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FORMULATION AND EVALUATION OF BUCCAL BIOADHESIVE TABLETS USING GLIMEPIRIDE AS A MODEL DRUG

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ABSTRACT

Objectives: The present investigation is concerned with formulation and evaluation of bioadhesive buccal tablets containing antidiabetic drug, Glimepiride to circumvent the first pass effect and to improve its bioavailability because bioadhesion has shown renewed interest for prolonging the residence time of bioadhesive dosage forms through various mucosal routes in drug delivery applications. Bioadhesive-based topical and local systems have shown enhanced bioavailability. Bioadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow. Drug delivery across the mucosa bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes and with reduction in dosing frequency and dose related side effects. **Methods:** The tablets were prepared by direct compression method. Six formulations were developed with varying concentrations of polymers like sodium alginate, PVP and magnesium stearate. The tablets were tested for weight variation, hardness, surface pH, drug content uniformity, percentage swelling index, bioadhesive strength, *ex-vivo* residence time *in-vitro* drug dissolution study, *in-vitro* drug release kinetic study, *ex-vivo* permeation study and Stability study. **Results:** FTIR studies showed no evidence on interactions between drug, polymers, and excipients. The surface pH, bioadhesive strength was found to be 6.22, 16g and, respectively. The formulation containing 4 mg of Glimepiride exhibited 6 h sustained drug release i.e. 93.98±0.8% with desired therapeutic concentration. The drug permeation from the formulation was slow and steady and 3.56 mg of Glimepiride could permeate through sheep buccal membrane with a flux of 0.27 mg hr^{-1} cm^{-2}. The *in-vitro* release kinetics studies reveal that the formulation fits well with zero order kinetics. **Conclusion:** Hence, it was concluded that the formulation was suitable for all the evaluation parameters and can be permeated through human buccal mucosa.

Keywords: Bioadhesive buccal tablets, Bioadhesive strength, Swelling index

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INTRODUCTION

The lining in the oral cavity serves as a potential delivery route that involves the administration of active pharmaceutical ingredients through buccal mucosa [**1, 2**]. Some bioavailability problems such as first pass metabolism and drug degradation in the gastrointestinal tract can be avoided by delivering the drug via buccal route [**3**]. The buccal route has auspicious benefits as an alternative to other traditional method of systemic drug administration and hence investigators worldwide have intensive attention on the development of buccal delivery [**4**]. Additionally, the buccal cavity is effortlessly accessible for self-medication and drug absorption is concluded in case of toxicity by removing the dosage form from the buccal cavity. The objective of the current research work is to formulate and evaluate bioadhesive buccal tablets containing Glimepiride to increase bioavailability of drug and to avoid hepatic first pass effect [**5, 6**].

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration-hyperglycemia-caused by insulin deficiency. Glimepiride was selected as model drug because the drug shows promising pharmacokinetics and physicochemical properties required for buccal delivery system. Glimepiride is medium to long acting sulfonyl urea antidiabetic drug. It is classified as first third generation sulfonyl urea, currently available for treating hyperglycemia in non-insulin dependent diabetes mellitus. It is used to treat type 2 diabetes mellitus. It lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors. It has protein binding >99.5% and half-life

of 5 hrs with molecular weight of 490.616 [**7**]. It has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy. Since It is usually intended to be taken for a long period, so for improving patient compliance buccal tablets of glimepiride are considered as a potential drug delivery system.

MATERIALS AND METHOD

Glimepiride, Sodium Alginate, PVP, Lactose, MCC, Talc, Magnesium stearate, buccal mucosa, Polyethylene for packing, phosphate buffer of pH 6.8, Tyrode solution.

Preformulation Studies

Bulk Density

Bulk density was determined (bulk density apparatus, konark instruments, India) by taking the dried granules in a measuring cylinder and measures the volume and weights of the total granules [**8**].

Bulk Density = Total Weight / Total Bulk Volume

Tapped Density

Tapped density was determined by taking the dried granules in a measuring cylinder and measures the volume of granules after 100 tapping and weight of the total granules.

Tapped Density = Total Weight / Total Tapped Volume

Compressibility Index

Compressibility index was determined by placing the dried granules in a measuring cylinder and the volume (Vo) was noticed before tapping, after 100 tappings again volume (V) was noticed. Compressibility index = (1- Vo/V) * 100

Where, Vo = volume of powder/granules before tapping

V = volume of powder/granules after 100 tappings.

Angle of Repose

Angle of repose was determined by measuring the height, radius of the heap of the powder bed. A cut system funnel was fixed to a stand and the bottom of the funnel was fixed at a height of 5 cm from the plane. Powder bed were placed in funnel and allowed to flow freely and measure the height and radius of the heap of powder bed. These studies were carried out before and after incorporating lubricants/ glidants.

$\tan \varphi = h/r$

Where h = height of heap of granules; R = radius of heap of granules

Hausner's Ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. Hausner's ratio is calculated by the formula:

H = Bulk Density/ Tapped Density

Where, H = hausner's ratio

Drug Excipient Compatibility Studies

The drug polymer and polymer-polymer interaction was studied by the FTIR spectrometer using. The characteristic peaks were recorded.

Preparation of Glimepiride Bioadhesive Buccal Tablets

Buccal tablets were prepared by a direct compression method. Before going to direct compression all the ingredients were screened through sieve no.100. Except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. The mixture is compressed using tablet compress machine. All tablets contained MCC as filler, magnesium stearate as lubricant and lactose as diluent and bioadhesive polymers sodium alginate and PVP [**9, 10**].

Evaluation of Glimepiride Bioadhesive Buccal Tablets

Weight Variation

Ten tablets were weighed using an electronic balance and the average weight was calculated.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated [**11**].

Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed, and the percentage loss was determined.

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper. The average values were calculated.

Content Uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture 4 mg of Glimepiride equivalent of mixture was extracted thoroughly with 100 mL of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 228 nm. This procedure was repeated thrice and this average was chosen.

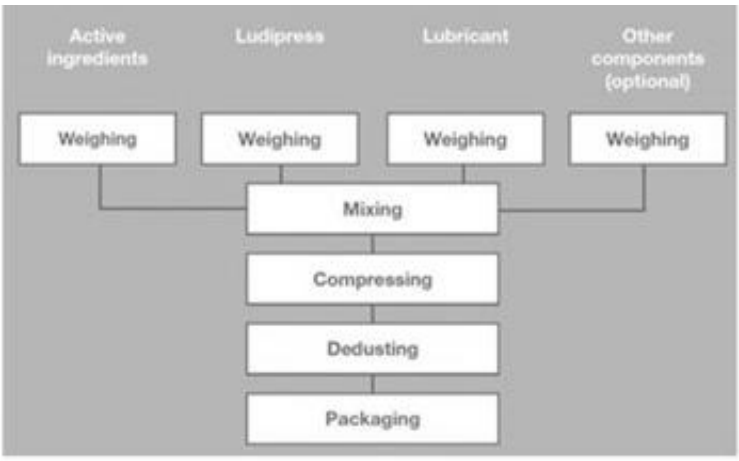

Figure 1: Flow diagram of tablets preparation.

Surface pH

The microenvironment pH (surface pH) of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Battenberg *et al* was used to determine the surface pH of the tablets. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 mL of distilled water (pH 6.5 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min [**12**].

Bioadhesion Studies

In evaluation of adhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. In present study, sheep buccal mucosa was used as a model mucosal surface for bioadhesion testing. Immediately after slaughter, the buccal mucosa was removed from the sheep and transported to laboratory in tyrode solution and kept it at 40ºC. The composition of tyrode solution (g/L) is sodium chloride 8, potassium chloride 0.2, calcium chloride dihydrate 0.134, sodium bicarbonate 1.0, sodium dihydrogen phosphate 0.05 and glucose 1.0 [**13**].

The Mucoadhesive forces of the tablets were determined by means of mucoadhesive measuring device. The sheep buccal mucosa was cut into strips/pieces and washed with tyrode solution. At time of testing a section of sheep buccal mucosa (c) was secured keeping the mucosal side out, on the upper glass vial (B) using rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1 cm. The vial with the sheep buccal mucosa (C) was stored at 37 °C for 10 min.

Then one vial with section of sheep buccal mucosa and another vial were fixed on height adjustable pan. To a lower vial a tablet was placed with the help of bilayered adhesive tape, adhesive side facing downward. The height of the lower vial was adjusted so that a tablet could adhere to the sheep buccal mucosa on the upper vial. A constant force was applied on the upper vial for 2 min, after which it was removed and the upper vial was then connected to the balance. Then the weight on right side pan was slowly added in an increment of 0.5 g, till the two vials just separated from each other. The total weight (g) required to detach two vials was taken as a measure of Mucoadhesive strength. From this mucoadhesive strength, the force of adhesive was calculated [**14**].

Force of adhesion (N) = Bioadhesive strength/100x9.81.

Swelling Study

Six buccal tablets were individually weighed (W1) and placed separately in Petri dishes with 5 mL of phosphate buffer of pH 6.8. At the time interval of 1, 2, 4, 6, 8 and 12 h, tablet was removed from the Petri dish and excess water was removed carefully using the filter paper. The swollen tablet was then reweighed (W2) and the percentage hydration were calculated using the following formula:

Percentage hydration = [(W2-W1)/ W1] ×100

In-vitro Dissolution Studies

The *in-vitro* dissolution study was conducted. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8). The release was performed at 37 °C ± 0.5°C, at a rotation of speed of 50 rpm. 5 mL samples were withdrawn at predetermined time intervals (1 to 6 h) and the volume was replaced with fresh medium. The samples were filtered through Whitman filter paper No.40 and analyzed for Glimepiride after appropriate dilution by UV spectrophotometer at 228 nm. The percentage drug release was calculated using the calibration curve of the drug in phosphate buffer pH 6.8 [**15**].

Drug Release Kinetic Studies

To analyze the mechanism of the drug release rate kinetics of the dosage form, the *in-vitro* dissolution data was fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model, to study the drug release from the dosage form [**16**].

RESULTS AND DISCUSSION

Sodium alginate is a polymer that imparts transmucoscal absorption promoting character and provides disintegrating property to help accelerate disintegration of the tablets. Magnesium stearate and talc are lubricants that provides anti adherent property so that powder can't stick to the surface of the punch machine. Lactose is a diluent that increases compressibility property of powder and Microcrystalline cellulose is used as a binder that compress the powder easily [**17-19**]. Angle of repose of powder was 31 that indicates good flow property because the lactose used as a diluent that increases the flow property as well as compressibility property. Bulk and tapped density was found out to be 3.47 g/ml and 5.26 g/ml respectively. In post compression parameters weight variation found to be 148.7 that is in the acceptable limits. Deviation occurs because of improper filling of die while compressing tablets or may be due to error in the instrument so the weight variation may be affected by compression force applied by punching machine. The hardness of the tablets was 3.78 kg/cm^2 that is within the acceptable limits. Friability percentage was 0.13% that is in acceptable limits. It can also be affected by increasing or decreasing the amount of binder. Bioadhesive strength was found to be 16 g and the bioadhesion characteristics were affected by concentration of the bioadhesive polymers and Bioadhesive force was found to be 1.57 N that is necessary for the drug to show adhesion property that is within the range [**20, 21**]. Drug release study showed that it follows zero order kinetics. Percentage hydration was observed, and it was found that the tablet was hydrated and this may be due to quick hydration of polymers like sodium alginate, PVP

Table 1: Rheological characteristics of powder mixture.

Bulk Density (g/ml)	0.47
Tapped Bulk Density (g/ml)	0.526
Angle of Repose (θ)	31(good)
Carr's Index **(%)**	14(good)
Hausner's Ratio	1.12(good/free flow)

Table 2: Hardness, thickness, weight variation, % friability, surface pH and drug content of glimepiride buccal tablets.

Hardness (Kg/cm^2)	3.78
Thickness (mm)	3.3
Wt.Variation (mg)	148.7±0.47
Friability (%)	0.13
Surface pH	6.22
Drug content (%)	95.35
Bioadhesive Strength(gm)	16
Bioadhesive Force (N)	1.57

Table 3: Percentage of hydration of glimepiride buccal tablets.

Time (hr)	% hydration
0	0
1	43.22
2	78.1
3	88.9
4	122.0
6	153.2
8	211.1

CONCLUSION

Glimepiride bioadhesive buccal tablets could be formulated using PVP and sodium alginate. The formulation was showing the maximum percentage drug release. The *in-vitro* drug release kinetics studies revealed that all the formulations fit to zero-order kinetics. It was concluded that the formulation was suitable for all the evaluation parameters and can be fruitful through human buccal mucosa.

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