtained [18].

$$\text{Moisturecontent } \% = \frac{\text{Initialweight} - \text{Finalweight}}{\text{Initialweight}} \times 100.^{[19]}$$

2.2.2.5 Determination of moisture uptake

After finishing the moisture content by putting the prepared films in the moisture analyzer, these films can be used again in determination of moistures uptake test. The dried films were weighed, put in desiccator and exposed to 70% relative humidity (obtained by using saturated sodium chloride solution) at room temperature. After equilibrium attained under these conditions, films were weighed to determine the weight difference [17].

$$\text{Moisture uptake } \% = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

where final weight is the weight of the film after exposure to 70% relative humidity and initial weight is the weight of the dried film [1].

2.2.2.6 Evaluation of mechanical properties

The mechanical properties are evaluated by measuring the following parameters which are tensile strength, % elongation at break and energy at break. These parameters are determined using Lloyd universal testing machine (LR 10K, Lloyd instruments, Fareham, 100 N load cell, UK). Speed of the instrument was 10mm/min [20]. Rectangular film strips of fixed width and length were attached to the crosshead and the base plate. The length of the film was 5 cm and the width was 1 cm [1].

Tensile strength and %elongation at break were determined as follows [21].

$$\text{Tensile strength} = \frac{\text{Breaking force (N)}}{\text{Initial} - \text{cross sectional area of the fi} \quad (\text{mm}^2)}$$

$$\%\ \text{Elongation at break} = \frac{\text{Increase in lenght at breaking point (mm)}}{\text{Original lenght (mm)}} \times 100$$

$$\text{Energy at break} = \frac{\text{AUC}}{\text{V}}$$

Where AUC is the area under the load vs. Displacement curve and V is the volume of the film located in the die cavity of the film holder (the energy at break is normalized to the film's volume) [22].

3. RESULTS AND DISCUSSION

3.1 Organoleptic Evaluation and Polymer and Plasticizer Selection

Concentration of the plasticizer used is very important to be well adjusted. Increase or decrease of this percent will result in significant influence on the properties of the film. Increasing concentration of plasticizers resulted in decreased tensile strength concomitant with an increase in elongation at break, and vice versa [23]. If the film has a low strength, it will be broken easily. So, it is not advisable to add much plasticizer to make the film more practical for use by the patient. It is preferable to add moderate amount of plasticizer to give the film the appropriate elasticity without losing its strength and also to avoid the brittleness and stiffness of the film. As well as, polymer concentration is crucial. Mucoadhesive force was found to be increased with increase in polymer concentration. Also, researches explained that tensile strength increases with the increase in the polymer content [13]. Thus, a correlation between polymer and plasticizer concentration should be done. If the polymer concentration increased, the strength will increase. Although, the increase in the polymer concentration may be beneficial in many parameters, it may be a bad aspect for others such as thickness. Thickness of the film will increase with high polymer concentration and this is not acceptable for the patient and not elegant.

Fortunately from Table 2, polyvinyl alcohol was the best polymer used in all previous prepared formulations for mucoadhesive films. F1, F2 and F3 films which prepared from this polymer have excellent physical properties. All organoleptic properties of these three films have rating scores of (+++).Combining the PVA with glycerin increased the organoloeptic properties as smoothness, flexibility, elegancy and folding [24] after mixing PVA with PG, visual properties of the film became colorless, transparent and soft with no spots corresponding to the homogeneity [25]. Data of F19 formula ensured that using PVA polymer alone is better than combing it with any other polymer. The addition of HPMC to PVA was not acceptable enough. Combining HPMC with PVA did not enhance the folding or elasticity property of the film [26].

Results also explained that F4, F5, F6 and F7 formulations gave high rating score. The addition of 20% plasticizer of the weight of the polymer is effective. The increase in the plasticizer affected the physical properties negatively. So, we used the plasticizer in concentration of 20%. There is a study showed that by using HPMC with PEG 200 30% of the weight of the polymer, the mechanical properties of the film as folding endurance will be acceptable [17] On the other hand, another study stated that preparing buccal film by mixing HPMC 1.3% w/w with PG 30% of the weight of the polymer gave low folding results [27]. So, the use of PEG by low concentrations is better than the other plasticizer during the film preparation.

It was observed from F8 and F9 formulations that addition of glycerin or PEG 400 to pectingave moderate results. Using glycerin as a plasticizer in pectin film is very effective in order to obtain good film properties [28]. Preparingmuco adhesive film with pectin and PEG enhanced the organoleptic properties such as smoothness, translucency, integrity and folding [29]. Moreover, F18, F21 and F22 informed us that the addition of cellulosic polymers to pectin in ratios 1:1 gave moderate results for organoleptic properties.

Also, Table 2 showed that using HEC by concentration 2% as F10, F11, F12 and F13 gave promising results. The results showed that using plasticizer 20% from the weight of the polymer which is low concentration is effective. El-Setouhy et al. prepared films that were composed of HEC and PG. The results showed that mechanical properties were affected negatively. This is due to high concentration of plasticizer (7.5 gm) used during the preparation. Also, the concentration of the polymer has a major role. By decreasing HEC concentration from 3gm to 1.5 gm, the results were enhanced to some extent [25].This confirms that concentration of polymer and plasticizer used in our experiment was effective. By addition of HPMC to HEC, moderate organoleptic properties were obtained. This may be due to absence of plasticizer. Plasticizer has an advanced role in organoleptic properties of the film [23].

As showed in F15, F16 and F17 films, preparing SCMC with addition of PG or PEG400 is more efficient than glycerin. Semalty et al. explained that films prepared with addition of SCMC 2% only without plasticizer did not give promising results. So, F14 has low organoleptic properties [30].

3.2 Determination of Rheological Properties of the Polymers

Rheological measurements on polymeric solutions used for constructing the mucoadhesive films are performed for the following reasons: 1) to understand the fundamental nature of a system; 2) for quality control of raw materials, and manufacturing processes such as mixing, pumping, and filling; and 3) to study the effect of different parameters such as temperature on the quality and acceptance of a final product. Rheological properties of polymers can be measured by shear rate, shear stress, viscosity and area of hysteresis loop. If the shear rate changes during an application, the internal structure of the sample will change and the change in stress or viscosity can then be seen. Pseudo-plastic or shear thinning fluids display viscosity reduction while the shear rate increases. Typical examples of these are colloidal system. The colloidal structure breaks down while shear rate increases, displaying reduced viscosity. By drawing some curves, rheological properties of the polymeric solutions can be measured. By plotting the shear stress versus shear rate, the flow curve can obtained. And by plotting the viscosity versus shear rate, the viscosity curve can be obtained. Area of hysteresis loop indicates how fast the sample structure will recover after the load is removed. It is calculated from the area between upward and downward curves [16].

Table 2. Effect of polymer and plasticizer type on organoleptic properties of mucoadhesive films

Film	Properties								
	Color	**Transparency**	**Gloss**	**Flexibility**	**Elasticity**	**Integrity**	**Strength**	**Smoothness**	**Homogeneity**
F1	Colorless	+++	+++	+++	+++	+++	+++	+++	+++
F2	Colorless	+++	+++	+++	+++	+++	+++	+++	+++
F3	Colorless	+++	+++	+++	+++	+++	+++	+++	+++
F4	Colorless	+++	++	+++	++	+++	+++	+++	++
F5	Colorless	+++	++	+++	+++	++	++	+++	++
F6	Colorless	+++	++	+++	+++	++	+++	+++	++
F7	Colorless	+++	++	+++	+++	+++	+++	+++	++
F8	Faint brown	+++	++	+++	-	++	+	+	+++
F9	Faint brown	+++	++	++	-	++	+	+	+++
F10	Colorless	+++	+++	+++	++	+++	+++	+++	+++
F11	Colorless	+++	+++	+++	++	+++	++	+++	++
F12	Colorless	+++	++	+++	+++	++	++	+++	+++
F13	Colorless	+++	+++	+++	+++	+++	++	+++	+++
F14	Colorless	-	-	--	---	-	+	+	+
F15	Colorless	+++	+	-	---	-	+++	+	+++
F16	Colorless	+++	+++	+++	+++	+++	++	+++	+++
F17	Off white	++	+	+++	+++	+++	+++	+++	++
F18	Faint brown	+++	++	++	--	-	+	++	+++
F19	Off white	+++	--	+++	-	-	-	++	++
F20	Off white	+++	++	+++	+	++	++	+++	+++
F21	Faint brown	++	++	+++	+	++	++	+++	+++
F22	Faint brown	+++	++	+	---	-	+++	+++	+++

Tables 3-4 and Figs. 1, 2.1 and 2.2 illustrated that most of solutions used in the preparation of films have low viscosity with high shear rate. Thus, these solutions can be considered as Non-Newtonian pseudoplastic which have the optimum rheological behavior that enhance pouring and flowing. Also, data showed that shear stress gives low values with low shear rate which indicates the limited resistance to flow and this is a characteristic for pseudoplastic flow. Pectin 2% polymeric solution gave pseudoplastic behavior. Moderate concentration of pectin solution exhibits non-Newtonian, pseudoplastic behavior characteristics. There are some factors that affect solubility and viscosity of pectin solution which are molecular weight and concentration of pH of the preparation [31].

HPMC 2% and SCMC 2% polymeric solutions were found to have pseudoplastic property. Pseudoplasticity increases with the increase in the macromolecules concentration. Changes of the degree of pseudoplasticity are more apparent in HPMC than SCMC. This is due to the ability of HPMC molecules to associate with each other and flexibility of macromolecular chains [32].

Rheological properties of HEC 2% exhibited a pseudoplastic flow. The increase in the polymer concentration will increase the rheological properties [33]. Rheology of PVA 2% was agreed with [34]. He explained that PVA solution behave as non-Newtonian fluids. In addition, combining PVA with other polymer in the solution gives the same result.

Each material or polymer solution has its own hysteresis area. Also, the increase in the hysteresis area indicates the enhancement of the thixotropic properties of the material which is required [35]. This is because; the most desirable type of flow behavior is thixotropic flow [16]. SCMC 2% polymeric solution has the highest hysteresis area which is 371.97(Pa/s). HPMC 2% polymeric solution has the lowest hysteresis area which is 0.16 (Pa/s).

The idea of mixing polymers with each other to produce polymer combination can introduce some changes in the rheological behavior of the preparation because different polymers present in the same solution make some reactions. These reactions can affect the solution positively or negatively [36]. As mentioned before, solution of polymer combination behaves a pseudo plastic flow, but the synergism was observed due to polymers interaction. Since, all the polymers used exhibited non-Newtonian pseudo plastic flow, so solution containing two polymers will behave the same flow. But some changes may be observed due to interactions between polymers.

Table 3. Rheological parameters of single polymeric solutions

SR (sec^{-1})	PVA 2%		HPMC 2%		Pectin 2%		HEC 2%		SCMC 2%	
	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)
0.5	-0.00022	-0.00044	-0.00016	-0.00032	0.193	0.385	0.438	0.875	15.8	31.5
0.851	-0.0017	-0.002	-0.00137	-0.0016	0.205	0.241	0.75	0.882	21.8	25.7
1.45	0.000507	0.00035	-0.00085	-0.00059	0.268	0.185	1.25	0.865	26	17.9
2.47	0.00971	0.00394	0.00154	0.000623	0.36	0.146	2.06	0.835	32.6	13.2
4.2	0.0242	0.00576	0.012	0.00286	0.52	0.124	3.29	0.784	42.1	10
7.15	0.0419	0.00587	0.0241	0.00337	0.761	0.107	5.19	0.726	53.3	7.46
12.2	0.0687	0.00565	0.0458	0.00376	1.08	0.0886	7.73	0.635	66.3	5.45
20.7	0.119	0.00574	0.0777	0.00375	1.65	0.0799	11.1	0.538	82	3.96
35.2	0.208	0.00591	0.142	0.00402	2.55	0.0724	15.5	0.44	101	2.87
60	0.349	0.00581	0.246	0.0041	3.99	0.0665	20.1	0.334	125	2.08
50	0.273	0.00546	0.202	0.00404	3.3	0.0661	18	0.359	114	2.28
42.9	0.229	0.00534	0.168	0.00392	2.87	0.0669	16.5	0.383	106	2.47
35.9	0.186	0.00517	0.138	0.00386	2.41	0.0673	14.9	0.415	96.8	2.7
28.8	0.143	0.00497	0.107	0.00373	1.95	0.0677	13	0.452	86.9	3.02
21.7	0.11	0.00505	0.081	0.00373	1.49	0.0688	10.9	0.503	75.4	3.47
14.6	0.071	0.00485	0.054	0.00368	1.02	0.0699	8.44	0.577	61.5	4.2
7.57	0.0331	0.00437	0.0255	0.00337	0.547	0.0723	5.34	0.706	43	5.68
0.5	-0.00729	-0.0146	-0.00546	-0.0109	0.0287	0.0574	0.585	1.17	7.73	15.5

Table 4. Rheological parameters of polymer combination solutions

SR (sec^{-1})	SCMC 2% + Pectin 2% (1:1)		HPMC 2% + Pectin (1:1)		HEC 2% + Pectin 2% (1:1)		HPMC 2% + PVA 2% (1:1)		HPMC 2% + HEC 2% (1:1)	
	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)	SS (Pa)	Viscosity (Pa.s)
0.5	0.954	1.91	0.0766	0.153	0.847	1.69	0.00904	0.0181	0.0744	0.149
0.851	1.48	1.74	0.0885	0.104	1.36	1.6	0.00734	0.00863	0.112	0.131
1.45	2.33	1.61	0.123	0.085	2.29	1.58	0.01	0.0069	0.174	0.12
2.47	3.64	1.48	0.173	0.0701	3.71	1.5	0.0153	0.00621	0.281	0.114
4.2	5.62	1.34	0.265	0.0631	5.57	1.33	0.0293	0.00698	0.454	0.108
7.15	8.53	1.19	0.385	0.0538	7.96	1.11	0.053	0.00742	0.709	0.0993
12.2	12.6	1.03	0.577	0.0474	10.9	0.895	0.0822	0.00676	1.09	0.09
20.7	18.1	0.875	0.899	0.0434	14.3	0.689	0.138	0.00665	1.68	0.0809
35.2	25.5	0.724	1.42	0.0402	18.1	0.513	0.214	0.00608	2.54	0.0719
60	35.4	0.59	2.21	0.0368	24.3	0.405	0.342	0.0057	3.79	0.0631
50	30.7	0.613	1.79	0.0358	21.1	0.422	0.274	0.00549	3.22	0.0644
42.9	27.1	0.632	1.52	0.0353	19	0.443	0.232	0.00541	2.83	0.0659
35.9	23.5	0.655	1.26	0.0351	16.7	0.466	0.193	0.00539	2.43	0.0679
28.8	19.8	0.687	1	0.0348	14.2	0.495	0.152	0.00529	2.02	0.0703
21.7	15.8	0.729	0.77	0.0354	11.6	0.532	0.12	0.00555	1.6	0.0737
14.6	11.6	0.791	0.536	0.0366	8.58	0.586	0.0817	0.00558	1.14	0.0782
7.57	6.83	0.902	0.302	0.0399	5.12	0.676	0.0472	0.00623	0.643	0.0849
0.5	0.705	1.41	0.0359	0.0719	0.469	0.939	-0.00524	-0.0105	0.0407	0.0813

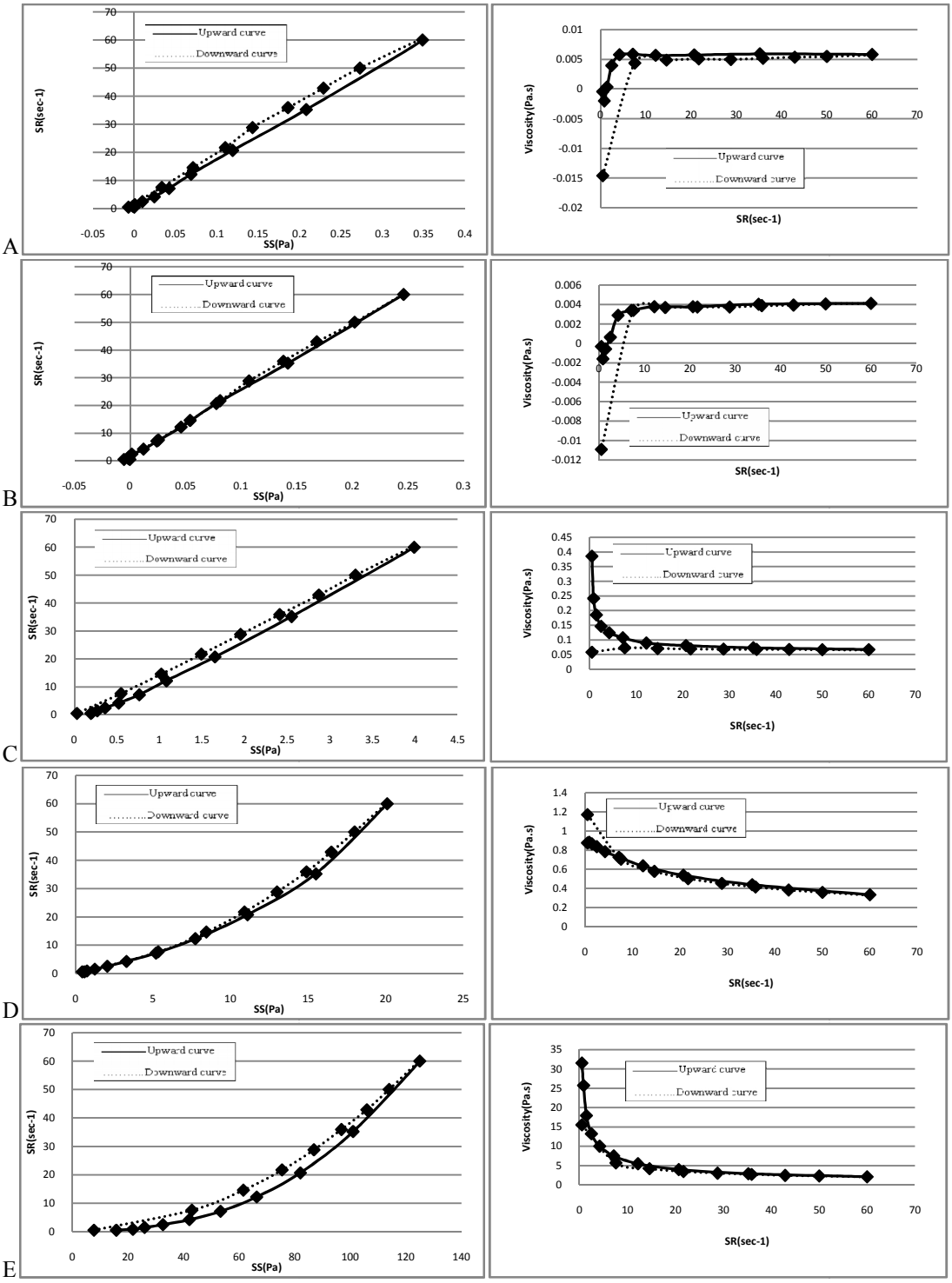

Fig. 1. Single polymeric solution rheograms of (A) PVA 2%, (B) HPMC 2%, (C) pectin 2%, (D) HEC 2% and (E) SCMC

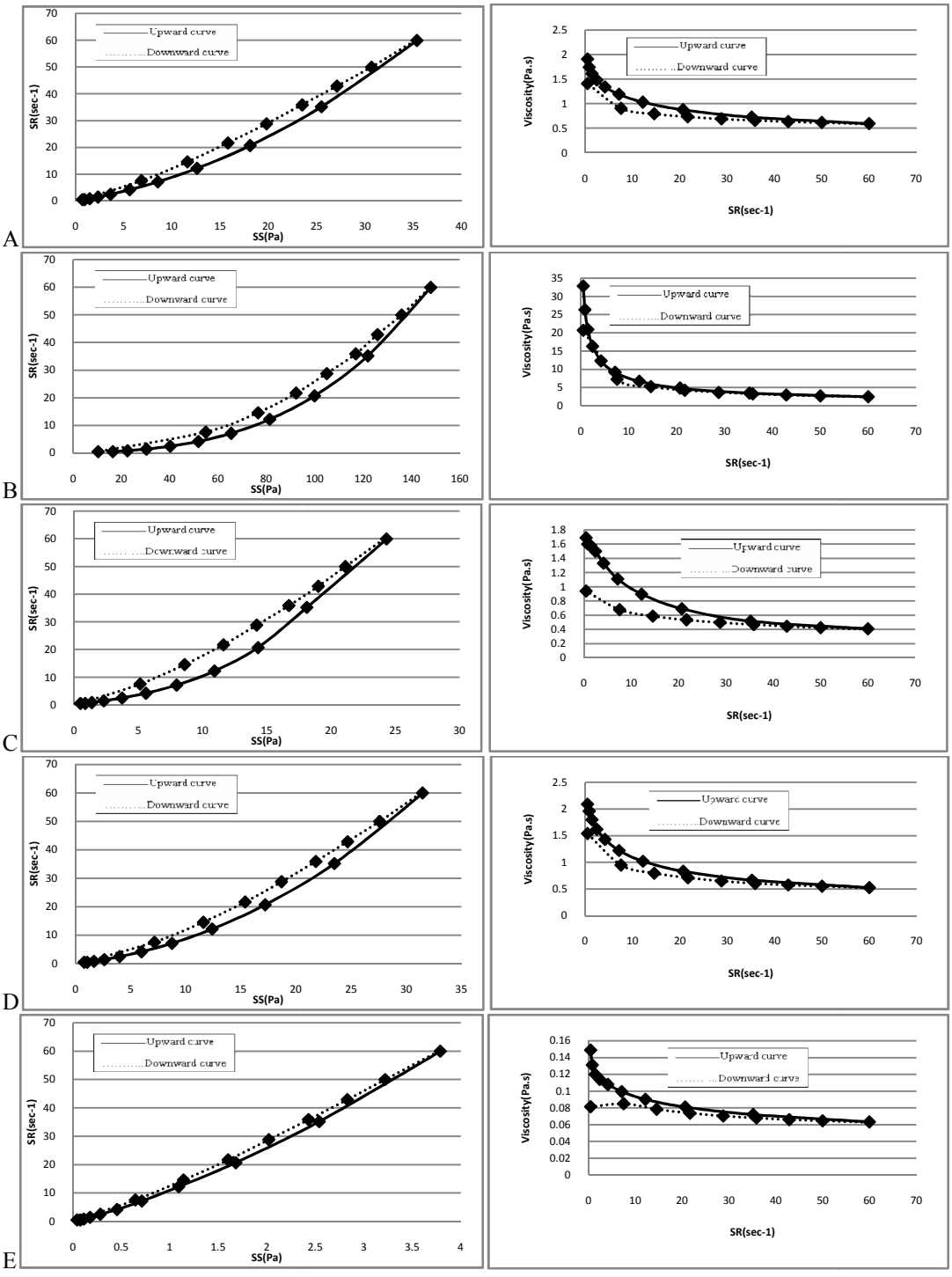

Fig. 2.1 Mixed polymeric solution rheograms of (A) SCMC 2% + Pectin 2% (1:1), (B) HEC 2% + SCMC 2% (1:1), (C) HEC 2% + Pectin 2% (1:1), (D) HPMC 2% + SCMC 2% (1:1) and (E) HPMC 2% + HEC 2% (1:1)

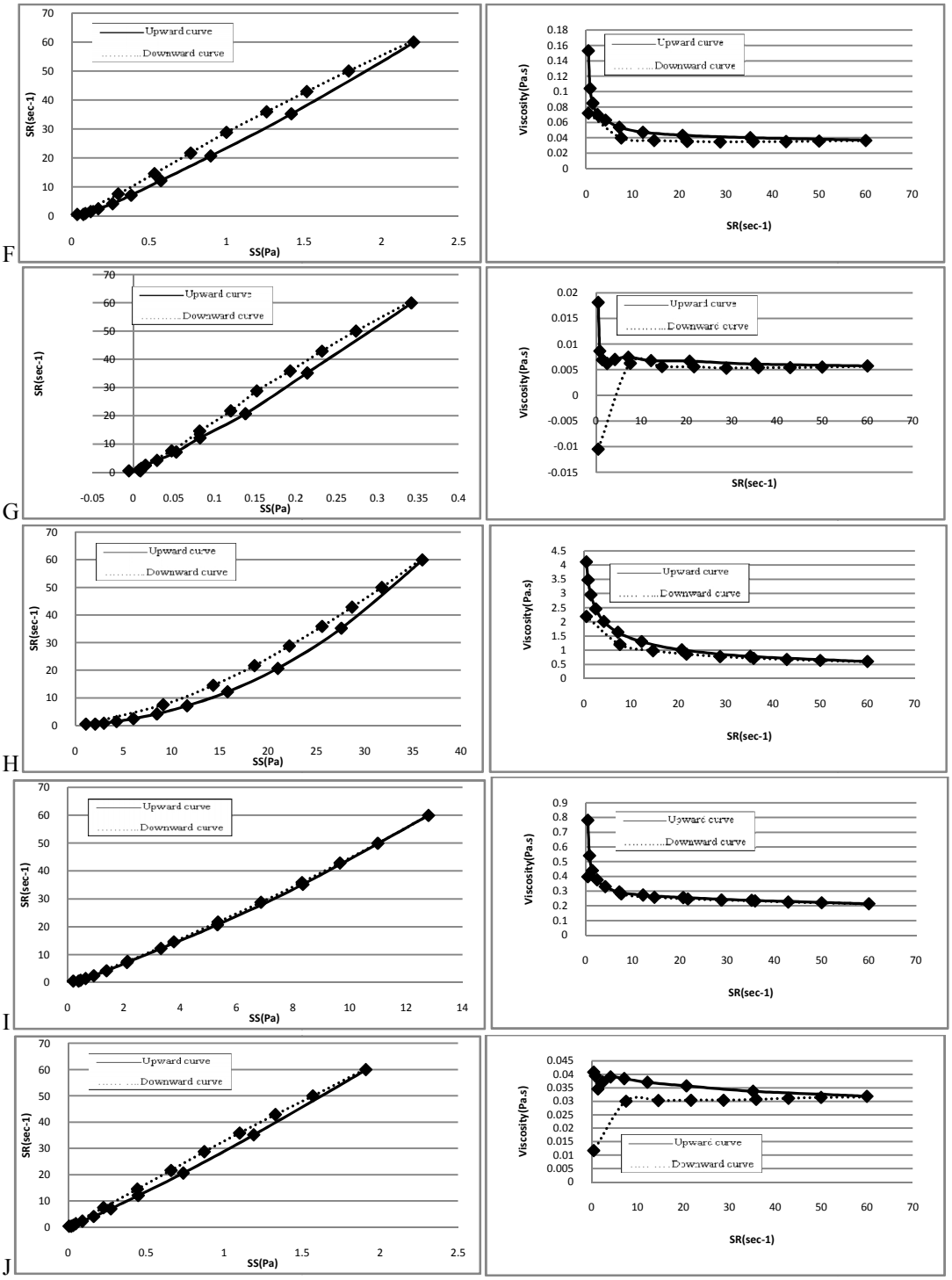

Fig. 2.2 Mixed polymeric solution rheograms of (F) HPMC 2% + Pectin 2% (1:1), (G) HPMC 2% + PVA 2% (1:1), (H) PVA 2% + SCMC 2% (1:1), (I) PVA 2% + HEC 2% (1:1) and (J) PVA 2% + Pectin 2% (1:1)

3.3 Film Thickness

Table 5 explained the thickness values for each film. The thickness of the prepared films ranged from 0.051±0.004 mm to 0.105 ± 0.011 mm. Most of films were thin and uniform which is better for mucoadhesion. The drug release will increase with the decrease in the thickness. 37 Results showed that PVA films have the lowest thickness values which are preferred. On the other hand, using pectin in preparing film resulted in an increase in the thickness of the film which is not required. The disintegration and dissolving times are prolonged as the film thickness increases [5]. Also, films constructed from HPMC, HEC, SCMC or polymer combinations exhibited a desired pattern in thickness that is not exceeding of 0.074 ± 0.004 mm. Vijayan et al. stated that film thickness of the films prepared from SCMC was 0.092 mm [17]. In addition, it was found that film prepared from HPMC and PEG has 0.068 mm thickness [38]. So, PVA can be considered better than other polymer to be used to configure a desirable thin film.

3.3 Determination of Moisture Content

The optimum moisture content in the films helps them to remain stable from being completely dried or brittle. Also, it protects the patches from bulkiness [39]. If the film is brittle, it will be broken during use. Also, the film should not be very dry, because this will affect physical properties of the film as flexibility and elasticity which is practically unacceptable. There is an important factor should be taken into consideration which is the concentration of the polymer. Moisture content and moisture uptake were found to increase with the increase in the concentration of hydrophilic polymers [40]. So, it is preferable to prepare the formulation with low polymer concentration.

The prepared films were arranged according to the moisture content in a descending order, F16 > F17 > F9 > F12 > F15 > F14 > F1 > F13 > F2 > F8 > F6 > F3 > F11 > F5 > F4 > F10 > F7.

Table 5 showed the results of moisture content percent. SCMC films have the highest moisture content especially with the addition of PG or PEG400. This is because; these plasticizers are hygroscopic in nature and have the ability to absorb water. Concerning PEG, there is a relation between hygroscopicity and molecular weight. Hygroscopicity decreases with the increase in the molecular weight [41]. Since, molecular weight used in PEG was 400, the hygroscopicity will be high. Thus, addition of PEG 400 to SCMC increases the moisture content in the formulation.

HPMC films were considered have the lowest moisture content. Addition of PG raised the moisture content a lot due to its hygroscopicity as mentioned before. Although, HPMC has hydrophilic hydroxypropyl substituents, it contains hydrophobic methoxyl groups. So, it exhibited low hygroscopic properties [42].

While PVA films have the optimum or the ideal moisture content. They are containing moderate amount of moisture which is desired. This is due to presence of hydroxyl group which makes the surface more hydrophilic to allow interaction with water [43]. Moreover absence of plasticizer resulted in lowering the moisture content. This is because plasticizer provides more active sites for interactions. These sites are hydrophilic hydroxyl groups that interact with water [44].

From the previous readings in table 5, we can conclude that addition of glycerin and PEG to SCMC, HEC, HPMC, PVA and pectin gave a moderate percent of moisture content within the film. While the inclusion of PG to the formulations resulted in more increase in the moisture content.

This experiment was not preceded for films containing two polymers. It was found that moisture content is an additive property [45]. So, there is no need to perform moisture experiments on those films.

3.4 Determination of Moisture Uptake

Moisture uptake of mucoadhesive film is a dangerous property that should be taken in consideration. This property affects the film badly. If the moisture uptake of the film increased, the probability for microbial growth and contamination will be enhanced. Dealing the patients with contaminated medications will infect them with microbes and this is not accepted at all. Also, the high moisture uptake has an effect on the physical properties of the film. So, it is a requirement to maintain the integrity of the film during its shelf life [46]. Also, moisture uptake was found to increase with the increase in the relative humidity [47]. So, storage conditions of these mucoadhesive films should be taken into considerations to avoid any problem that can occur from excess percent of moisture.

Table 5 showed the moisture uptake % of the films. This is the percent of moisture uptake of the polymers arranged in a descending order, CMCS > HEC > Pectin > PVA > HPMC. A more detailed arrangement for films through studying the effect of plasticizer which is F4 <F7 <F6 <F3 <F5 <F1 <F2 < F10 <F8 <F13 <F9 <F17 <F12 <F11 < F14 <F15 <F16.

Not only the type of the polymer can determine the amount of moisture in mucoadhesive film, but also plasticizer type which is added to the formulation affects this amount [48] Results from Table 5 showed that there are variations in the percent of moisture uptake between samples. SCMC films have the highest values for moisture uptake especially with glycerin and PG. CMCS is considered a water absorbing agent. It is hygroscopic and under high humidity conditions it can absorb a large quantity of water more than 50% [49]. This is considered a reason for being CMCS has the highest percent moisture uptake.

HPMC films have the lowest values of moisture uptake especially in the film prepared without plasticizer. As mentioned before, HPMC is not a highly hygroscopic polymer. But, presence of glycerin in the film raised the moisture uptake. Glycerin molecules are small and have high capacity for interaction. In addition, glycerin is a highly hydrophilic plasticizer and combines at higher affinity with water [50].

PVA remains also in the moderate level of moisture uptake. Film containing PVA and PG has high percent of moisture uptake, because this plasticizer is hygroscopic and has high ability to absorb water as mentioned before.

Table 5 showed that addition of plasticizer to polymers gave variable results. The highest percent of moisture uptake in HPMC and HEC films were observed with glycerin. But the degree of increase in the moisture in HEC films is higher than HPMC films, because it is more hygroscopic [42]. Moreover, the highest percent of moisture uptake in PVA and SCMC films were observed with PG. While, the highest percent of moisture uptake in pectin films was observed with PEG 400.

From the previous results, it was noted that percent of moisture content and moisture uptake within some formulations are not matched or approximated with each other. Some research papers found that in some formulations, there is a big difference between values of moisture content and moisture uptake for the entire film [19,38]. so; it is not a rule to find the moisture uptake value near from moisture content.

3.5 Evaluation of Mechanical Properties

Films which are intended to be used for buccal delivery should possess sufficient strength to resist mechanical stress during production, handling and application. [13] the mechanical properties of a polymer involve its behavior at stress. These properties give much information about the suitability of the polymer to be used as a matrix in the formulation of mucoadhesive films. To say that this polymer can be used or not, you have to answer some questions. Firstly, how strong is the polymer? How much can you stretch it before it breaks? Secondly, how stiff is it? How much does it bend when you push on it? Thirdly, is it brittle? Does it break easily if you hit it hard? Fourthly, is it hard or soft? Fifthly, does it hold up well under repeated stress? [51]. To answer these questions, some parameters should be measured such as tensile strength, %elongation at break and energy at break [52]. The tensile strength is the property that measures the ability of the film to withstand rupture, mechanical pressures or the force needed to break the film [53]. The % elongation at break is the elongation at the moment of rupture of the film divided by the initial length of the film and multiplying by 100 [54]. So, we can say that the energy at break is the amount of energy needed to break the film.

Presence of plasticizer in the formulation helps in imparting strength to the film by lubrication effect of plasticizer and reduction of the cohesive force between chain molecules of polymer. As a result tensile strength of the film will be reduced [55]. Plasticizer functions by weakening the intermolecular attractions between polymer chains [20]. So, elongation of the film will increase by addition of plasticizer to the formulation. Moreover, tensile strength increases with the increase in polymer content [56]. So, it is important to adjust the plasticizer and polymer concentration well to produce mechanically accepted film.

Polymer combination is another factor that must be taken into consideration during the determination of the mechanical properties of the film. Interactions between polymers can affect tensile strength and elongation at break positively or negatively. So, ratios in each combination should be studied well to avoid any problem in the film processing. Relative humidity and moisture content can also increase or decrease the mechanical properties of mucoadhesive film, so it is important to evaluate these factors [57].

Table 5 and Figs. 3 and 4 showed the mechanical properties of the formulated polymers. Tensile strength of films under study without addition of plasticizer showed that tensile strength of F4 was 4.34 ± 0.13 N/mm^2 with 173.80 ± 71.76 % elongation and 0.12 ± 0.04 J energy at break. F10 had 1.44 ± 0.17 N/mm^2 tensile strength with 252.16 ± 37.20 % elongation and 0.05 ± 0.01 J energy at break. Tensile strength of F14 was 4.63 ± 0.43 N/mm^2 with 105.78 ± 20.51 % elongation and 0.07 ± 0.02 J energy at break. So, absence of the plasticizer enhanced the tensile strength of the polymer. Plasticizers are high boiling point organic liquids that reduce the glass transition temperature of the polymer where the films changes from brittle to flexible. Thus, absence of plasticizer in the formulation decreased the elongation at break due to increase in the tensile strength [58]. As a result, it is preferable to add plasticizer in the polymeric film.

Table 5. Physical and mechanical properties of mucoadhesive films

Film	Thickness (mm) ± SD	% Moisture content ± SD	% Moisture uptake ± SD	Tensile strength (N/mm^2) ± SD	% Elongation at break ± SD	Energy at break (J) ± SD
F1	0.052±0.009	15.59 ± 2.25	17.97 ± 3.57	2.17±0.60	3878.42±965.79	0.49±0.17
F2	0.052±0.003	15.02 ± 0.63	20.15 ± 5.07	0.70±0.33	4664.12±978.25	1.02±0.05
F3	0.052±0.003	13.69 ± 1.03	15.78 ± 2.57	2.42±0.05	3571.39±973.61	1.94±0.23
F4	0.055±0.003	8.67 ± 1.19	12.01 ± 6.93	4.34±0.13	173.80±71.76	0.12±0.04
F5	0.069±0.003	11.59 ± 3.88	16.35 ± 4.43	1.08±0.36	152.46±39.02	0.03±0.01
F6	0.061±0.005	13.17 ± 1.05	13.74 ± 1.48	1.92±0.76	354.20±104.78	0.20±0.05
F7	0.072±0.004	6.13 ± 0.21	12.25 ± 0.43	2.20±0.63	391.18±53.52	0.15±0.03
F8	0.105±0.011	13.97 ± 0.55	23.18 ± 3.03	2.17±0.28	50.65±4.77	0.01±0.003
F9	0.076±0.008	18.46 ± 2.67	25.47 ± 2.07	2.89±0.18	130.74±7.26	0.06±0.01
F10	0.051±0.004	8.37 ± 0.70	22.55 ± 6.31	1.44±0.17	252.16±37.20	0.05±0.01
F11	0.065±0.006	12.78 ± 0.48	27.64 ± 3.24	0.68±0.23	752.41±70.79	0.04±0.01
F12	0.060±0.010	17.26 ± 5.14	26.84 ± 3.85	0.65±0.16	623.24±21.24	0.02±0.002
F13	0.055±0.003	15.55 ± 3.85	24.45 ± 3.85	1.67±0.55	810.80±34.95	0.09±0.03
F14	0.063±0.004	15.81 ± 0.74	29.06 ± 5.33	4.63±0.43	105.78±20.51	0.07±0.02
F15	0.074±0.004	17.08 ± 4.02	34.17 ± 5.05	2.26±0.97	263.40±68.16	0.10±0.04
F16	0.068±0.002	20.54 ± 1.55	34.22 ± 2.57	3.84±0.44	424.96±19.70	0.20±0.02
F17	0.067±0.006	19.22 ± 1.36	25.62 ± 1.81	3.96±0.36	135.75±21.28	0.08±0.02
F18	0.072±0.003	N.A.	N.A.	4.11±1.19	38.93±8.58	0.01±0.008
F19	0.061±0.013	N.A.	N.A.	0.43±0.11	165.45±28.53	0.05±0.02
F20	0.050±0.005	N.A.	N.A.	2.33±0.25	155.52±25.63	0.05±0.01
F21	0.051±0.001	N.A.	N.A.	2.56±0.26	221.74±3.17	0.06±0.003
F22	0.057±0.003	N.A.	N.A.	5.48±0.43	66.05±10.58	0.04±0.01

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

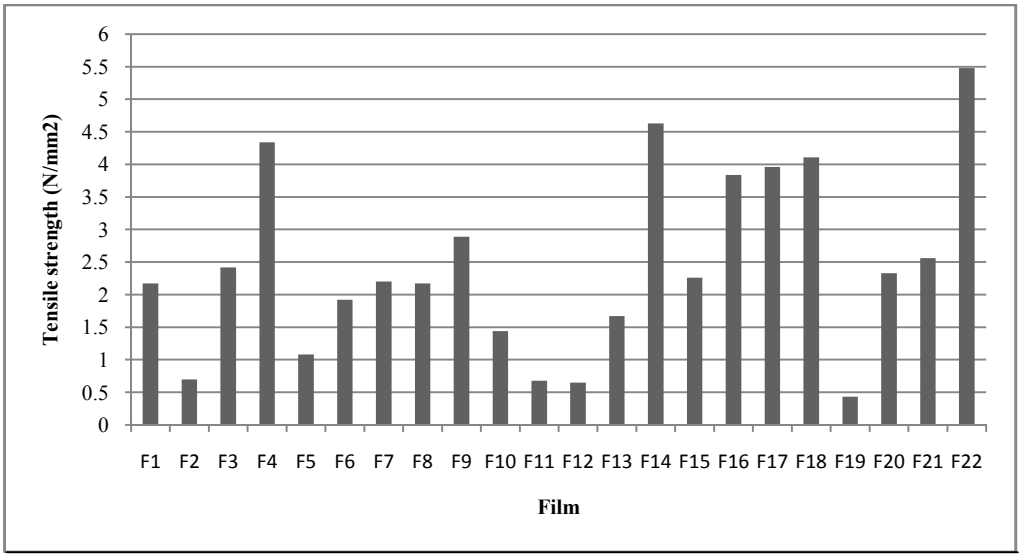

Fig. 3. Tensile strength of mucoadhesive films containing single or mixed polymer

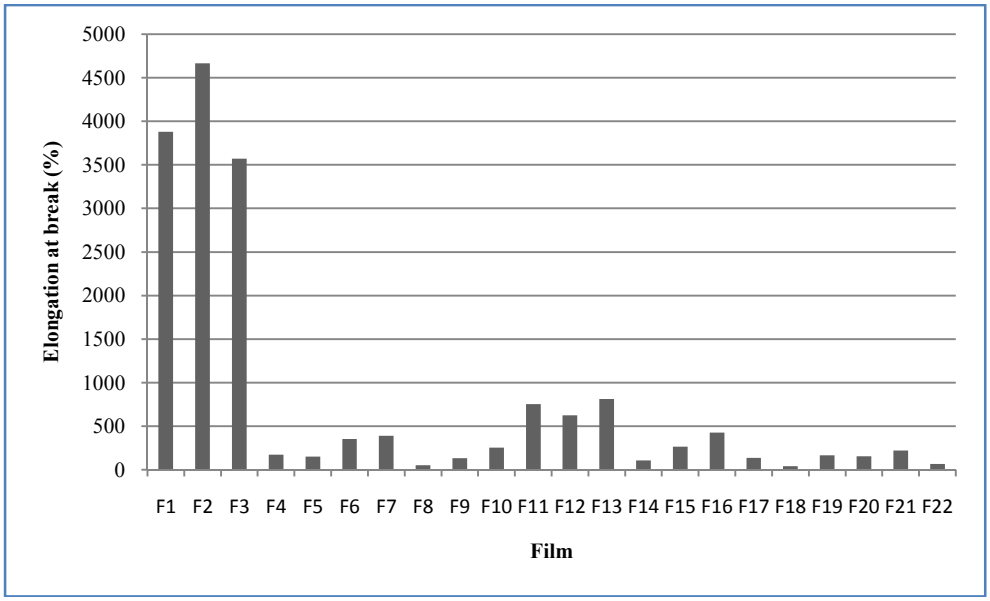

Fig. 4. % Elongation at break of mucoadhesive films containing single or mixed polymer

After addition of different types of plasticizers to the films, it was found that the plasticized films containing PEG 400 exhibited different mechanical properties than others. Commonly, addition of plasticizer decreases the tensile strength of the film as mentioned before. But, with the inclusion of PEG to the formulation, the tensile strength was increased [59].This may be explained by the two facts. Firstly, PEG as a plasticizer has longer carbon chain (number of carbons per chain = 16) compared with glycerin and PG (number of carbons per chain = 3). As a result, the extent of the increase in tensile strength produced by increased

PEG concentration was greater than those for the other two plasticizers [60]. Secondly, PEG 400 at concentration 10% from the weight of the polymer gave the lowest glass transition temperature [52].Since our films were prepared by 20% plasticizer, so it was found that glass transition increased. So, tensile strength will be increased. Results obtained from mechanical properties test for F3, F7, F9, F13 and F17 films were agreed with those theories. For example, F3 film containing PEG 400 has the highest tensile strength (2.42 ± 0.05 N/mm^2 with 3571.39 ± 973.61 % elongation and 1.94 ± 0.23 J) compared with F1 and F2.

In most formulations, the addition of glycerin or PG to the formulations, decreased the tensile strength and increased elongation of the film. Glycerin can perform this action through increasing mobility and reducing interactions or electrostatic forces between molecules. Also, glycerin structure contains 3 hydroxyl groups only. As a result, a flexible film can be obtained due to few interactions that may happene [61]. In addition, Limetal**,** blended PVA with PG. The result was decrease in the tensile strength and increase in the elongation at break [62]. Results from table 5 showed that PG has greater ability to increase the elongation of the film than glycerin. For example, tensile strength of F1 containing glycerin was 2.17 ±0.60 N/mm^2 and elongation was 3878.42 ± 965.79 % with 0.49 ± 0.17 J energy. While F2 containing propylene glycol, its tensile strength was 0.70 ± 0.33 N/mm^2 and elongation was 4664.12 ± 978.25 % with 1.02 ± 0.05 J energy. Tensile strength of F15 containing glycerin was 2.26 ± 0.97 N/mm^2 and elongation was 263.40 ± 68.16 % with 0.10 ± 0.04 J energy. While F16 film containing PG, its tensile strength was 3.84 ± 0.44 N/mm^2 and elongation was 424.96 ± 19.70 % with 0.20 ± 0.02 J energy. These results were agreed with the results of [63]. They used plasticizers similar to those used in our experiment. Parris etal examined the effect of poly(propylene glycol) and glycerin on mechanical properties of the film. They found that films containing glycerol: poly(propylene glycol) ratio of 1:3 exhibited elongation values about fifty times higher than plasticized films with glycerol only.

Dealing with mechanical properties of polymer combination films will be the same as films formulated from one polymer without addition of plasticizer. As mentioned before, absence of plasticizer increases the tensile strength and decreases the elongation of the film. So, most films formulated from polymer combination exhibited high values of tensile strength as F18 and F22.

F2 formula has the highest elongation values due to presence of PG. Orodispersible film should possess moderate tensile strength and high elongation at break [25].

4. CONCLUSION

The purpose of this study was to prepare a mucoadhesivebuccal film that can be used as a carrier for drugs to be directed through this route, the characterizations determined informed us with required data to select the best formula. Through the organoleptic properties, it was proved that PVA films have excellent characteristics and the rheological parameters showed that all polymeric solutions used have Non-newtonian pseudo-plastic flow which is required. Also, results of thickness concluded that PVA films have the needed thickness that allowed for fast drug release. Moreover, moisture content and moisture uptake values for PVA films were ideal. F1 and F3 films exhibited the required mechanical properties due to high elongation and moderate tensile strength. So these formulae are considered ideal to prepare mucoadhesive because they have excellent organoleptic, thickness, rheological, moisture content, moisture uptake and mechanical properties values.

COMPETITION INTERESTS

Authors have declared that no competing interests exist.

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