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Design, Development and In vitro Characterization of Pioglitazone Loaded Mucoadhesive Buccal Devices

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RESUMEN

Objetivo: Los parches de mucoadherente bucal fueron desarrollados y evaluados por la administración sistémica de la pioglitazona en la cavidad oral. Pioglitazona pertenece a una clase nueva de medicamentos antidiabéticos orales conocida como tiazolidindionas.

Material y Método: los parches mucoadherente bucal de pioglitazona fue formulado con Eudragit RS100 y HPMC K4M (polímero mucoadherentes) y fueron elaboradas por el método de fundición solvente. Se evaluaron diferentes formulaciones de parches mediante parámetros físicos como uniformidad de espesor, índice de hinchazón, pH de la superficie, uniformidad de peso, resistencia al plegado, fuerza mucoadherentes y parámetros *in vitro* como uniformidad de contenido del fármaco y estudios de liberación y estudios *ex vivo* del tiempo de mucoadhesión del fármaco.

Resultados: Los resultados obtenidos para los parámetros estudiados fueron: uniformidad de espesor, 0.27±0.45 mm; uniformidad de peso, 40.81±0.66 mg; pH superficial, 6.5; resistencia al plegado, > 300. Los ensayos *in vitro* dieron los siguientes resultados: uniformidad de contenido del fármaco, 98.58±2.05%; índice de hinchazón, 131±0.79%; fuerza mucoadherente, 38.20±1.75; y tiempo de liberación del farmaco (95.18±1.98%) y el ensayo ex vivo del tiempo de mucoadhesión del fármaco fue de 4±1.26 h. Los datos también se ajustaron a distintos modelos cinéticos para ilustrar su difusión anómala (no Fickian).

Conclusiones: El resultado reveló que los parches bucales de pioglitazona fue el modo más adecuado de fármacos de acción terapéutica prometedora. Los Parches bucales de pioglitazona pueden resultar una potencial forma de dosificación farmacéutica para sostener la liberación del fármaco y reducir la frecuencia de la dosis.

PALABRAS CLAVE: Eudragit, HPMC K4M, Método de fundición solvente de Mucoadhesion.

ABSTRACT

Aim: The mucoadhesive buccal patches were developed and evaluated for systemic administration of Pioglitazone in the oral cavity. Pioglitazone belongs to a novel class of oral antidiabetic drugs known as Thiazolidinediones.

Materials and Methods: The mucoadhesive buccal patches of Pioglitazone was formulated using Eudragit RS100 and HPMC K4M (mucoadhesive polymer) and were prepared by solvent casting method. Different patch formulations were evaluated for its physical parameters like thickness uniformity, swelling index, surface pH, uniformity of weight, folding endurance, mucoadhesive strength and *in vitro* parameters like drug content uniformity and drug release studies, and *ex vivo* parameters like mucoadhesion time.

Results: Data for the parameters was found to be: thickness uniformity (0.27±0.45mm); uniformity of weight (40.81±0.66 mg), surface pH (6.5), folding endurance (>300), drug content uniformity (98.58±2.05%), swelling index (131±0.79%), mucoadhesive strength (38.20±1.75), *in vitro* drug release studies (95.18±1.98%) and *ex vivo* mucoadhesion, time of optimized formulation (4±1.26 h). The data was also fitted to different kinetic models to illustrate its anomalous (non-fickian) diffusion.

Conclusions: The result revealed that Pioglitazone loaded buccal patches was most suitable mode of drug delivery for promising therapeutic action. Buccal patches of Pioglitazone can prove to be potential pharmaceutical dosage form for sustaining the drug release and reducing the dose frequency.

KEY WORDS: Eudragit, HPMC K4M, Mucoadhesion, Solvent casting method.

INTRODUCTION

In recent years, there has been outstanding interest in the buccal drug delivery of active medicaments, particularly in overcoming deficiencies associated with conventional oral drug delivery system. Problems such as extensive hepatic first-pass metabolism and drug degradation in the gastrointestinal environment can be prevented by administering the drug via the buccal route of oral cavity[1]. Moreover, there are enormous advantages of buccal drug delivery like increased bioavailability due to by-pass of first pass metabolism, improved patient compliance due to the elimination of associated pain with injections and sustained release for prolonged duration of time. Large contact surface area of buccal region contributes to rapid and extensive drug absorption and can be used in case of unconscious and less cooperative patients[2,3]. Buccal patches are a novel form of mucoahesive systems, which are thin, flexible, elastic and soft and usually prepared by mild bioadesive and biodegradable polymers[4]. Mucoadhesion is known to increase the intimacy and duration of contact between drug-containing polymer and a mucous surface[5]. Type II diabetes mellitus is a chronic illness with progressively leading to micro and macrovascular complications. Pathophysiology of diabetes mellitus is related with development of insulin resistance in target tissues, increased hepatic glucose production and ultimately failure of insulin secretion by pancreatic β-cell. These pathologies lead to hyperglycemia and hyperinsulinism[6]. Pioglitozone is chemically (RS)-5-(4-[2-(5-ethylpyridin-2-yl) ethoxbenzylthiazolidine-2, 4-dione and is an anti-diabetic drug which is used in the treatment of type II diabetes[7]. It is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPARγ receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle and liver[8]. Its $t_{1/2}$ is 3-7 hours. It is extensively bound to plasma protein (>99%), principally to serum albumin. It undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. Oral dose of drug is excreted into the bile either unchanged or as metabolites and eliminated in the feces[9]. Thus, the aim of present research work is to design, development and *in vitro* characterization of pioglitazone loaded mucoadhesive buccal devices.

MATERIALS AND METHODS

Materials

Pioglitazone was generously gifted by Panacia Biotec, Baddi (H.P.) India. Eudragit, Polyethylene glycol 300 and HPMC K4M were purchased from Central Drug House, New Delhi. All other chemicals used were of analytical grade.

Methods

Pioglitazone loaded mucoadhesive buccal patches were prepared by solvent casting technique. The weighed and measured quantities of Eudragit RS 100 (controlled release polymer) and Hydroxy propyl methyl cellulose K4M (mucoadhesive polymer) were dissolved in solvent system i.e. ethanol and the mixture were stirred until they were completely dissolved. Pioglitazone was separately dissolved in ethanol and added to polymeric solution. Later on, polyethylene glycol 300 (plasticizer) was added in the drug polymer mixture. The mixtures were prepared with a magnetic stirrer and cast into a petridish of 10 cm diameter and allowed to dry overnight at room temperature. The films were accurately observed and checked for possible imperfections upon their removal from the petridish[10]. The composition of the various formulations is mentioned in the Table 1.

Table 1. Formulation Table of Pioglitazone Loaded Mucoadhesive Buccal Patches.

FC	Eudragit RS 100 (%w/v)	HPMC K4M (%w/v)	PEG300 (ml)	Drug (mg)
F1	5	5	0.5	20
F2	10	5	0.5	20
F3	15	5	0.5	20
F4	10	2.5	0.5	20
F5	10	7.5	0.5	20

FC: Formulation code

Evaluation of mucoadhesive buccal patches

Thickness uniformity: The thickness of each patch was measured using a micrometer screw gauge at different positions of the patch and the average was calculated.

Uniformity of weight: Patch was cut into 1×1 cm^2. Weight of each patch was taken and the weight variation of a batch of ten patches was averaged.

Surface pH: The surface pH of patches was ascertained so as to investigate/ examine the possible side effects due to change in pH *in vivo*, since an acidic or basic pH may cause irritation to buccal mucosa. Buccal patches were left to swell for 2 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.8. The surface pH was measured by means of electrode of pH meter placed on the surface of the swollen patch[11].

Folding endurance: The folding endurance was computed by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered satisfactory to show good patch properties. The number of times of patch could be folded at the same place without

breaking/cracking gave the value of folding endurance[12].

Drug content uniformity: A patch of size 1×1 cm^2 was cut and placed in a beaker. Ten ml of a phosphate buffer (pH 6.8) solution was added. The contents were stirred in ultrasonic cleaner to dissolve the patch and filtered. The contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 269 nm[13].

Swelling index: The patches were allowed to swell on the surface of the agar plate (2% w/v agar in simulated salivary fluid of pH 6.8). Measurement of the weight of the swollen patch was done using digital weighing balance at hourly intervals for 4 h. The swelling was calculated from the following equation:

$$S\ (\%) = [(W_t - W_0)/\ W_0] \times 100$$

Where, S (%) is the percent change in swelling of patches, W_t is the weight of the swollen patches after time t; W_0 is the weight of patch at time zero[14].

Mucoadhesive strength: Mucoadhesion is essential parameter for buccal drug delivery systems since it can increase the residence time of drug in the body. Modified Pan Balance technique was used to determine the mucoadhesive strength. An alantoine membrane (i.e. mucosal surface) obtained from an egg was covered the bottom portion of a small beaker and placed inverted in a large beaker containing phosphate buffer (pH 6.8), kept at 37±1°C. The patch was placed on the alantoine membrane. Then, the left side pan was placed at the patch attached to membrane. The weights were added slowly in increasing order to the right pan till the patch separates from the alantoine membrane. The weights required for complete detachment of the patch from mucosal surface was noted. Average of three determinations was calculated[15].

Ex vivo mucoadhesion time: It was carried out by applying patch on freshly cut porcine buccal mucosa. The mucosa was fixed on the internal bottom side of beaker with help of starch mucilage. The patch was wetted with 50 ml of simulated saliva fluid and was pasted to mucosa by applying light force by hand. The beaker was filled with 100 ml SSF and kept at 37°C. After 2 m, a 50 rpm stirring rate was applied to simulate the buccal cavity. The time taken for patch to completely erode or detach from mucosa was observed as *ex vivo* mucoadhesion time. Dissolution media was continuously stirred using teflon coated magnetic bead to maintain sink conditions[16].

In vitro drug release studies: The *in vitro* release of Pioglitazone was studied in simulated salivary fluid (SSF) (pH 6.8) as dissolution media using sigma dialysis membrane as diffusion membrane. The membrane was tied to one open end of double ended tube which acts as donor compartment. A patch of 1×1 cm^2 sizes was cut and attached to the membrane. The assembly was placed in beaker contained 500 ml of SSF. 5 ml sample was withdrawn at intervals of 0, 15, 30, 60, 120, 240, 360, 480, 600, 720, 960, 1200 and 1440 min and replaced simultaneously with fresh fluid. The collected samples were analyse with the help of UV spectrophotometer at 269 nm. Finally, the cumulative amount of drug release from the formulation was calculated with the help of calibration curve of Pioglitazone to determine the release pattern. All measurements were carried out in triplicate and average values plotted.

Release kinetic study: In order to understand the mechanism and kinetics of drug release, the drug release data of *in vitro* dissolution study was analyzed with various kinetic models like zero-order, first order, Higuchi and Korsmeyer-Peppas model. Regression (R^2) values were calculated for the linear curves obtained by regression analysis[17].

RESULTS AND DISCUSSION

Preparation of Patches: Preparation of Pioglitazone loaded mucoadhesive buccal patches was done by using Eudragit RS100 as sustained release and film forming polymer and HPMC K4M as mucoadhesive polymer with polyethylene glycol 300 as plasticizer. Ethanol was used as solvent to keep both polymers in solution. The solvent casting method was used to prepare buccal patches. The formulation F1, F2 and F3 was formulated by varying the concentration of Eudragit and formulation F4, F5 formulated by varying the concentration of HPMC K4M. Patches with higher concentration of Eudragit or HPMC could not be prepared since they could not be removed easily from the petridish in which they were cast and tended to fragment. Different formulations of pioglitazone loaded buccal patches are shown in Figure 1.

Thickness uniformity: The thickness of each patch was measured using screw gauge at different positions of the patch and the average was calculated. The thickness of patches for F1, F2, F3, F4 and F5 formulations were found to be 0.26±0.02, 0.27±0.45, 0.30±1.10, 0.29±0.98 and 0.30±0.63 mm respectively. All the patches have uniform

Figure 1. Different formulations of Pioglitazone loaded buccal patch.

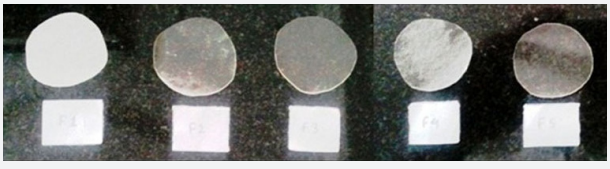

Table 2. Evaluation Parameters of Pioglitazone loaded Mucoadesive Buccal Patches.

Evaluation Parameters	F1	F2	F3	F4	F5
Thickness (mm)[a]	0.26±0.02	0.27±0.45	0.30±1.10	0.29±0.98	0.30±0.63
Uniformity of weight (mg)[a]	30.46±1.75	40.81±0.66	50.27±1.68	50.69±1.29	60.23±1.92
Surface pH	6.7	6.5	6.6	6.2	6.0
Folding endurance	>300	>300	>300	250	180
Drug content uniformity (%)[a]	85.04±0.54	98.58±2.05	92.64±1.14	90.35±0.91	96.07±0.84
Swelling index (%)[a]	135±0.63	131±0.79	110±0.94	66.66±1.12	75±2.16
Mucoadhesive strength[a]	21.77±0.26	38.20±1.75	31.57±1.47	23.95±2.22	37.13±0.98
Ex vivo mucoadhesion time (h) [a]	2±0.56	4±1.26	4.5±0.45	2±0.36	6±0.87
Cumulative *In vitro* drug release (%)[a]	69.91±0.99	95.18±1.98	89.04±2.27	80.74±0.45	85.32±2.25

[a] Each value indicate the mean ± SD (n=3)

thickness throughout. Average thickness was found 0.284 mm. The thickness of patches was increased on increasing the polymer concentration[18].

Uniformity of weight: The uniformity of weight of the patches for F1, F2, F3, F4, and F5 formulations were found 30.46±1.75, 40.81±0.66, 50.27±1.68, 50.69±1.29 and 60.23±1.92 mg respectively.

Surface pH: The surface pH of buccal patches containing pioglitazone was found in the range 6.0 to 6.7. The surface pH of all formulations was within range of salivary pH and hence no mucosal irritation was expected and ultimately achieves patient compliance. The average of three determinations for each formulation is shown in Table 2.

Folding Endurance: Folding endurance was considered adequate to reveal good patch properties. The patches show folding endurance values in between 180 and >300. The formulations F1, F2, F3 patches did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. The patches were found uniform. But the F5, F6 formulations shows 150 and 80 times folding of patches which means patches were not uniform. The folding endurance of the patches decreases with increase in polymer concentration. The folding endurance of the patches is more than 300 which show the patches are having high mechanical strength and good elasticity[19]. F5 showed minimum folding endurance. However, all the patches showed satisfactory flexibility.

Drug content uniformity: Drug content uniformity of formulation F1 to F5 varied from 85.04±0.54 to 98.58±2.05%. The results of drug content uniformity from table 2 indicated that the drug was uniformly dispersed. The drug content of all the patches was found to be uniform with low SD values, which indicates that the drug was distributed uniformly in all the patches.

Swelling Index: The swelling index of formulations F1, F2, F3, F4 and F5 was found to be 135±0.63, 131±0.79, 110±0.94, 66.66±1.12 and 75±2.16% respectively after 4 h. The Eudragit contained buccal patches showed highest swelling index[13].

Mucoadhesive strength: As the amount of mucoadhesive polymer (HPMC K4M) increases the mucoadhesion was found to be increase. Peak detachment force is the maximum applied force at which the patch detaches from tissue. The mucoadhesive strength for formulation F1, F2, F3, F4 and F5 was found to be 21.77±0.26, 38.20±1.75, 31.57±1.47, 23.95±2.22 and 37.13±0.98 respectively.

Ex vivo mucoadhesion time: The patches composed of larger amounts of the mucoadhesive polymer, HPMC showed the greatest mucoadhesion time of nearly 6 h indicating their suitability for use in buccal drug delivery. Comparatively shorter mucoadhesion time was observed with patches containing higher amounts of the retardant polymers.

In vitro drug release studies: The *in vitro* drug release of formulations F1, F2, F3, F4 and F5 was found to be 69.91±0.99, 95.18±1.98, 89.04±2.27, 80.74±0.45 and 85.32±2.25% in 24 h (i.e. 1440 min) respectively. At pH 6.8, Eudragit RS100 retarded the release rate of drug from HPMC patches. An increase in the polymer content was associated with a corresponding decrease in the drug-release rate[5]. The data for cumulative *in vitro* drug release for all formulations are given in Table 3 and illustrates in Figure 2.

Figure 2. Cumulative In vitro Drug Release for All Formulations.

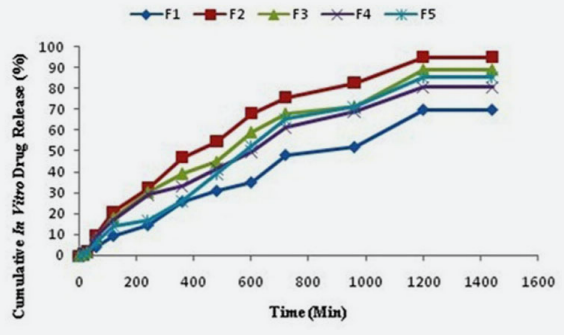

Table 3. Data for Cumulative In vitro drug release for all Formulations.

Time (Min)	Formulations				
	F1[a]	F2[a]	F3[a]	F4[a]	F5[a]
0	0	0	0	0	0
15	0.71±0.21	0.84±0.56	0.79±1.03	0.52±1.59	0.68±0.98
30	1.05±0.54	2.35±1.35	1.91±2.01	1.98±0.83	1.71±0.61
60	4.29±1.08	9.89±2.77	8.67±1.61	9.55±0.094	6.49±0.27
120	9.67±0.53	21.04±1.45	18.21±2.48	17.11±0.67	14.23±2.36
240	14.79±1.59	32.51±1.41	30.60±0.59	29.45±1.39	17.02±0.82
360	26.00±2.64	47.26±1.62	39.35±1.21	33.16±0.44	26.39±1.94
480	31.15±0.74	54.79±0.97	44.87±1.68	41.78±2.64	39.07±.96
600	35.18±1.58	68.24±2.03	59.12±1.50	50.02±0.78	52.41±0.39
720	48.32±0.43	76.05±1.27	67.97±2.99	61.45±0.81	65.27±2.46
960	52.08±2.08	83.11±0.35	71.32±1.76	69.20±1.49	71.08±1.76
1200	69.91±0.99	95.18±1.98	89.04±2.27	80.74±0.45	85.32±2.25
1440	69.91±0.99	95.18±1.98	89.04±2.27	80.74±0.45	85.32±2.25

[a] Each value indicate the mean ± SD (n=3)

Release kinetic study: The kinetics and mechanism of drug release was determined using zero order, first order, Higuchi's square root equation and further analysis was performed using Korsemeyer-Peppas equation. All formulations were found to be followed Higuchi's square root equation as the plot showed high linearity (R^2= 0.956 to 0.984) as shown in Table 4. This equation indicates that the amount of drug release is proportional to the square root of time for the diffusional release of a drug from the formulation. The calculated 'n' values from power law equation (Korsemeyer- Peppas equation) for drug release profiles were between 0.745-0.782, suggest that drug release mechanism from formulations followed Non-Fickian (anomalous) transport mechanism, which indicates that the drug release rate is controlled by coupled diffusion and erosion[20]. The *in vitro* release kinetics data for all formulations are given in Table 4.

CONCLUSION

A novel mucoadesive buccal patch of Pioglitazone was successfully fabricated via solvent casting technique using HPMC K4M as mucoadhesive polymer and Eudragit RS100 as controlled release polymer. Prepared patches have shown higher mucoadhesive strength with sustained release characteristics. The observed data for all physical and *in vitro* evaluation parameters illustrates F2 as optimized formulation among all. Thus, it can be concluded that the current research on pioglitazone loaded mucoadesive buccal patches can prove to be promising dosage form for the active ingredient in comparison with conventional dosage forms.

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Table 4. In vitro release kinetics data for all formulations.

Formulation code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	K	R^2	K	R^2	K	R^2	n	R^2
F1	0.052	0.973	0.001	0.692	2.042	0.960	0.745	0.867
F2	0.072	0.913	0.001	0.591	2.926	0.983	0.782	0.899
F3	0.066	0.936	0.001	0.607	2.660	0.983	0.771	0.892
F4	0.060	0.941	0.001	0.590	2.416	0.984	0.768	0.867
F5	0.066	0.956	0.001	0.672	2.588	0.956	0.770	0.884

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