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FORMULATION AND EVALUATION OF BUCCAL PATCHES OF GLIPIZIDE

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ABSTRACT

There has been a tremendous increase in interest for buccal drug delivery in chronic manageable diseased conditions like diabetes, hypertension etc to reduce the frequency of dosing and bypass the extensive hepatic first-pass metabolism. For improving bioavailability glipizide buccal patches of glipizide were prepared by solvent evaporation technique. Buccal patches were prepared using hydroxy propylmethylcellulose 5 cps (HPMC 5 cps), polyvinylpyrrolidone (PVP) and eudragit S-100 as polymers. Propylene glycol (PG) was used as penetration enhancer. Polyethylene glycol (PEG) 400 was used as plasticizer. Methanol and dichloromethane were used as solvents. Prepared buccal patches were evaluated for parameters like weight variation, thickness, folding endurance, percentage moisture content, surface pH of films, swelling percentage, drug content, ex vivo mucoadhesion, In-vitro drug release. Patches prepared, from each batch, gave release profile for over 8 hours. Cumulative amount of drug release in 8 hours from all the prepared formulations were found to be in following order: F1 > F2 > F3 > F4. Prepared patch from HPMC 5 cps and Eudragit S-100 (F1) exhibited good characteristics for sustained release action and other parameters evaluated.

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INTRODUCTION

Buccal mucosa is an attractive route for systemic delivery of drugs since it is relatively permeable with a rich blood supply. A drug can be easily applied and localized to the application site and can be removed from there if necessary [1]. The oral mucosal drug delivery systems can be localized easily and well accepted by patients [2]. The total surface of the oral cavity is about 100 cm [3]. Problems such as high first pass metabolisms and drugs degradation in the gastrointestinal tract can be circumvented by administrating the drug buccal

routes [4], [5]. The buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules [6].

Glipizide is a second generation sulfonylurea used as oral hypoglycaemic agent. Glipizide provoke release of insulin from pancreas by acting on sulfonylurea receptors on the pancreatic ß cell membrane. It also up regulates insulin receptors in the periphery, which seems to be the primary action. Its short biological half-life (3.4 ± 0.7 h) necessitates its administration in 2 or 3 doses of 2.5 to 10 mg per day. Glipizide is used in NIDDM (Non insulin dependent diabetes mellitus) and acts by increasing the release of endogeneous insulin and its peripheral effectiveness [7].

MATERIALS AND METHODS:

Materials:

Glipizide was received as a gift sample from Ronak Pharmaceuticals pvt Ltd., Patan. Eudragit RS 100 was received as a gift sample form Roehm Pharma polymers. HPMC 5 cps, PVP K 30, Propylene glycol, PEG 400, Methanol and Dichloromethane were purchased from Central Drug House (P) Ltd., New Delhi.

Method: [1], [10], [12], [14]

Baccal patches loaded with Glipizide were prepared by solvent evaporation method. Composition of of various formulations is mentioned in Table 1. Required quantities of polymers were weighed and dissolved in 10 ml mixture of methanol and dichloromethane in the ratio 1:1. This solution was stirred for 1 hour on a magnetic stirrer at 400rpm. 166.5 mg of glipizide was weighed and added to the above solution. Required quantity of PEG 400 (as plasticizer) and propylene glycol (as penetration enhancer) were measured and added to the above solution. Stir on a magnetic stirrer at 400 rpm for 2 hours. The resulted uniform solution was cast on a Petri dish of area 66.50 cm^2, previously containing a layer of mercury. An inverted funnel was placed over the Petri dish to prevent the fast evaporation of the solvent. After 24 hours, the dried buccal patches were taken out, cut into pieces of 2 cm × 2 cm (area = 4 cm^2 and containing 10mg of the Glipizide) and stored in a desiccator.

Table 1: Formula for glipizide buccal patchs

BATCH CODE	INGREDIENTS				
	HPMC 5 cps (mg)	Eudragit S-100 (mg)	PVP K30 (mg)	PG (mg)	PEG 400 (ml)
F1	450	850	-	210	0.5
F2	650	650	-	210	0.5
F3	980	-	320	210	0.5
F4	1070	-	230	210	0.5

EVLUATION: [8]-[17]

1. **Investigation of drug-polymer compatibility:**
   Drug - polymer compatibility was checked by comparing the IR spectra of formulations with that of the pure drug.
2. **Weight uniformity:**
   The prepared buccal patches are to be dried at 50ºC for 4 hours before testing. Weight uniformity was done by weighing 3 different patches of each batch. All the buccal patches, selected at random, should be uniform in size (2cm × 2cm). Calculate the average weight of three.
3. **Thickness of the patch:**

The buccal patch thickness was measured using Digital vernier caliper at five different places of 3 patches and the mean value was calculated.

4. **Percentage moisture content:**
Three buccal patches of the same composition were weighed and kept on desiccators containing fused calcium chloride at 37ºC until no change in weight of the individual patches was observed. This weight was noted as the final weight. The percentage moisture content was calculated as a difference between individual and final weight. An average is shown in table.

5. **Folding endurance:**
Folding endurance of the film was determined by repeatedly folding one patch at the same place till it broke. A strip of specific area (2cm × 2cm) is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance.

6. **Surface pH of films:**
Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2 % w/v agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then pouring the solution into a petridish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of three reading was recorded.

7. **Swelling percentage (S %):**
A drug loaded films were placed in a thoroughly cleaned petridish and a graph paper was placed beneath the petridish, to measure the increase in area due to swelling of the film. Fifty ml of pH 6.8 phosphate buffer was poured into the petridish. An increase in the weight of the patch was noted in 15 min intervals for 60 min and the weight was calculated. The swelling percentage was calculated by using the following formula,

$$\% S = \frac{A - B}{B} \times 100$$

Where % S = Swelling percentage, A = Weight of swollen film after time t, B = Weight of film at zero time.

8. **Drug content:**
The film of 2cm × 2cm was cut into small pieces and taken into 100ml volumetric flask containing 20ml methanol. This methanolic solution was diluted with phosphate buffer pH 7.4 up to 100ml. the solution was filtered through whatmann filter paper and the drug content was determined on UV spectrophotometer at λ_{max} 275nm after suitable dilutions.

9. **Ex Vivo Mucoadhesion Study:**
Mucoadhesive strength of all fabricated buccal patches was measured ex vivo (n=3) on a modified physical balance. A piece of porcine buccal mucosa was tied to the open mouth of a glass vial filled completely with isotonic phosphate buffer, pH 6.8. The glass vial was tightly fitted in the center of a beaker filled with isotonic phosphate buffer (pH 6.8; temperature, 37±1°C). The patches were stuck to the lower side of the rubber stopper with glue. The mass (in gram) required to detach the patches from the mucosal surface gave the measure of mucoadhesive strength (shear stress). The following parameters were calculated from mucoadhesive strength;

$$\text{Forse of adhesion} = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

$$\text{Bond strenth} = \frac{\text{Force of adhesion}}{\text{surface area}}$$

10. **In-vitro drug release studies:**
The in-vitro drug release studies were carried out in a Franz diffusion cell. The cellulose acetate membrane (pore size = 0.45µm) was mounted between donor and the receptor compartment of the diffusion cell. The buccal film was placed on the cellulose acetate membrane and covered with aluminum foil. The receptor compartment was filled with freshly prepared phosphate buffer pH 7.4 (55ml). The whole assembly was fixed on a magnetic stirrer with hot plate apparatus. The solution in receptor compartment was stirred

at 35-45 rpm and temperature was maintained at 32±0.5ºC. Sample (3ml) was withdrawn at different interval and replaced with the same volume of the phosphate buffer pH7.4. Samples were analyzed spectrophotometrically at 275nm.

Table 2: Physicochemical evaluation

BATCH CODE	PARAMETERS			
	WEIGHT VARIATION (Mean (mg) ± SD)	THICKNESS (Mean (mm)± SD)	MOISTURE CONTENT (Weight %)	FOLDING ENDURANCE
F1	90 ± 2	0.24 ± 0.022	2.43	192 ± 3.5
F2	89 ± 4	0.25 ± 0.054	2.36	180 ± 4.4
F3	92 ± 2	0.23 ± 0.045	3.44	155 ± 2.9
F4	92 ± 5	0.26 ± 0.073	3.76	150 ± 5.7

Table 3: Evaluation parameters

BATCH CODE	PARAMETERS			
	Surface pH	Swelling percentage (S %)	% Drug content	% cumulative drug release
F1	6.62 ± 0.196	59.34 ± 1.54	97.98 ± 2.87	75.43 ± 0.146
F2	6.59 ± 0.275	55.67 ± 1.87	96.78 ± 3.98	72.76 ± 0.019
F3	6.65 ± 0.185	48.39 ± 1.09	94.43 ± 5.36	64.22 ± 0.123
F4	6.68 ± 0.169	44.56 ± 0.98	93.64 ± 6.89	63.43 ± 0.098

Table 4: Ex Vivo Mucoadhesive Characteristics of glipizide Buccal Patches

BATCH CORD	Mucoadhesive strength (g)	Force of adhesion (N)	Bond strength (N m^{-2})
F1	24.88 ± 1.19	0.24 ± 0.01	135.60 ± 4.62
F2	23.06 ± 1.35	0.23 ± 0.02	125.68 ± 2.16
F3	22.11 ± 1.09	0.22 ± 0.01	120.50 ± 3.34
F4	20.00 ± 2.62	0.20 ± 0.02	109.00 ± 6.85

Figure 1: In vitro release profiles (F1 to F4)

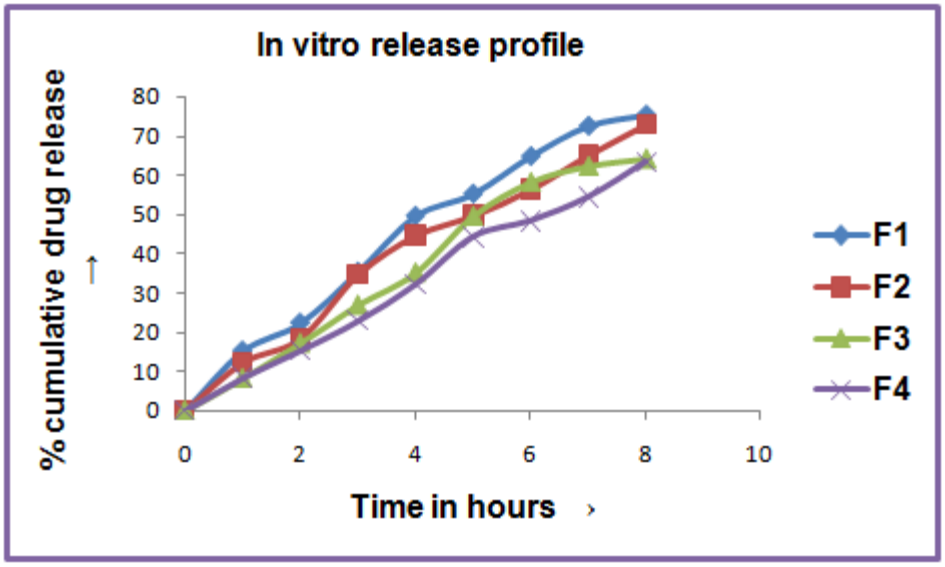


Figure 2: IR spectra of glipizide

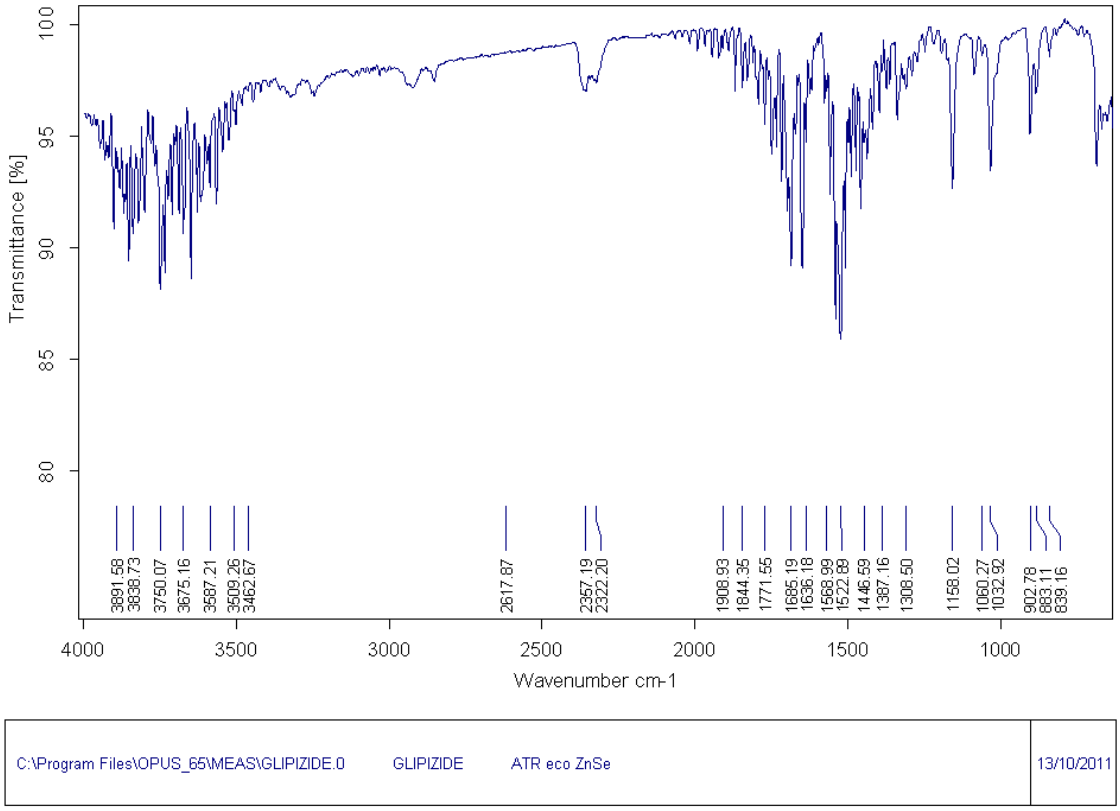


Figure 3: IR spectra of glipizide, HPMC 5cps & PVP K30

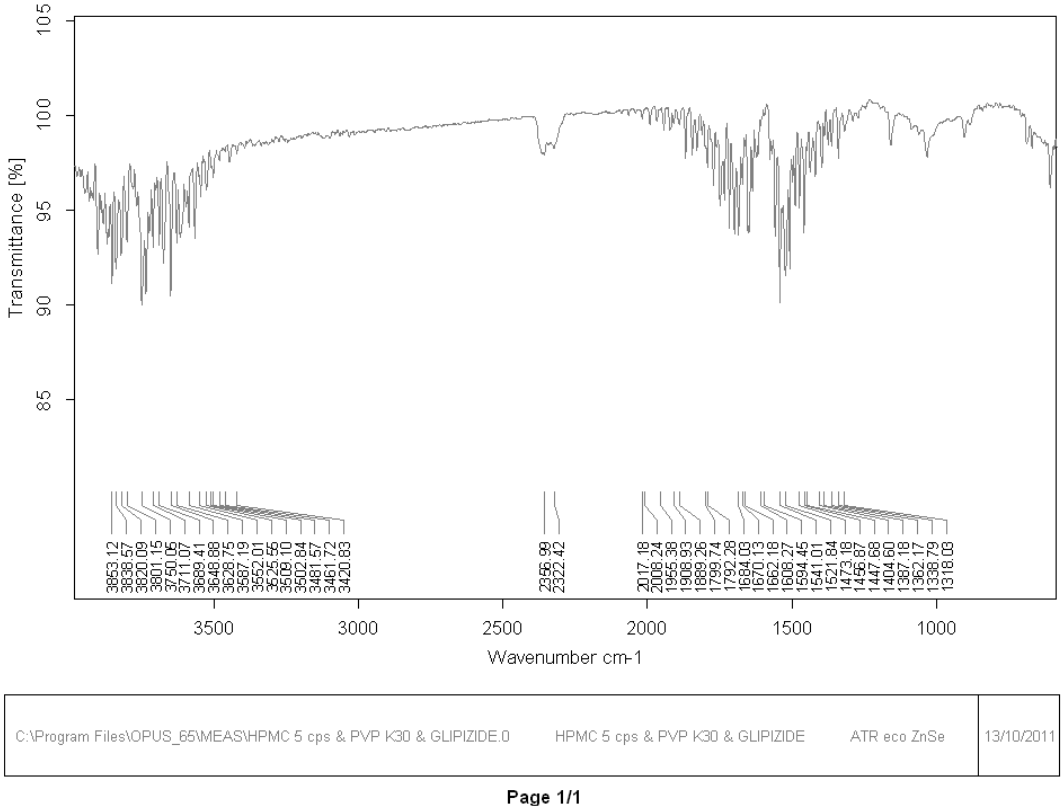
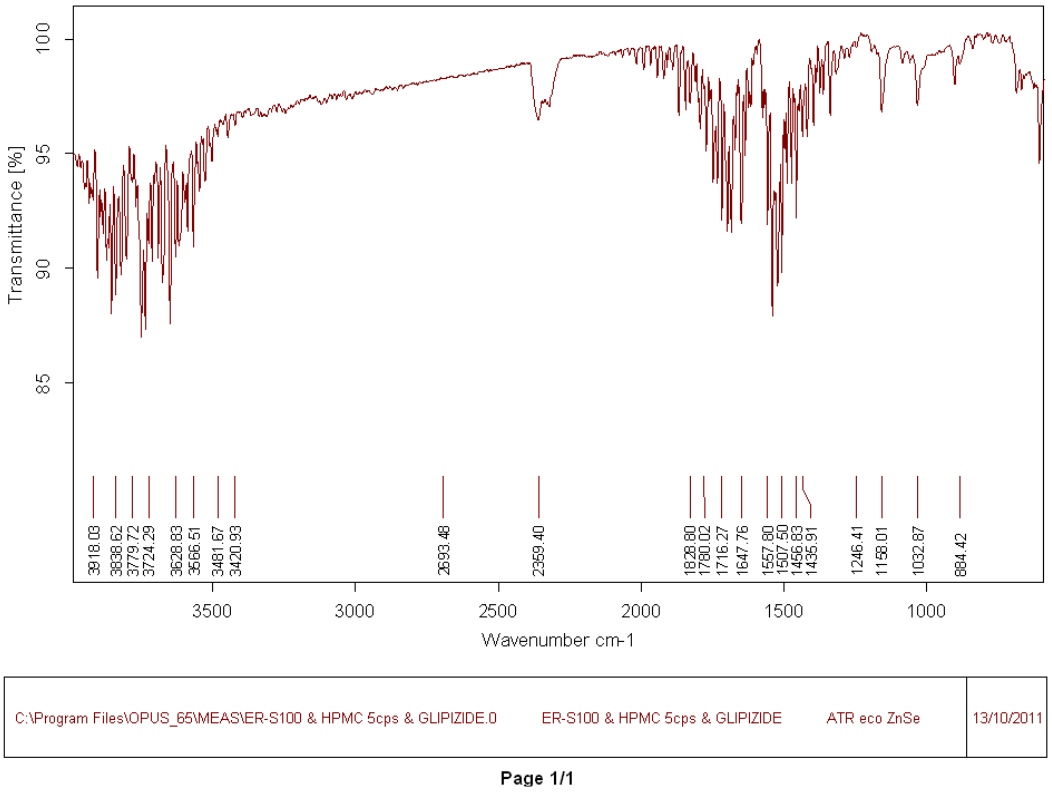


Figure 4: IR spectra of Glipizide, Eudragit S-100 & HPMC 5cps



RESULTS AND DISCUSSION:

Buccal patches of glipizide were prepared by solvent evaporation method in a Petri-dish on a mercury platform with an inverted funnel to control the rate of evaporation of the solvent. Different formulation (as shown in table 1) containing glipizide were prepared to achieve the sustain release pattern within the therapeutic range.

Investigation of drug-polymer compatibility:

Drug - polymer compatibility was checked by comparing the IR spectra of formulations with that of the pure drug. No significant changes in the functional groups between the two spectra were observed. This ensured the compatibility of polymer with that of the drug.

Physicochemical evaluation of buccal patches:

The results of the physicochemical evaluation of the buccal patches are described in table 2, table 3 and table 4. All the formulations (F1, F2, F3 and F4) show uniformity in weights. The weight variation of all the formulations varied in between 89 ± 4 to 92 ± 5. The formulation F2 was having minimum average weight while the formulation F3 was having maximum average weight. Results are shown as Mean ± standard deviation in table 2**.**The film thicknesses were observed uniform. The variation in the thickness of all the formulation was in the range 0.23 ± 0.045 to 0.26 ± 0.073. The formulation F3 was having minimum average thickness while the formulation F4 was having maximum average thickness. Results are shown as Mean ± standard deviation in table 2. Moisture content of these patches was found to vary from 2.36 % to 3.76 %. The formulation F1 was having minimum average moisture content while the formulation F4 was having maximum average moisture content. This difference in the moisture content and water absorption was may be due to the difference in hydrophilicity of the polymers and extent of solvent evaporation during formulation. Folding endurance was found to be in between 150 ± 5.7 to 192 ± 3.5. The formulation F4 was having minimum average folding endurance while the formulation F1 was having maximum average folding endurance. Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa .The surface pH of the buccal films was

determined to optimize both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close as salivary pH. The Surface pH of all the formulations varied in between 6.59 ± 0.275 to 6.68 ± 0.169. The Swelling percentage of all the formulations varied in between 44.56 ± 0.98 to 59.34 ± 1.54. The formulation F4 was having minimum average swelling percentage while the formulation F1 was having maximum average swelling percentage. The mucoadhesive strength of all formulations varied between 20.00 ± 2.62 to 24.88 ± 1.19. The formulation F4 was having minimum average mucoadhesive strength while the formulation F1 was having maximum average mucoadhesive strength. The % drug content of all the formulations varied in between 93.64 ± 6.89 and 97.98 ± 2.87. The formulation F4 was having minimum average % drug content while the formulation F1 was having maximum average % drug content. On this basis, it was found that the drug was dispersed uniformly throughout the film. The comparative % drug content of various formulations was in order of F1>F2>F3>F4. The % cumulative drug of all the formulations varied in between 63.43 ± 0.098 and 75.43 ± 0.146. The formulation F4 was having minimum average % cumulative drug while the formulation F1 was having maximum average % cumulative drug. The comparative % cumulative drug of various formulations was in order of F1>F2>F3>F4.

CONCLUSION:

IR studies revealed that the drug and polymer were compatible with each other. Buccal patches of glipizide using polymers like eudragit S-100, HPMC 5 cps and PVP K 30, in various proportions and combinations showed satisfactory physicomechanical and mucoadhesive characteristics. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formulated glipizide buccal patches. It may be concluded that the films containing 10 mg glipizide in F1, show good swelling, a convenient residence time and promising controlled drug release, thus seems to be a potential candidate for the development of buccal film for effective therapeutic use. From the present investigation, it can be concluded that such buccal patches of glipizide may provide sustained buccal delivery for prolonged periods in the management of used in Non insulin dependent diabetes mellitus, which can be a good way to bypass the extensive hepatic first-pass metabolism.

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