Research Article

Development and characterization of mucoadhesive buccal Patches for controlled delivery of antihyperglycemic agent

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Abstract

Objective: The aim of the present investigation was to develop a controlled release drug delivery device of Metformin (anti-diabetic drug) to maintain its bioavailability over an extended period of time and to circumvent the hepatic first pass effect. **Materials and methods:** To achieve this object, Drugcoat RL 100 and HPMC E 15 were used as a primary and secondary layer polymer for the preparation of controlled release bilayerd buccoadhesive patches of Metformin. The prepared patches were evaluated for various *in vitro* and *in vivo* studies. **Results:** The drug content of the patches was found to be approximately more than 95%. The patches exhibited controlled release over more than 6 hr. The selected formulation showed a drug release of 98.41±1.34% in 8 hrs. The *in vitro* permeation of drug through porcine buccal membrane in 8 hr was found to be 51.1±1.6%. Stability studies of optimized patch were carried out in simulated human saliva. The results of stability studies suggested that both drug and buccal patches were stable in simulated human saliva. **Conclusion:** From the study it was concluded that the developed bilayered buccoadhesive delivery system bears potential to deliver the drug in a controlled manner over an extended period of time.

Keywords*:* Buccal absorption, polymeric patches, antidiabetic, blood glucose level.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance diabetes (Arunachalam et al., 2002; Mura et al., 210). Non insulin dependent diabetes mellitus (NIDDM) represents a heterogeneous group comprising milder form of diabetes that occurs predominately in adults. Vast majority of diabetic patients have NIDDM (type 2 diabetes) and Metformin is one the most commonly prescribed drug for the treatment of type II diabetes (Mura et al., 2010; Davis et al., 1996; Nolte et al., 2001).

Metformin is an oral antihyperglycemic drug used in the management of type 2 diabetes. It acts by stimulating the release of insulin from pancreas. It lowers both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours necessitates its administration in multiple doses daily. The oral therapy with Metformin has also been associated with gastric disturbances like stomach pain or discomfort. and sometimes severe and fatal hypoglycemia.[2] Since this drug is usually intended to be taken for a long period, so patient compliance is also very important (Gua et al., 1995; Gandhi et al., 1992; Harris et al., 1992; Takahshi et al., 1997; Libero et al., 2007). Therefore, there is always a need to develop a sustained release formulation of Metformin. Thus an attempt has been made to develop controlled released buccoadhesive patches bearing. Metformin for improving

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and enhancing bioavailability in controlled release fashion and circumvent the hepatic first pass effect by administering the drug through buccal mucosa. The present work deals with the formulation and characterization of Metformin bearing mucoadhesive patches which were prepared by solvent casting method using drug coat RL 100 and HPMC E 15 as polymer.

Materials and methods

Chemicals and reagents

Metformin (USP) was received as a gift sample from Cipla, Mumbai. Mucoadhesive polymers HPMC E 15 and Drugcoat RL 100 were purchased from Himedia, Mumbai and. All others chemical used in the study were of analytical grade.

Preparation of buccal patches

Controlled released bilayered buccoadhesive patches were prepared by solvent casting technique given by Takahshi et al., 1997, using aluminium foil cup with ethylcellulose as a backing layer, Drugcoat RL 100 as a primary layer, and HPMC E 15 as a secondary layer polymers along with propylene glycol as a plasticizer. Ethyl cellulose (500 mg) was dissolved in 10 ml of acetone and then 0.2 ml of dibutylphthalate was added which serve as a film forming agent. This solution was poured over aluminium foil cups of diameter 9 cm and kept for drying. Primary layer solution was prepared by dissolving Drugcoat RL 100 in 10 ml acetone, followed by addition of propylene glycol and 25%w/w Metformin with stirring. Then solution of primary polymer was poured over pre-dried backing layer. Petridish was kept aside for complete evaporation of acetone and for drying. Secondary layer was prepared by dissolving HPMC E 15 in 10 ml water followed by addition of propylene glycol and 200 mg Metformin. After stirring, this solution was poured over pre-dried primary layer and kept aside for 24 hr for drying. Different patches were formed using different concentration of Drugcoat RL 100 **(Table 1)**.

Characterization of buccal adhesive Patches

Film weight and Thickness

For evaluation of film weight three films of same size from every formulation were taken and individually weighed in digital balance (Shimadzu, AY 220). The average weights were calculated. Similarly, three films of each formulation were taken and the film thickness was measured using micrometer Screw Gauge (NISCO) at three different places and the mean value was calculated (Table 2).

Folding Endurance

Three films of each formulation of size 22 cm^2 were cut using 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 (Table 2).

Tensile Strength

A tensile strength of patch is the total weight, which is required to break the patches dosage form. The tensile strength was determined by a device having rectangular frame with two plates made up of Plexiglas. This device consist of two plate in which one is stationary and another is movable, which can be pulled by loading weights on the string (Betz et al., 2003; Satishbabu et al., 2008). The 22 cm^2 film of each formulation was fixed between the stationary and movable plate. The force needed to fracture the film was determined by measuring the total weight loaded on the string. The weight loaded to break the patches was taken as tensile strength. Measurements were run in three replicates for each film, and results shown in Table 2. The following equation was used to calculate the tensile strength of the films:

Tensile strength (gcm^{-2}) = Force at break (g)/ Initial cross-sectional area of the sample (cm^2)

Surface pH

For the determination of surface pH of the patches, a combined glass electrode was used. The films were allowed to swell by keeping them in contact with PBS (pH 6.8) for 2 hr at room temperature and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 min. The mean value of three films was calculated and results were recorded in Table 2.

Percent Swelling

After determination of the original film weight, three films of each formulations were allowed to swell on the surface of agar plate (2%) kept in an incubator maintained at 370.2°C (Dhote et al., 2015). Increase in weight of the film (n=3) was determined at every 1 hr interval for up to 6 hr.

The Percent swelling (% S) was calculated using the following equation:

Percent swelling (% S) = $(X_t - X_0)/ X_0 \, 100$

Where,

X_t is the weight of the swollen film after time t

X_0 is the initial film weight at time t_0

The mean values of three readings were calculated and results were shown in figure 2.

Percent moisture sorption

Three films (11 cm size) of each formulation were dried in the oven at (30 2°C). After drying, the weight of each film was measured. The films were successively transferred to desiccators over saturated salt solutions of sodium nitrite at 25°C. After each 1st, 3rd and 5th day, the conditioned films were weighted (without exposure to atmosphere) and placed back to desiccators.

Percent moisture sorption was calculated using following formula:

% Moisture content ={(weight of exposed film-weight of conditioned film)/weight of conditioned film}x100

The mean value of three readings was calculated and results were shown in figure 3.

Drug Content

The patches (n=3) of specified area were weighed and dissolved in 10 ml PBS (pH 6.8) using dimethylformamide as co-solvent. The solution was filtered prior to drug analysis. The samples were analyzed spectrophotometrically at λ_{max} of 276 nm (Table 3).

***In-vitro* Studies**

Drug Release

The USP six station dissolution apparatus type-II was used for drug release study. The release study was carried out at 37 0.5ºC in PBS (pH 6.8) with a rotation speed of 50 rpm for 8 hr. The samples were withdrawn periodically and analyzed spectrophotometrically at λ_{max} of 276 nm. Figure 4 shows the results of *in vitro* drug release studies. Considering the desirable swelling index, drug content and other parameters as well as *in vitro* drug release the formulation BP2 was selected for further studies.

In-vitro Bioadhesion Test

The binding capability of the patches containing Metformin to buccal mucosa was evaluated in triplicate by following the method reported by Kumar *et al.* 2010. The reported device for studies was composed of two arm balance. The left arm of the balance was replaced by a small platinum lamina vertically suspended through a wire. The same side of movable platform was maintained in the bottom in order to fix the model mucosal membrane. For determination of the bioadhesion, the film was fixed to the platinum lamina using cyanoacrylate adhesive. A piece of goat intestinal mucosa, (3 cm long) was also glued to the same platform; the exposed film surface was moistened with 15 µl PBS (pH 6.8) and left for 30 sec for initial hydration and swelling. The platform was then raised upward until the hydrated film was brought into contact with the mucosal surface. A preload of 20 gm was placed over the platinum lamina for 3 min as initial pressure. On the right pan, a constant weight of 5 gm was added at 2 min intervals. The total weight required for complete detachment of film was recorded and the bioadhesion force per unit area of the film was calculated as follows.

$$F = (Ww \cdot g)/A$$

Where F is the bioadhesive force (g $cm^{-1}s^{-2}$), Ww is the mass applied in gm, g is the acceleration due to gravity in cms^2 and A is the surface area of the film in cm^2.

In Vitro Residence Time

The i*n vitro* mucoadhesive residence time was determined with the help of IP disintegration apparatus. The disintegration medium was 800 ml of PBS (pH 6.8) maintained at 37 2°C. The segment of buccal mucosa of goat (3 cm length) was glued to the surface of a glass slab, and then mucoadhesive films of BP2 formulation were hydrated on one surface using PBS (pH 6.8) and the hydrated surface was brought into contact with the mucosal membrane. Then glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded.

In vitro Buccal Permeation Studies

In vitro buccal permeation study was conducted using modified diffusion cell (Hango et al., 1997). It consists of an open-ended glass cylinder of approximate 4 cm diameter and a beaker filled with 100 mL PBS (pH 7.4). The excised goat buccal mucosa was tied delicately on to one end of the glass cylinder. The cylinder acts as donor compartment while the beaker act as a receptor compartment. The glass cylinder was fixed vertically in the glass beaker in such a way that the mucus membrane just baths the content of the beaker. This assembly set up was placed over a magnetic stirrer for constant stirring at temperature 371°C.

A piece of buccal patch (1x1 cm^2) was placed over the goat buccal mucosa. The samples were withdrawn at different time intervals, filtered, diluted suitably and drug concentration was measured spectrophotometrically at λ_{max} 276 nm.

Result and discussion

Buccoadhesive patches of Metformin were prepared using mucoadhesive polymers HPMC E15 and with different concentration of Drugcoat RL 100. The developed patches were characterized for their physical characteristics, bioadhesive performance, release characteristics, surface pH, thickness, folding endurance, drug content uniformity, percent swelling, *ex vivo* permeation and *in vivo* performance. Physicochemical characteristics of the patches were shown in Table 2. Based on the quantities of the polymer Drugcoat RL 100, ranging from 2 to 8% *w/v*, the film weight was found to increase from 32.7 0.80 to 38.2±0.13 mg, respectively with the marginal increase in thickness that was found to be 0.33 0.012 to 0.43 0.025 mm. This may be due to increase in concentration of polymer. The surface pH of all the formulations were determined in order to investigate the possibility of any irritation effects. The surface pH of all the formulations was found to be near to salivary pH, this indicates that all the

formulations are free from any type of mucosal irritation.

Table 1. Different Patch combinations

Formulation code	Formula Composition			
	Drug concentration (%w/w)	Polymer 1 (mg)	Polymer 2 (mg)	Propylene glycol (%)
P1	25	200	500	30
P2	25	400	500	30
P3	25	600	500	30
P4	25	800	500	30

Polymer 1- Drugcoat RL 100; Polymer 2- HPMC E 15

Table 2. Physical evaluation of different Buccal Patches

Parameters	BP-1	BP-2	BP-3	BP-4
Film weight (mg)	32.7 ± 0.8	34.1 ± 0.32	37.0 ± 3.35	38.2 ± 0.13
Thickness (mm)	0.33 ± 0.012	0.37±0.03	0.43±0.04	0.43 ± 0.025
Folding Endurance	266 ± 23	278 ± 04	284 ± 55	289 ± 03
Tensile strength (gcm^{-2})	281 ± 3.5	289 ± 1.9	295 ± 2.5	332 ± 4.2
Surface pH	6.6 ± 0.1	6.7 ± 0.1	6.6 ± 0.2	6.7 ± 0.2

Mean ± SD (n=3)

Table 3. Drug content of different buccal patches

Parameters	BP-1	BP-2	BP-3	BP-4
Drug content (%)	94.23±2.1	95.13±3.4	96.22±2.15	97.11±3.2

Mean ± SD (n=3)

Table 4. *In vitro* Bioadhesion Studies of Selected Buccal Patch

Formulation code	Bioadhesive strength ($g/cm.s^2$)
BP2	76.65±3.86

Mean ± SD (n=3)

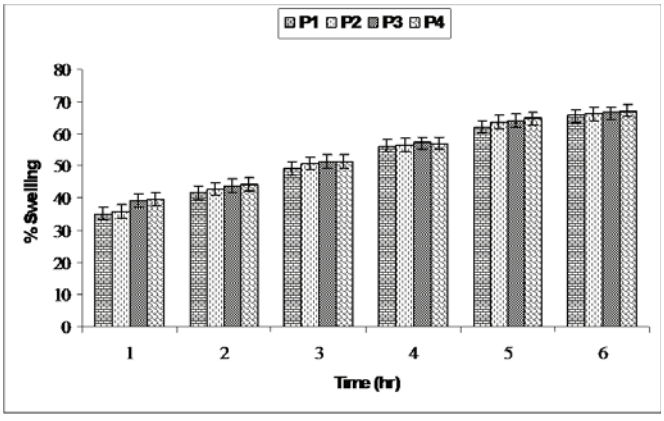

Figure 1. Percent swelling of different buccal patches

To find out the flexibility and tensile strength of the patches, folding endurance test and tensile strength test were performed. The folding endurance values range from 266±23 to 289±03 whereas tensile strength values range from 284 3.5 to 332±4.2 g/cm² **(Table 2)**. The result of studies showed that upon increasing the concentration of polymer, the flexibility and tensile strength of the patches increases. This may be due to strong covalent bonding between polymer and drug (Birudaraj et al., 2009; Kumar et al., 2010).

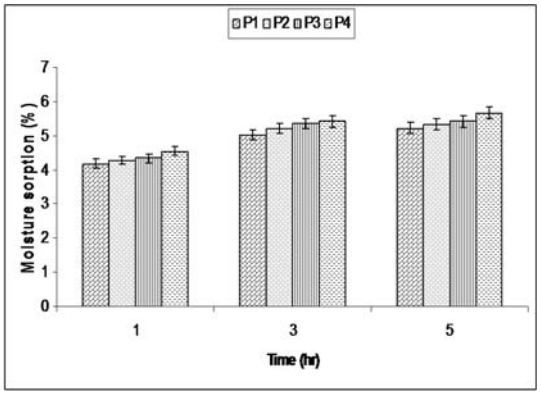

Figure 2. Percent moisture sorption of different buccal patches

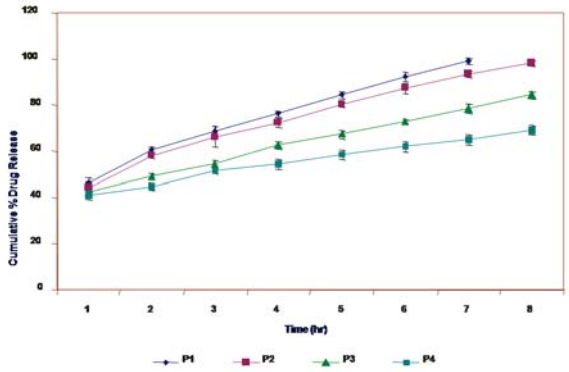

Figure 3. Cumulative % drug release from different buccal patches

Appropriate swelling behavior of buccal films is the essential property for uniform and prolonged release of the drug with effective mucoadhesion. During the swelling studies, it was found that, in the first hr approximately 38% swelling occurred in all the four formulations. This may be due to the hydrophilic nature of the secondary layer polymer, which was HPMC E 15. Further, negligible change in swelling and moisture sorption of the films from BP1 to BP4 were observed i.e., apporoximatly 56 % in 6 hr **(Figure 1 and 2)**. This may be due to the hydrophobic nature of the Drugcoat RL 100 polymer which avoided the penetration of water to the patches.

Drug content of different formulations were found to be in the range of 94.23 ± 2.1 % to 97.11 ± 3.2 % of Metformin for formulation BP1 to BP4 **(Table 3)**. On the basis of drug content studies it was concluded that the drug was dispersed uniformly throughout the film.

The drug release profiles of Metformin from formulations BP1 to BP4 are shown in **Figure 3**. Results of drug release studies clearly indicate that the drug release was governed by polymer concentration. No lag time was observed as when the patch was directly exposed to the dissolution medium. In the first hr approximately 40% drug was released. This fast release of the drug was due to the

erodible, hydrophilic layer of polymer HPMC E 15. The initial high percentage of drug release may be because of high water absorption capacity of hydrophilic polymer which leads to the high rate of dissolution. The hydrophilic polymer HPMC E15 dissolves and creates pores as well as channels for the diffusion of drug from patches. Further slow release of the drug is due to the hydrophobic layer of Drugcoat RL 100. The presence of hydrophobic polymer reduces the penetration of the dissolution medium into the patches and retarded the drug release from the formulation patches BP1 to BP4. Maximum drug release 98.41 ± 1.34% within 8 hr was found to be with formulation BP2, therefore it was selected for further studies.

The bioadhesive force of the formulation BP2 was found to be 76.65±3.86 g/cms^2 **(Table 4)** and the mucoadhesive residence time on the buccal mucosa of the goat was found to be 8.2±0.2 hr. The mucoadhesive studies indicated that the formulation BP2 films showed good mucoadhesive property, which is desirable property for route of drug administration.

Therefore, the results suggested from in vitro release that when the drug loaded buccal patch will administered the it will reduce the blood glucose level for longer period of time due to controlled release of Metformin from the patches. Thus it can be concluded that the developed bilayered buccoadhesive system have potential to deliver Metformin in controlled fashion.

Conclusion

The *in vitro* drug release studies suggested that mucoadhesive buccal films bearing Metformin were able to deliver the drug at a controlled rate for an extended period of time. The proposed system is expected to be a substitute of the tablets. Newly developed system would also likely to overcome all the drawbacks of the presently available therapy of Metformin. Thus, developed system might be completely safe, effective and convenient drug delivery system for treatment of diabetes.

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