Preparation and pharmaceutical evaluation of glibenclamide slow release mucoadhesive buccal film

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Abstract

Buccal mucoadhesive systems among novel drug delivery systems have attracted great attention in recent years due to their ability to adhere and remain on the oral mucosa and to release their drug content gradually. Buccal mucoadhesive films can improve the drug therapeutic effect by enhancement of drug absorption through oral mucosa increasing the drug bioavailability via reducing the hepatic first pass effect. The aim of the current study was to formulate the drug as buccal bioadhesive film, which releases the drug at sufficient concentration with a sustain manner reducing the frequency of the dosage form administration. One of the advantagees of this formulation is better patient compliances due to the ease of administration with no water to swallow the product. The mucoadhesive films of glibenclamide were prepared using hydroxypropyl methylcellulose (HPMC) K4M, K15M and Eudragit RL100 polymers and propylene glycol as plasticizer and co-solvent. Films were prepared using solvent casting method, and were evaluated with regard to drug content, thickness, weight variations, swelling index, tensile strength, *ex vivo* adhesion force and percentage of *in vitro* drug release. Films with high concentrations of HPMC K4M and K15M did not have favorable appearance and uniformity. The formulations prepared from Eudragit were transparent, uniform, flexible, and without bubble. The highest and the lowest percentages of swelling were observed for the films containing HPMC K15M and Eudragit RL100, respectively. Films made of HPMC K15M had adhesion force higher than those containing Eudragit RL100. Formulations with Eudragit RL100 showed the highest mean dissolution time (MDT). Drug release kinetics of all formulations followed Higuchi's model and the mechanism of diffusion was considered non-Fickian type. It was concluded that formulations containing Eudragit RL100 were more favorable than others with regard to uniformity, flexibility, rate and percentage of drug release.

Keywords: Glibenclamide; Mucoadhesive; Buccal film; Eudragit polymer

INTRODUCTION

Mucoadhesive drug delivery systems are among the novel drug delivery systems that release the drug in a long time in a slow and controlled manner; providing a high plasma concentration level of the drug and improving the drug efficiency (1). When buccal muco-adhesive drug formulations come in contact with the mucosa for a long time, they release the drug into blood circulations directly via oral mucosa, and increase the drug bioavailability by reducing the hepatic first pass effect and enzymatic degradation in the gastrointestinal system (2). Bioadhesion is defined as a state at which two materials, one of which is biological, are held together for a long time through interfacial forces. The adhesion can occur between a biological membrane such as mucosa and a synthetic material like a polymer. In such case, it is referred to as mucoadhesion (3). The oral mucosa is preferred because of its availability, robust epithelium, and high permeation (4). Mucoadhesive polymers contain several hydrophilic groups such as hydroxyl, carboxyl, amide and sulphate, which adhere to the mucosa via hydrogen bonds as well as electrostatic and hydrophobic forces. In contact with water, these polymers become

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hydrated and inflated, and their adhesive parts become exposed (1). The most appropriate region to place slow-release product in the oral cavity is the upper gum.

Glibenclamide is a sulfonylurea derivative and is used in the treatment of type II diabetes mellitus. In its oral administration, gliben-clamide undergoes the hepatic first pass effect; such that only 40-45% of the drug is absorbed and considering its short half-life, the patient has to take the drug in several divided doses to maintain the desired therapeutic effect. Furthermore, gastrointestinal adverse effects have been reported for the drug, which decreases the patients' compliance (5). Glibenclamide fall in class II of the biopharmaceutics classification system (BCS), which means the drug is poorly water soluble, while showing a good permeability in the GI mucosa (6).

Furthermore, the drug has a low dose in the formulation and lacks undesirable smell and taste. These characteristics make glibenclamide a good candidate for adminis-tration via the oral mucosa. The muco-adhesive film formulation of glibenclamide adheres to the buccal mucosa and releases the drug slowly and in a long time; thus, it provides a higher bioavailability owing to its higher absorption via the oral mucosa. Additionally, the required dosage of the drug is reduced and consequently the adverse effects would be less. This is while the patient does not experience the sensation of

presence of the film in the mouth and can follow his or her routine daily activities such as eating, drinking, and talking. Other advantages of this drug formulation is compliance of the patient, ease of taking the drug, and not requiring water to swallow it. Buccal mucoadhesive films of glibenclamide would be better accepted by the patients for easier and more effective treatment of diabetes (7).

The aim of the current study was preparation and evaluation of buccal mucoadhesive films of glibenclamide using different types of mucoadhesive polymers; hydroxypropyl methyl-cellulose (HPMC) K4M, K15M and Eudragit RL100, and propylene glycol, as the plasticizer and permeation enhancer; so that the drug can be released at an appropriate rate within 4-6 h after placing the film on the mucosal surface.

MATERIALS AND METHODS

Materials

The material used was glibenclamide powder (Mahbanshimi Company, Iran), hydroxypropyl methylcellulose K4M and K15M (Dow Company, USA), Eudragit RL100 (Rohm GmbH & Co.KG. Germany), sodium lauryl sulfate, propylene glycol and acetone (Merck, Germany), ethanol 96% in pharmaceutical grade.

Table 1. The compositions of formulations for glibenclamide buccal mucoadhesive films.

Formulation code	Polymers			Glibenclamide (mg)
	HPMC K4M (mg)	HPMC K15M (mg)	Eudragit RL100 (mg)	
F1	300	-	-	28
F2	400	-	-	28
F3	500	-	-	28
F4	600	-	-	28
F5	700	-	-	28
F6	800	-	-	28
F7	-	300	-	28
F8	-	400	-	28
F9	-	500	-	28
F10	-	600	-	28
F11	-	700	-	28
F12	-	800	-	28
F13	-	-	600	28
F14	-	-	700	28
F15	-	-	800	28
F16	-	-	900	28
F17	-	-	1000	28
F18	-	-	1100	28

Preparation of the mucoadhesive films

The film was prepared by the solvent casting method. The desired amount of the polymers (HPMC K4M, K15M and Eudragit RL100) were weighed and added to the solvent according to the data given in Table 1. HPMC was dissolved in water and Eudragit was dissolved in alcohol and acetone (v/v 1:4) using a magnetic stirrer (IKA RH, Brazil) at 60 ºC to form a viscous solution.

Then, the calculated amount of glibenclamide was weighed and dissolved in alcohol and propylene glycol as the plasticizer and co-solvent and was gradually added to the polymer solution to achieve a transparent and uniform solution. The solution obtained was poured into paraffinized or siliconed plates, and then the plates were placed in the autoclave (Ehret Gmbh & Co KG, Germany) at 40-55 ºC to evaporate the solvent.

The films were cut into 16×25 mm pieces, containing 2.5 mg glibenclamide, and placed in a desiccator.

Determination of the amount of glibenclamide in the film

The prepared films were dissolved in 100 mL phosphate buffer at pH 6.8 containing 1% sodium lauryl sulfate. After complete dissolution, the sample absorbance was measured against a blank using the UV-Vis spectrophotometer (UV-1650 PC, Shimadzu, Japan) at the wavelength of 291.8 nm, and then the drug amount was determined using constructed calibration curves (8).

Study of physicochemical properties of glibenclamide films

Appearance of the films was macroscop-ically evaluated. The films should have smooth, soft, transparent appearance without bubble.

Determination of weight and thickness of the films

The weight of three 16×25-mm pieces of prepared film was determined using a digital scale (Sartorius Portable GC 803S, Germany), and the thickness was measured by a digital micrometer (Calper GB/T14899-94, China), and the mean values were calculated.

Swelling studies

After determining the primary weight of the film (w_1), the samples were placed on 2% agar plates, and incubated at 37 ºC. At 1-2 h intervals and when the weight became constant, the films were taken away and the extra water on their surface was removed using a filter paper, the weight of inflated films (w_2) were again determined, and the swelling index (SI) was calculated according to following formula (4).

$$SI = (W_2-W_1)/W_1\times100 \tag{1}$$

Film surface pH

The surface pH of buccal film may cause irritation to the buccal mucosa; therefore the surface pH of the films was determined by a pH meter (Metrohm Herisau, Switzerland) using a method described byBottenberg and coworkers (9). The 16×25 mm piece of film was left in a petridish containing 5 mL distilled water and allowed to swell for 2 h in 37 ºC. The pH was measured by bringing the pH meter electrode near to the surface of the swollen film (4, 9).

Determination of mechanical properties of the films

Mechanical properties of the films were determined using SANTAM instrument (STM-1, Iran). In this method, the film was placed between the clamp levers of the equipment, and an extension force at the speed of 30 mm/min was applied to the film. The amount of force and increase in the film length was measured at the time of tearing of the film. The value of film elongation shows the change occurred in the film length after applying the force, which is calculated according to formula below.

Elongation at break (%) = increase in length at breaking point (mm)/original length (mm) × 100   (2)

The maximal force applied to the film, which leads to tearing of it, indicates the tensile strength of the film, and is calculated by formula 3 (10,11).

Tensile strength (N/mm^2) = breaking force (N)/cross-sectional area of sample (mm^2) (3)

Study of ex vivo adhesion strength of the film

In this study, mucosal lining of the cow

cheek was employed as a model to determine the adhesion strength of the film. To this end, the film was attached to the upper lever of the SANTAM instrument, while a piece of mucosal lining of the cow was made wet by some drops of water and attached to the constant lever of the instrument. Then, the film was kept in full contact with the mucosa for one min. The force required for detachment of the film from the mucosal surface was calculated and reported as the adhesion force of the film (12).

Evaluation of in vitro drug release

Drug release from the selected formulations was performed by a Franz cell (Franz cell device attached bath Gallenkamp Thermostirrer 100, EEC). The film was cut into 16×25 mm pieces and placed on 0.45 μm filters in the Franz cell. Phosphate buffer solution with pH 6.8 containing 1% sodium lauryl sulfate was added to the cells and the cells were placed at 37 °C at 50 rpm.

At time intervals of 10, 20, 30, 60, 90, 120, 180, 240, 300 and 360 min, 1 ml of samples were withdrawn and replaced with fresh phosphate buffer. The samples were analyzed by UV-Vis spectrophotometer at the wavelength of 291.8 nm, and drug concentration was measured using previously constructed calibration curve.

Determination of dissolution parameters and drug release kinetics

The parameters used to compare the drug dissolution profiles were mean dissolution time (MDT) and percentage of dissolution efficiency (%DE) (13).

$$\text{MDT} = \sum_{i=1}^{n} t_{mid} \times \Delta M / \sum_{i=1}^{n} \Delta M \qquad (4)$$

where t_{mid} is the midpoints between times t_i and t_{i-1} and ΔM is the amount of the drug dissolved between times t_i and t_{i-1}.

$$\text{DE\%} = (\text{AUC}_{0-t} / y_{100} \times t) \times 100 \qquad (5)$$

where AUC_{0-t} is the area under the dissolution curve up to the time t, and y_{100} is the loading dose.

In order to describe the kinetic of drug release from glibenclamide buccal films, in vitro release data of selected formulations were fitted in zero order, first order, and Higuchi models.

$$M_t = k_0 t \qquad \text{(Zero order) (6)}$$
$$\text{Ln} (M_\infty - M_t) = k_1 t \qquad \text{(First order) (7)}$$
$$M_t = k_H t^{0.5} \qquad \text{(Higuchi) (8)}$$

Furthermore, drug release mechanism was determined according to the Korsmeyer-Peppas equation.

$$\text{Log} (M_t/M_\infty) = \log k + n \log t \qquad (9)$$

Where, M_∞ is the amount of drug released after infinite time, M_t, cumulative amount of drug released at any specified time (t), k, release rate constant, and n, the release exponent (14,15).

Fourier transform infrared spectroscopy experiments

The drug and physical mixtures of optimized formulation were subjected for Fourier transform infrared spectroscopy (FTIR) analysis. The samples were prepared by employing potassium bromide disc method. 5 mg of samples were mixed with about 100 mg potassium bromide and compressed into disc under pressure of 10000 to 15000 pounds per square inch. The samples were scanned over a range of 4000-400 cm^{-1} using Fourier transformer infrared spectrophotometer (Rayleigh.WQF-510, China). Spectra were analyzed for drug polymer interactions.

Differential scanning calorimetry studies

The pure drug, polymer and their combination were subjected to differential scanning calorimetry (DSC) analysis using differential scanning calorimeter (NETZSCH DSC 200 F3, Japan). The instrument was calibrated using indium/zinc standards. Samples (5 mg) were sealed in an aluminum pan. The pan was placed in the DSC instrument and heated at a constant rate 10 °C /min over a temperature range of 0-300 °C using nitrogen as blanket gas (6).

RESULTS

The results related to the measurements of weight, thickness, swelling index and glibenclamide content are demonstrated in Table 2.

Table 2. Physical properties of glibenclamide buccal mucoadhesive films.

Formulation code	Mean weight (mg) ± SD	Mean thickness (µm) ± SD	Swelling index (%) after 1 h	Swelling index (%) after 2 h	Drug content (mg) ± SD
F1	23.4 ± 0.20	95 ± 3.60	31.27 ± 0.40	45.26 ±0.11	2.45 ± 0.046
F2	28.1 ± 0.40	118 ± 2.64	32.64 ± 0.16	46.78 ± 0.20	2.42 ± 0.031
F3	34.5 ± 0.26	130 ± 2.52	33.06 ± 1.00	49.51 ± 0.67	2.47 ± 0.036
F4	37.8 ± 0.20	141 ± 3.05	36.12 ± 0.70	53.60 ± 0.61	2.46 ± 0.030
F5	41.4 ± 0.26	154 ± 2.08	37.55 ± 0.60	54.87 ± 0.19	2.39 ± 0.041
F6	45.6 ± 0.30	163 ± 2.52	38.19 ± 0.30	55.48 ±0.27	2.35 ± 0.035
F7	28.3 ± 0.26	125 ± 2.52	31.85 ± 0.71	47.52 ± 0.19	2.38 ±0.045
F8	34.8 ± 0.30	133 ± 2.08	32.62 ± 1.50	48.89 ± 0.27	2.42 ± 0.031
F9	39.5 ± 0.20	145 ± 3.55	33.41 ± 0.90	51.36 ± 0.63	2.43 ± 0.052
F10	43.3 ± 0.36	151 ± 3.63	36.67 ± 0.64	55.71 ± 0.80	2.39 ± 0.032
F11	54.8 ± 0.40	162 ± 2.08	39.50 ± 0.27	57.43 ± 0.67	2.41 ± 0.040
F12	58.5 ± 0.20	169 ± 2.52	41.95 ± 0.61	61.26 ± 0.44	2.43 ± 0.056
F13	65.5 ± 0.35	189 ± 2.67	17.43 ± 0.26	25.49 ± 0.76	2.43 ± 0.027
F14	69.9 ± 0.67	221 ± 3.51	18.52 ± 0.20	27.51 ± 0.80	2.45 ± 0.031
F15	74.6 ± 0.20	247 ± 3.51	18.95 ± 0.87	28.91 ± 0.67	2.41 ± 0.015
F16	96.6 ± 0.42	256 ± 2.08	21.43 ± 1.50	30.80 ± 0.42	2.43 ± 0.020
F17	104.6 ± 0.30	266 ± 2.87	22.75 ± 0.72	33.74 ± 0.40	2.48 ± 0.020
F18	121.5 ± 0.52	283 ± 3.05	25.33 ± 0.52	34.55 ± 0.71	2.45 ± 0.032

Table 3. Mechanical properties and *ex vivo* bioadhesive strength of glibenclamide films.

Formulation code	Elongation at break (%)	Tensile strength (N/mm^2)	Bioadhesion force (N)
F1	52.00	15.88	6.34
F2	50.28	17.72	6.72
F3	46.86	18.32	7.27
F4	45.14	18.57	7.81
F5	40.86	19.89	8.25
F6	39.71	20.19	8.55
F7	38.28	19.27	8.19
F8	37.43	19.41	8.68
F9	35.71	20.75	9.50
F10	32.86	22.15	10.23
F11	30.86	22.58	10.85
F12	26.57	23.40	11.38
F13	77.46	13.61	4.37
F14	74.86	14.03	4.56
F15	74.00	14.28	4.82
F16	72.28	14.91	5.11
F17	70.86	15.10	5.25
F18	65.71	15.71	5.62

Table 4. The release parameters of optimized glibenclamide films with HPMC K4M

Formulation code	Kinetic parameters DE (%)	MDT (min)	Kinetic models (R^2) Zero order	First order	Higuchi	Peppas parameters n	k	R^2
F3	61.98	61.40	0.981	0.723	0.989	0.689	36.47	0.945
F4	57.77	62.93	0.979	0.765	0.991	0.572	22.96	0.986
F5	55.95	74.93	0.985	0.800	0.994	0.896	109.65	0.995

Table 5. The release parameters of selected glibenclamide films with HPMC K15M.

Formulation code	Kinetic parameters DE (%)	MDT (min)	Kinetic models (R^2) Zero order	First order	Higuchi	Peppas parameters n	k	R^2
F9	64.97	70.43	0.977	0.681	0.982	0.775	59.70	0.982
F10	63.64	75.27	0.905	0.737	0.968	0.740	53.21	0.985
F11	50.11	98.50	0.982	0.660	0.993	0.924	167.88	0.953

Table 6. The release parameters of optimized glibenclamide films with Eudragit RL100.

Formulation code	Kinetic parameters		Kinetic models (R2)			Peppas parameters		
	DE (%)	MDT (min)	Zero order	First order	Higuchi	n	k	R²
F14	69.10	93.33	0.986	0.776	0.990	0.733	53.70	0.949
F15	65.14	108.63	0.982	0.689	0.992	0.817	88.92	0.953
F16	57.08	119.63	0.979	0.781	0.986	0.965	228.56	0.946
F17	61.96	122.43	0.985	0.852	0.992	0.815	99.31	0.971
F18	60.29	116.36	0.988	0.673	0.996	0.760	76.91	0.973
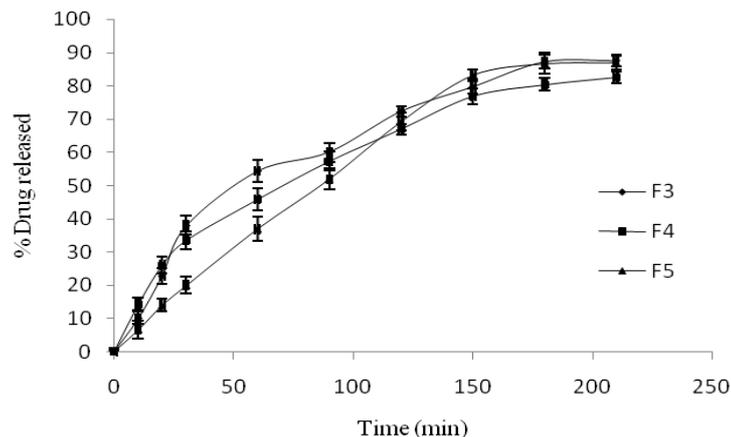
Fig. 1. Drug release profiles of glibenclamide optimized films with HPMC K4M.
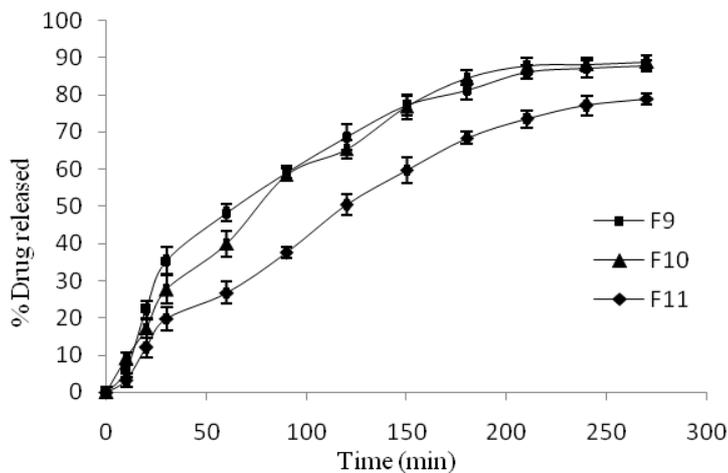
Fig. 2. Drug release profiles of glibenclamide optimized films with HPMC K15M.

The weight of the films was found in the range of 23.4 ± 0.20 to 121.5 ± 0.52 mg and the film thicknesses were observed in the range of 95 ± 3.60 to 283 ± 3.05 mm. The percentage swelling of various formulations ranged between 25.49 ± 0.76 and 61.26 ± 0.44 after 2 h. The assayed drug content of films varied between 2.39 ± 0.041 and 2.48 ± 0.020 mg. The surface pH of all films was found to be in the range of 6.24 ± 0.04 to 6.65 ± 0.03.

The results obtained for adhesion force and the mechanical properties of the films including the percentage of elongation and tensile strength are given in Table 3. The *in vitro* drug release test was performed for selected formulations which are shown in Figs 1-3. As seen, the percentage of drug release from formulations F3, F4, and F5 containing HPMC K4M at the end of 210 min were 87%, 87.6%, and 82.5%, respectively. Formulations

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F9, F10, and F11 containing HPMC K15M released 87%, 88.8%, and 78.9% of their drug content at the end of 270 min. The drug release percentage for formulations containing Eudragit RL100 F14, F15, F16, F17, and F18 were 93%, 93.3%, 85.5%, 93.9%, and 89% at the end of 360 min, respectively. Parameters related to the drug dissolution including MDT

and %DE are also shown in Tables 4-6. Drug release kinetic parameters along with n, k, and R^2 values are provided in Tables 4-6.

Fig. 4 represents FTIR *spectra* of glibenclamide powder alone and in combination with Eudragit RL100. The DSC thermograms of pure drug, polymer and their combination are shown in Fig. 5.
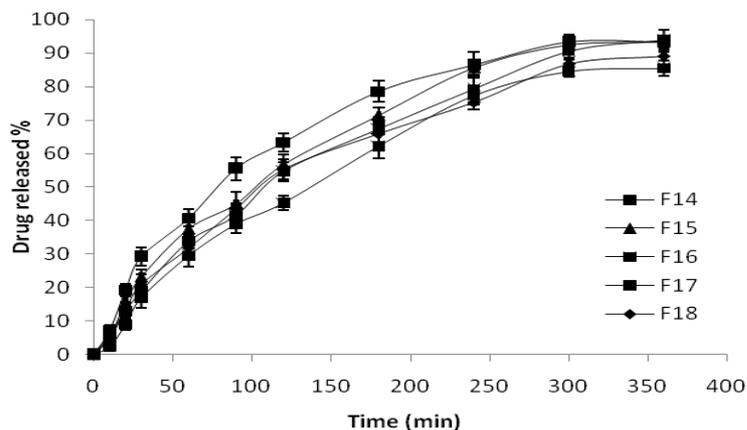
Fig. 3. Drug release profiles of glibenclamide optimized films with Eudragit RL100.
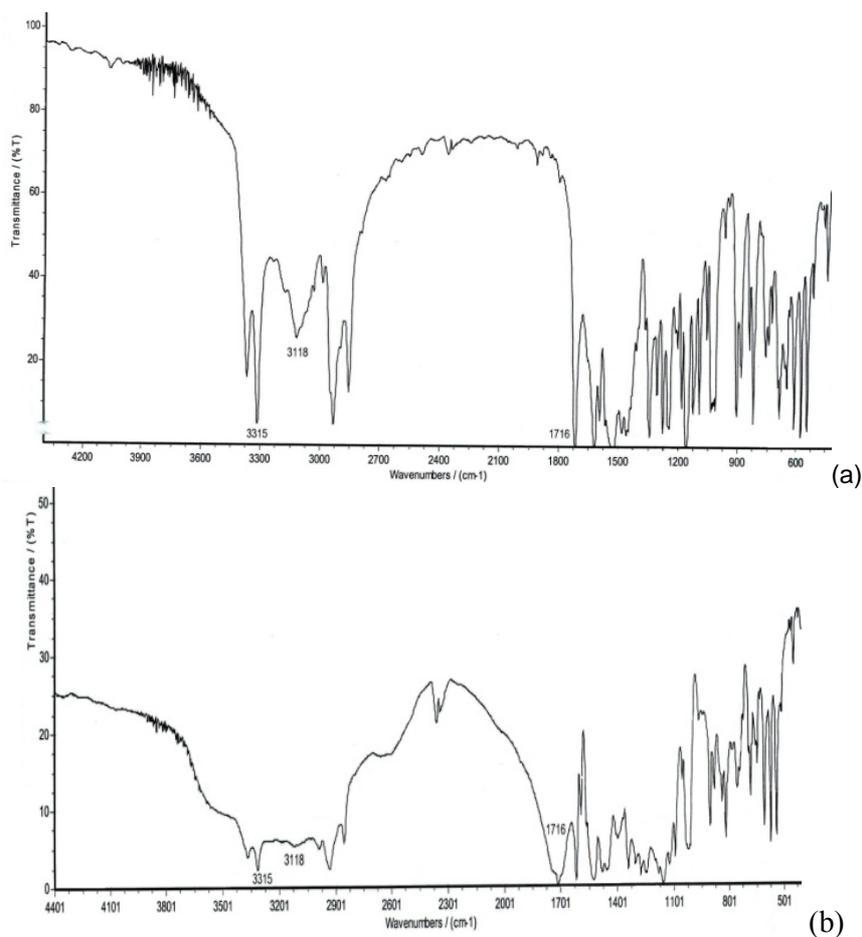
Fig. 4. FTIR spectra of (a); glibenclamide pure drug and (b); glibenclamide with Eudragit RL100.

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(a)   (b)

(c)
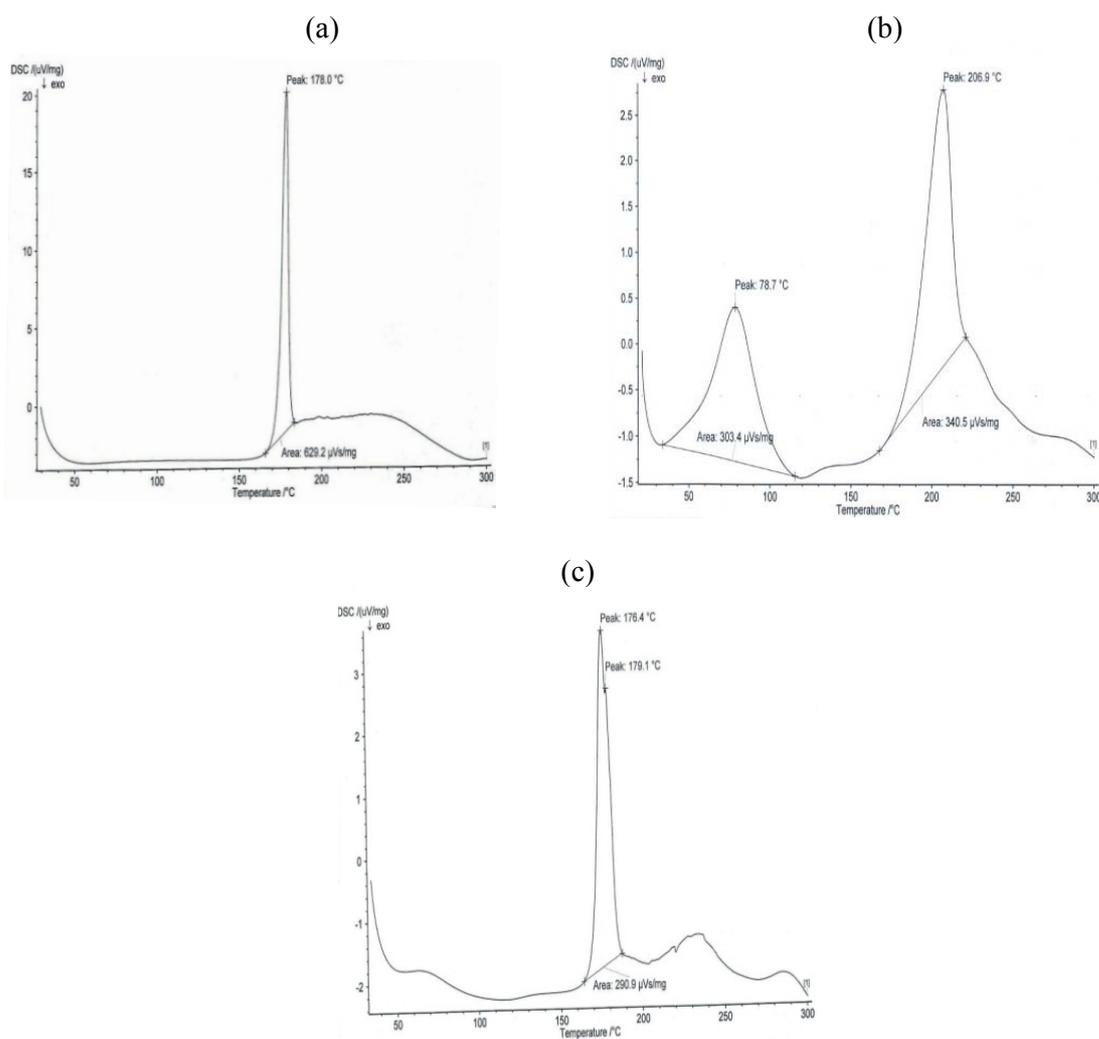
Fig. 5. DSC thermogram of (a); glibenclamide pure drug, (b); polymer EudragitRL100 and (c); glibenclamide with Eudragit.

DISCUSSION

One of the aims of preparation of novel drug delivery systems is to provide drug formulations with the least adverse effects and maximal therapeutic effect; such that by taking the formulation the patient experience the drug effects more rapidly at lower doses of the drug. To this end, film formulations comprise one of the major drug formulations, which have been studied extensively. Considering the comfort of patients in taking film formulations, the delivery system deserves receiving more attention in the treatment of chronic diseases such as diabetes. Therefore, glibenclamide as a commonly prescribed drug in the treatment of type 2 diabetes mellitus selected as a candidate for this drug formulation (5,16).

The problem existing with the oral formulation of glibenclamide is the low bioavailability, which is a consequence of the high first hepatic pass effect; such that almost 50% of the drug is converted into its inactive metabolite by the liver before entering systemic circulation (17). Therefore, using mucosal formulations would overcome this major shortcoming experienced by glibenclamide via reducing the hepatic first pass effect. To achieve the maximal absorption, the drug release should be close to the zero order kinetic.

Several studies have been carried out to prepare mucoadhesive formulations of glibenclamide. For instance, Rajkumar and coworkers designed bucoadhesive tablets of glibenclamide using high concentrations of

HPMC, which finally released 65.4% of the drug (17). In another study, Gupta and colleagues developed transdermal patch of glibenclamide using HPMC, PVP, and Eudragit RS 100, which showed 55.46% effectiveness (18). Philip and coworkers used HPMC and CP polymers to produce buccoadhesive gels of glibenclamide, which showed 54.5% efficiency (19). Since the mucosa of the oral cavity has non-keratinized epithelium, it has a better penetration for drug release compared with the body skin (1). Furthermore, it should be noted that mucoadhesive films are more flexible than mucoadhesive tablets and the patients use them with more comfort. Also the films do not have the limitation of relatively short residence time, as observed by the oral gels (1). Thus, mucoadhesive buccal films of glibenclamide can be an appropriate alternative for other drug dosage forms.

The results obtained from evaluation of various formulations demonstrated that the films containing high concentrations of HPMC K4M and K15M do not have desired appearance and uniformity characteristics. Moreover, longer time was required to prepare a transparent and uniform polymer solution and the air bubbles trapped in the polymer solution, were removed with difficulty. In contrast, the formulations containing Eudragit RL100 polymer had a transparent and uniform appearance, without air bubble. Determination of glibenclamide content showed that the drug was uniformly dispersed in the film. The films containing both two grades of HPMC showed a higher swelling index than those prepared by Eudragit RL100 (Table 2). This finding is in agreement with the results reported by Muzib and coworkers (4). They evaluated glibenclamide buccal film prepared from different grades of HPMC and reported the swelling index of 45.51 ± 1.5 to 63.98 ± 0.7 after 2 h. They believed that the higher swelling percent of formulations containing HPMC K15M and K100M polymers were due to the presence of more hydroxyl groups than HPMC 3000 cps (4). In addition, the results of our study revealed that the inflation percent of films was increased as the polymer concentrations increased.

The film surface pH was measured to determine the possibility of side effect due to acidic or alkaline pH of films that could hurt buccal mucosa (5). The surface pH of all prepared films was found near the neutral pH indicating its compatibility with buccal pH, causing no irritation to the mucosa and achieves patient compliance.

The results obtained from the tensile strength test of the films showed that formulations containing HPMC K15M had the highest tensile strength and the lowest elongation. However, the buccal films prepared by Eudragit RL100 showed the maximum elongation percent and the minimum tensile strength among the formulations. Increased elasticity of Eudragit films decreases the force required for the film tension. In the study performed by Khan TA and colleagues, (11) mechanical properties of chitosan films were evaluated. They reported an amount of 21.35 to 67.1% for elongation at break and 59.87 to 67.11 (N/mm^2) for tensile strength. For mucoadhesive buccal administration, strong and flexible films are more preferable. In this respect, the buccal films prepared by Eudragit RL100 (F13 in Table 1) was softer and more flexible compared with the other formulations.

From ex-vivo mucoadhesive strength studies, it was observed that adhesion force of the films depends on the type of the polymer used; such that formulations containing HPMC (F12) have higher adhesion force than those prepared by Eudragit RL100 (F13). It was also observed that the mucoadhesive strength of the films was improved as the concentration of the polymers increased. The mucoadhesiveness of the formulations was satisfactory for maintaining buccal films in upper gum for desired period of time. In the study performed by Vinod and coworkers mucoadhesive polymers and their mechanism of mucoadhesion were completely explained (20).

The DE% and MDT were used to compare efficiency of the type and concentrations of the polymers in drug release. According to the values of % DE, it was concluded that drug release was slightly decreased with increasing the polymer concentration. The MDT values of glibenclamide buccal films

with HPMC K4M and HPMC K15M increase as the polymer concentration increase (Tables 4 and 5).

The films containing Eudragit RL100 released the highest amount of the drug up to the end of the drug release time with a slow release profile. The calculated MDT values for all the samples investigated (Table 4-6) support this finding.

As shown in Table 6, formulation F17 containing 1000 mg Eudragit RL100, represented better *in vitro* dissolution profile as compared with the rest of the formulations.

The drug release mechanisms for various formulations were determined by fitting the data into various kinetic models. In all the formulations, correlation coefficient of the Higuchi's model was higher than correlation coefficients of other kinetics (Table 4-6). Thus, in drug release of all formulations, the Higuchi's kinetics was dominant.

The in vitro release data was fitted into korsmeyer- peppas equation to determine the mechanism of drug release from the films. When n value is 0.5 or less, the Fickian diffusion phenomenon dominates, and n value between 0.5 and 1 is non-Fickian diffusion (anomalous transport).

The mechanism of drug release follows case-II transport when the n value is 1 and for the values of n higher than 1, the release is characterized by super case-II transport (14,15). Drug diffusion for all formulations was of non-Fickian type. Non-Fickian drug release means that the drug is released from the film via diffusion mechanism and also another process called chain relaxation (21). The diffusion that is not according to the Fickian type is a step toward continuous and uniform drug release; as it is similar to the drug release of zero order (22).

The FTIR studies were carried out to assess any possible interaction between drug and carrier in the solid state. The FTIR spectrum of pure glibenclamide in Fig. 4a presents NH stretch at the wave number of 3315 cm^{-1}, Ar-H (aromatic group) absorption peak at the wave number of 3118 cm^{-1}, C=O absorption peaks at 1716 cm^{-1}. The FTIR spectrum of selected formulation in Fig. 4b, also presents all the major absorption peaks of the drug with decreased intensity which could be due to the dilution of the mixture by the polymer. No new bands observed in the spectrum, which confirms the absence of new chemical bonds between the drug and the polymer indicating the absence of interaction between the drug and polymer.

The DSC studies were performed to evaluate the thermal behavior of the drug, polymer and drug-polymer admixture to detect any possible interaction between the drug and polymer.

The DSC thermogram of pure glibenclamide showed a sharp endothermic peak at 178.0 ℃ corresponding to its melting point. The DSC thermogram of Eudragit RL100 displayed two endothermic peaks, a broad endotherm at 78.7 °C representing the glass transition temperature (Tg) and a sharp peak at 206.9 °C attributed to the melting point of the polymer. The DSC thermogram of glibenclamide and polymer mixture did not reflect any change in drug melting point endotermic peak showing no interaction between drug and polymer. It was suggested that when gliben-clamide melts at 178 °C, the polymer is dissolved in the molten and eliminating the endothermic peak of the polymer.

CONCLUSION

Comparing the results obtained in the present study, the most appropriate formulation was F17, containing Eudragit RL100, which showed desirable physical and appearance characteristics, and released almost 94% of its drug content within six h in a controlled and slow manner according to the non-Fickian model. FTIR and DSC studies revealed the absence of any chemical interaction between drug and polymer used.

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