Original Research Article

Mucoadhesive buccal films of glibenclamide: Development and evaluation

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Abstract

Background: Glibenclamide is an oral hypoglycemic drug completely metabolized in the liver, the principal metabolite being very weakly active, buccal delivery may be useful for the treatment of diabetes more effectively. The aim of the present study was to design formulations and systematically evaluate *in vitro* and *ex vivo* performances of buccal films of glibenclamide so that the required therapeutic plasma concentrations can possibly be achieved more rapidly using the different grades of hydroxypropyl methyl cellulose (HPMC) as the base matrix. **Materials and Methods:** Mucoadhesive buccal films of glibenclamide were prepared by solvent casting technique using different grades of HPMC with different ratios. Prepared films were evaluated for weight, thickness, surface pH, swelling index (SI), folding endurance, drug content uniformity, *in vitro* release, and *ex vivo* permeation studies. **Results:** The film thickness and weight were in the range of 0.213–0.4892mm and 22.25–39.83 mg, respectively. The films exhibited controlled release over more than 6 h. HPMC, HPMCK100, and HPMC3000 films exhibited satisfactory swelling. Surface pH of buccal films was found to be 6.4–6.8. SI observed to be highest for GF12 (275.3 ± 12.17) and lowest for GF1 (173.5 ± 5.65). The films exhibited controlled release over more than 6 h. HPMC exhibited satisfactory swelling, an optimum residence time, and promising drug release. The Higuchi plots were found to be linear with correlation coefficient values of 0.8933, 0.9138, and 0.9947 for GF4, GF8, and GF9, respectively. **Conclusions:** Among all the formulations, GF9 shows good controlled release results correlated with *ex vivo* permeation studies.

Key words: Buccal film, *ex vivo* permeation studies, glibenclamide, *in vitro*, mucoadhesive drug delivery

INTRODUCTION

In recent years, significant interest has been shown in the development of controlled drug delivery to, or via mucous membranes by the use of bioadhesive polymers. These dosage forms can be administered by different routes, including ocular, nasal, rectal, and vaginal, for local or systemic delivery.[1-4] Mucoadhesion is a state in which 2 materials, one of which is mucus or a mucous membrane, is held together for an extended period of time.[5] Various mucoadhesive polymers have been investigated and identified are generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups, and will hydrate and swell when placed in contact with an aqueous solution.[6] These materials need to be in the hydrated form to become adhesive. Among the various routes of delivering mucoadhesive dosage forms, the buccal route appears to offer advantages of good accessibility, robust epithelium, quick and easy removal of the dosage form in case of need, good drug absorption, reduction of the first-pass metabolism, and patient compliance. Attempts have been made to formulate various mucoadhesive devices, including films,[7-11] tablets,[12,13] patches,[14-18] strips,[19] devices,[20] ointments,[21] gels,[22,23] and disks.[24] Mucoadhesive buccal film may be preferred over adhesive tablet in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva.

Glibenclamide is a second generation and one of the most potent sulfonylurea used in the treatment of maturity-onset diabetes as an oral hypoglycemic agent.[25] It is chemically -chloro-N-(4-[N-(cyclohexylcarbamoyl)sulfamoyl]phenethyl)-2-methoxybenzamide. The plasma half-life is about 5–6 h. In the present work, a trial has been made to develop mucoadhesive buccal films dosage form of glibenclamide for improving and

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enhancing bioavailability in a controlled release manner. It may also be possible to circumvent the hepatic first-pass effect by administering the drug through buccal mucosa, which is richly perfuse with blood vessels and offers greater permeability than the skin. The required therapeutic plasma concentration of glibenclamide can possibly be achieved more rapidly by using such buccal dosage forms. Different grades of hydroxypropyl methyl cellulose (HPMC), which are biodegradable, were used in the present study.

MATERIALS AND METHODS

Glibenclamide was a gift sample from Hetero Drugs Pvt Ltd (Hyderabad, India). HPMCK15M, HPMCK100M and HPMC3000 cps were procured from Matrix (Hyderabad, India) as gift samples. Propylene glycol was purchased from E. Merck (P) Ltd, Mumbai. All other reagents used were of analytical grade.

Preparation of mucoadhesive buccal films

Buccal films of glibenclamide were prepared by solvent casting technique,[26] employing aluminium foil cups (placed on glass surface) as a substrate. Composition of a single circular cast film of various formulations of buccal films were prepared by using drug and HPMCK15M with the ratio of [GF1 (1:15), GF2 (1:20), GF3 (1:25), GF4 (1:50)], HPMCK100M [GF5 (1:15), GF6 (1:20), GF7 (1:25), GF8 (1:50)], and HPMC3000 [GF9(1:15), GF10 (1:20), GF11 (1:25), GF12 (1:50)] with 50 mg of glibenclamide. Propylene glycol, which acts as a plasticizer and permeation enhancer, is used in the concentration of 30% v/v. Dichloromethane and ethanol (50:50 v/v) was used as a solvent system. The calculated amounts of polymers were dispersed in solvent (dichloromethane and ethanol). Fifty milligrams of glibenclamide was incorporated in the polymeric solutions after levigation with 30% w/w propylene glycol, which served the purpose of plasticizer as well as penetration enhancer. The medicated gels were left overnight at room temperature to obtain clear, bubble-free gels. To prevent evaporation of the solvent, medicated gels were filled into the vials and closed tightly by rubber closures. The gels were caste into aluminium foil cups (10 × 8 cm^2 diameter), placed on a glass surface was covered with inverted funnel, the end of which was plugged with cotton wool to allow controlled evaporation of the solvent. These were allowed to dry at room temperature (30°C) to form a flexible film. The dried films were cut into the size of 20 mm^2 diameters, packed in aluminium foil and stored in desiccators until further use.

Study of physical characteristics of the formulations

Weight variation and thickness variation test

Each formulation was prepared in triplicate (n = 3) and 10 films equivalent to 2 × 2 cm^2 area were cut from each plate. Their weight was measured using Keroy digital balance. The average weight was calculated [Table 1]. The thickness of the films was measured by digital screw gauge (Digimatic Outside Micrometer, Mitutoyo, Japan). The mean ± SD (n = 3) values were shown in Table 1.

Surface pH of films

The surface pH of films was determined to know the possibility of side effects, *in vivo* as an acidic or alkaline pH may cause irritation to the buccal mucosa. It was our aim to keep the surface pH as close to neutral as possible. The surface pH was determined by taking 3 films of each formulation and the films were allowed to swell for 2 h on the surface of 2% agar plate. The surface pH was measured by using a pH paper placed on the surface of the swollen film. A mean of 3 readings was recorded (n = 3) [Table 1].

Percent swelling

After determination of the original film weight (W1), the samples were placed on the surface of 2% agar plate kept in an incubator at 37°C ± 0.2°C and examined for any physical change. At regular 1-hr intervals until 3 h, the films were removed from the gel plates and excess surface water was removed carefully using filter paper. The swollen films were then reweighed (W2) and the swelling index (SI) was calculated using the following formula.

SI = (W2 − W1)/W1 × 100. The experiments were performed in triplicate, and average values were reported [Table 1].

Table 1: Physical properties of glibenclamide buccal films

Formulation code	Mean weight (mg) ± SD	Mean thickness (mm) ± SD	Surface pH	Folding endurance	Content uniformity	Swelling index with drug (2 h)
GF1	22.25 ± 1.25	0.213 ± 0.005	6.65 ± 0.002	173.5 ± 5.65	2.42 ± 0.005	55.43 ± 0.4
GF2	26.18 ± 1.36	0.225 ± 0.003	6.73 ± 0.001	186.4 ± 4.66	2.44 ± 0.016	58.87 ± 0.16
GF3	33.73 ± 1.52	0.233 ± 0.007	6.82 ± 0.002	198.5 ± 5.71	2.43 ± 0.043	59.36 ± 1.0
GF4	35.62 ± 1.98	0.248 ± 0.006	6.72 ± 0.003	209.4 ± 8.91	2.41 ± 0.017	63.98 ± 0.7
GF5	24.21 ± 1.26	0.245 ± 0.002	6.73 ± 0.004	236.8 ± 8.81	2.45 ± 0.053	53.61 ± 1.5
GF6	27.46 ± 1.30	0.252 ± 0.005	6.81 ± 0.003	243.5 ± 2.73	2.47 ± 0.016	54.63 ± 0.6
GF7	32.35 ± 2.13	0.259 ± 0.005	6.72 ± 0.006	252.9 ± 11.6	2.48 ± 0.052	61.26 ± 1.8
GF8	34.06 ± 1.20	0.259 ± 0.005	6.83 ± 0.001	258.6 ± 8.93	2.48 ± 0.062	53.21 ± 0.3
GF9	29.26 ± 1.74	0.357 ± 0.016	6.82 ± 0.003	248.3 ± 10.8	2.43 ± 0.008	58.59 ± 1.2
GF10	32.62 ± 1.48	0.388 ± 0.012	6.67 ± 0.003	254.9 ± 8.52	2.46 ± 0.076	52.47 ± 0.7
GF11	36.33 ± 1.83	0.453 ± 0.022	6.62 ± 0.001	260.5 ± 11.36	2.43 ± 0.081	50.09 ± 0.3
GF12	39.83 ± 1.35	0.489 ± 0.012	6.83 ± 0.005	275.3 ± 12.17	2.48 ± 0.065	45.51 ± 1.5

Folding endurance

From each formulation 3 films of size (2 × 2 cm) were cut by a sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of 3 readings (n = 3) and standard deviation are shown in the Table 1.

Drug content uniformity

Drug content uniformity was determined by dissolving the films in solvent and filter with Whatman filter paper. The resultant filtrate was evaporated and the drug residue was dissolved in 100 mL of pH 6.8 phosphate buffer. Absorbance of the sample was measured using UV–Vis spectrophotometer (Systronics) 011, Hyderabad, at a wavelength of 274 nm against pH 6.8 phosphate buffer used as blank. The experiments were carried out in triplicate and average values are reported in table 1.

In vitro release studies

Drug release from buccal films was studied by using dissolution rate test apparatus ElectrolabTDT 087 USP, Mumbai. The assembly for release study was prepared with the film being adhered onto a glass slide with one side of the film facing upward using a solution of cyanoacrylate adhesive, then placed in dissolution apparatus maintaining temperature at 37°C ± 0.2°C and rpm 50 using dissolution medium 900 mL phosphate buffer pH 6.8. Samples (5 mL) were collected at different time intervals: 10, 15 min, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 7 h and replaced with fresh medium. The samples were analyzed by using UV–Vis spectrophotometer at 274 nm. The release data were analyzed to study release kinetics using zero-order, first-order, Korsmeyer–Peppas, and Higuchi equations (n = 3). The release studies were performed in 6 replicates and mean ± SD values were calculated.

Ex vivo buccal permeation studies

Ex vivo buccal permeation of glibenclamide studied with fresh sheep buccal mucosa as a barrier membrane. The buccal pouch of freshly sacrificed animal was procured from local slaughter house and was used within 2 h of slaughter. The buccal mucosa was excised and trimmed evenly from the sides. The membrane was washed with distilled water and then with phosphate buffer (pH 6.8). The *ex vivo* permeation studies were carried out using the modified Franz diffusion cell at 37°C ± 0.2°C. A film of (2 × 2 cm diameter) each formulation under study was placed in intimate contact with the excised sheep buccal mucosa and the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 15 mL of pH 7.4 phosphate buffer. The cell contents were stirred with a magnetic stirrer and temperature of 37°C ± 0.2°C was maintained throughout the experiment. The samples were withdrawn at predetermined time intervals, filtered, diluted suitably, and then analyzed using UV-spectrophotometer at 274 nm (n = 3).

RESULTS AND DISCUSSION

In the present study, mucoadhesive buccal films of glibenclamide were prepared for controlled drug delivery, using HPMC-K15M, HPMC-K100M, and HPMC3000 cps. Propylene glycol was used as plasticizer as well as permeation enhancer. The drug delivery system was formulated as a matrix. The films were characterized for their physical characteristics, release characteristics, such as surface pH, thickness, folding endurance, drug content uniformity, and percentage swelling [Table 1]. The film thicknesses were observed to be in the range of 0.213 ± 0.005 mm to 0.4892 ± 0.0012 mm and weight was found to be in the range of 22.25 ± 1.25 mg to 39.83 ± 1.35 mg. The film thickness and weight increased with increasing polymer content. Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion.[27] Attempts were made to keep the surface pH as close to buccal/salivary pH as possible, by the proper selection of the polymers for developing the buccal films. The surface pH of all the films was within the range of salivary pH (6.4-6.8). No significant difference was found in surface pH of different polymers containing films.

Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin.[28] Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occur.

The effect of glibenclamide on the swelling behavior of various mucoadhesive polymers was also observed [Table 1]. The medicated films showed high SI in comparison to plain films. The addition of the water-insoluble drug increased water uptake of the film. This is possibly due to micronized drug particles, which exist between the polymer chains allowing each chain to hydrate freely, resulting in weak hydrogen-bonding areas around the glibenclamide molecules. These areas may increase the strength of the swollen layer followed by an obvious increase in the amount of penetrated water. The influence of drug on the swelling properties of polymer matrices is primarily dependent on the substituted groups of the polymer. The hydroxyl group in the molecules plays an important role in the matrix integrity of the swollen hydrophilic cellulose matrices.

The amount and properties of the incorporated drug determine matrix integrity. The comparative percentage swelling for various formulations was in the following order: (GF1 < GF2 < GF3 < GF4), (GF5 < GF6 < GF7 < GF8), and (GF9 < GF10 < GF11 < GF12) [Table 1]. The films containing HPMCK15 showed a higher percent swelling due to the

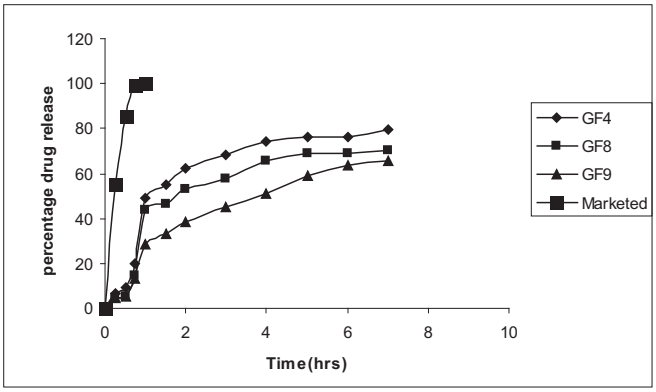

Figure 1: Zero-order drug release profile for selected formulations of glibenclamide buccal films and marketed immediate release tablet

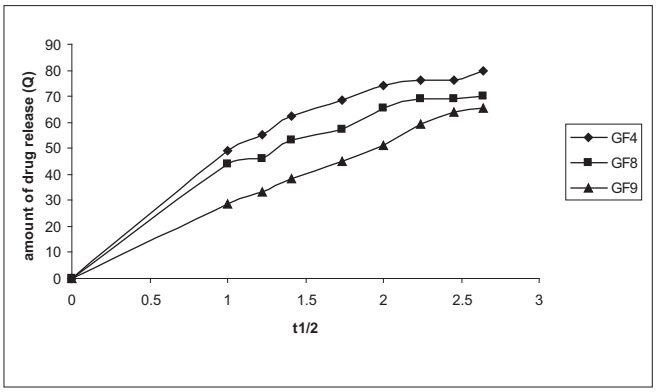

Figure 2: Higuchi plots for selected formulations of glibenclamide buccal films

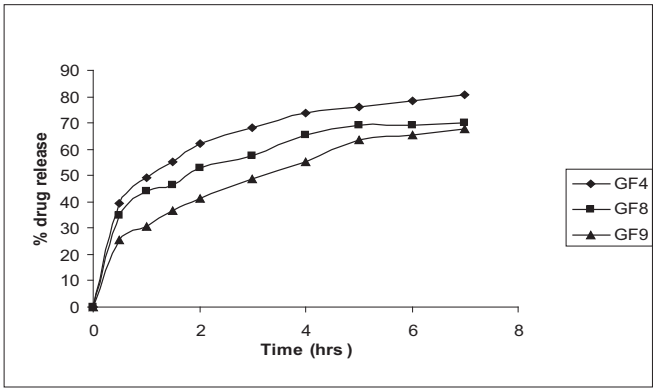

Figure 3: Zero-order drug release profiles for ex vivo permeation studies with selected glibenclamide films of hydroxypropyl methyl cellulose using sheep buccal mucosa

presence of more hydroxyl groups in the HPMC molecules. The water-soluble hydrophilic additive dissolves rapidly, resulting in high porosity.

The void volume is thus expected to be occupied by the external solvent diffusing into the film, and thereby accelerating the dissolution of the gel.[29] The incorporation of the drug induced significant reduction in the residence time of various formulations. As the particle swells, the matrix experiences intramatrix swelling force, which promotes disintegration and leaching of the drug leaving behind a highly porous matrix. Water influx weakens the network integrity of the polymer, thus influencing structural resistance of the swollen matrices, which in turn results in pronounced erosion of the loose gel layer. *In vitro* residence time of the film was in the order of GF4 > GF3 > GF2 > GF1. The folding endurance was measured manually by folding the films repeatedly at a point till they broke. The breaking time was considered as the end point. Folding endurance was found to be highest for GF12 (275.3 ± 12.17) and lowest for GF1 (173.5 ± 5.65) [Table 1]. It was found that the folding endurance of HPMC films were increased with increasing concentration of polymer. The comparative folding endurance of formulations was in the following order: (GF1<GF2<GF3<GF4), (GF5<GF6<GF7<GF8) and GF9<GF10<GF11<GF12)

Drug content in formulations being 2.46 ± 0.02 to 2.48 ± 0.08 mg/20 mm indicated that the drug was dispersed uniformly throughout the film. *In vitro* release studies of various formulations were performed using pH 6.8 phosphate buffer as dissolution medium and drug concentration was measured spectrophotometrically at 226 nm. HPMCK100M shows good release characteristics, as has been already discussed that the release of the drug from the film takes more time when the weight of the polymer increased. HPMC K15M with 0.75 g releases the drug faster than the following weights 1.0, 1.25, and 1.5 g. During dissolution, the loosely bound polymer molecules with HPMC in these films were readily eroded, allowing the easy release of glibenclamide. It was found that the drug release from the films varied with respect to the proportion of polymers. Preliminary studies done with the groups of formulations, from which these 4 formulations were selected, showed that increase in the polymer concentration reduced the diffusion of drug from the matrix [Figure 1]. If the viscosity increases, the entrapment of drug is tightly bound in between the cross-links of the polymer; thereby the drug will take time to release from the film. The different ratios of polymer used were HPMCK15M (GF1, GF2, GF3, GF4), HPMCK100M (GF5, GF6, GF7, GF8), and HPMC3000 (GF9, GF10, GF11, GF12). From the above-mentioned polymers, the drug release after 4 h was found to be GF1 (90.95%), GF2 (85.22%), GF3 (82.83%), GF4 (79.86%), GF5 (78.41%), GF6 (75.81%), GF7 (71.92%), GF8 (69.98%), GF9 (65.36%), GF10 (51.12%), GF11 (45.51%), and GF12 (45.19%). The percentage of drug release from the film is selected, and showed that the increase in the polymer concentration reduced the diffusion of drug from the matrix. Due to its high viscosity, increasing the concentration of HPMC3000 slows down the drug release. During dissolution, the thick gel layer formed on the swollen film surface is capable of preventing matrix disintegration and controlling additional water penetration. Hence the drug release from HPMC3000 films delayed with increasing concentration, that is, GF10 (51.12%), GF11 (45.51%), and GF12 (45.19%) after 4th h [Figure 1].

The mechanism of drug release whether diffusion, swelling, or erosion was confirmed by Higuchi's plots showing the graphical representation of cumulative percentage drug release vs. square root of time [Figure 2]. The Higuchi plots were found to be linear

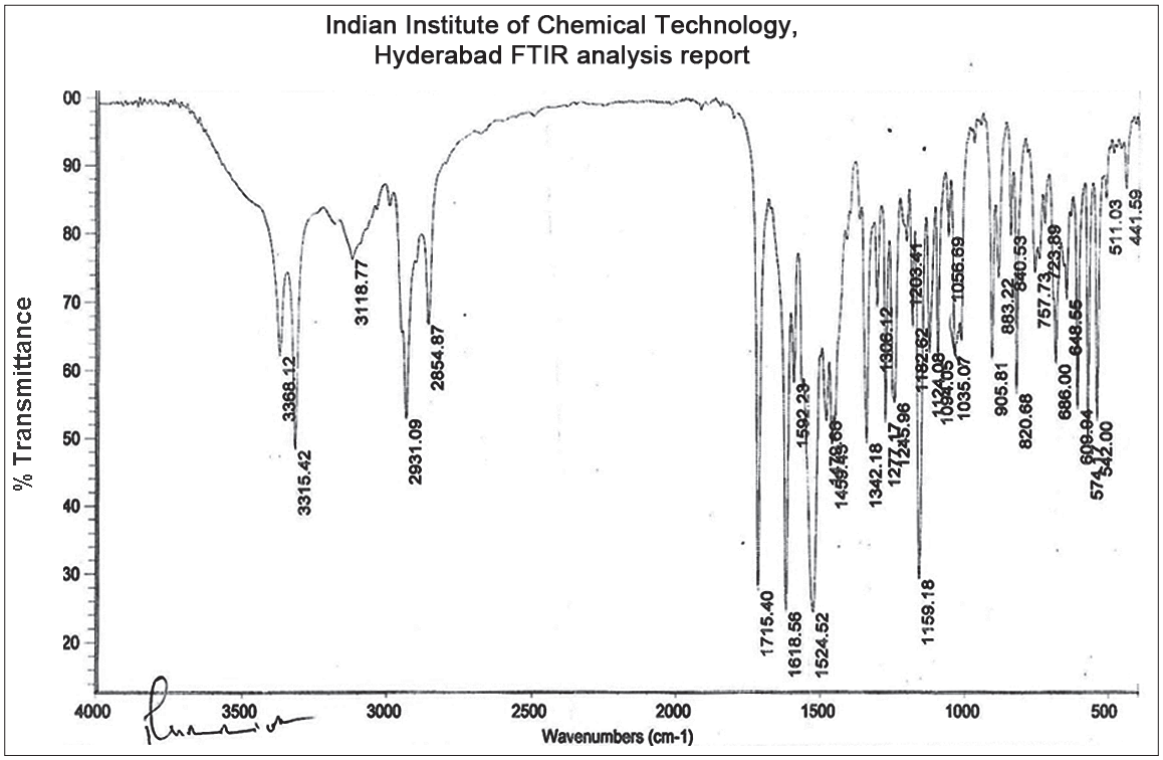

Figure 4: FTIR spectra of pure drug glibenclamide

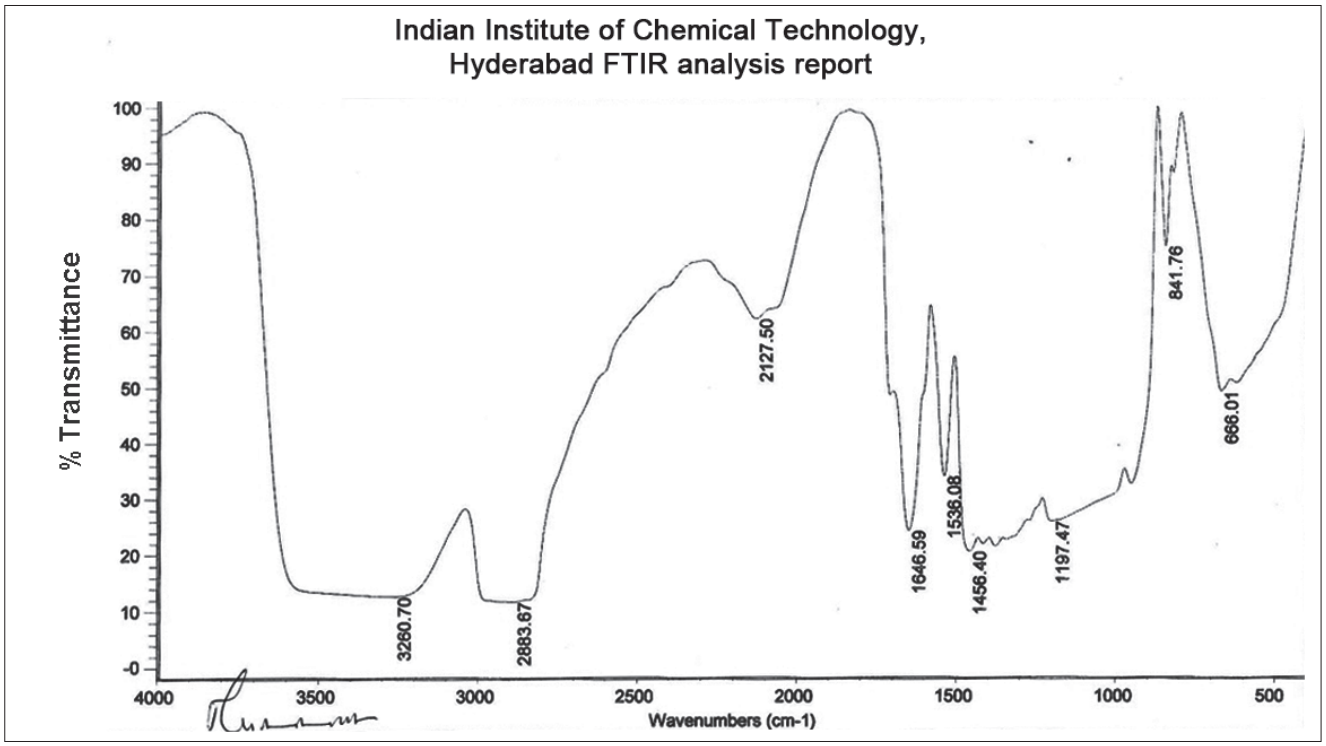

Figure 5: FTIR spectra of pure drug glibenclamide and polymer

with correlation coefficient values 0.8933, 0.9138, and 0.9947 for GF4, GF8, and GF9, respectively. It was concluded that the release of the drug from the films followed the diffusion controlled mechanism in all the formulations.

It was found that formulations GF4, GF8, and GF9 showed good swelling, a convenient residence time, as well as promising drug release pattern. On the basis of release pattern, swelling, and residence time, GF4, GF8, and GF9 formulations were selected for

ex vivo study. In *ex vivo* study, drug permeation through the sheep buccal mucosa was determined for formulations GF4, GF8, and GF9 [Figure 3]. The drug permeation was found to be 89.44%, 82.93%, and 65.72% in GF4, GF8, and GF9, respectively, after 4 h as they are correlated with *in vitro* drug release profile. These films also subjected to FTIR studies showed no interaction between the polymer and the drug, glibenclamide [Figures 4 and 5].

CONCLUSIONS

The present study indicates a good potential of erodible mucoadhesive buccal HPMC films containing glibenclamide for systemic delivery with an added advantage of circumventing the hepatic first-pass metabolism. From the results it can be concluded that HPMC3000 at low concentrations can be useful for buccal delivery of glibenclamide in a controlled manner. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible attractive alternative for noninvasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

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