

## PREPARATION OF GLIMEPIRIDE MUCOADHESIVE TABLETS BY DIRECT COMPRESSION METHOD AND THEIR IN-VITRO EVALUATION

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**Objectives:** The present investigation is concerned with formulation and evaluation of mucoadhesive buccal tablets containing antidiabetic drug, glimepiride, to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. **Methods:** The tablets were prepared by direct compression method. The tablets were tested for weight variation, hardness, surface pH, drug content uniformity, percentage swelling index, bio adhesive 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, bio adhesive strength, ex-vivo residence time and swelling index of formulation was found to be  $6.80 \pm 0.02$ ,  $36.3 \pm 0.04$ g, 325min and  $289.8 \pm 0.52\%$ , respectively. The formulation containing 4 mg of glimepiride exhibited 6 h sustained drug release i.e.  $93.98 \pm 0.8\%$  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  $0.27 \text{ mg hr}^{-1} \text{ cm}^{-2}$ . The in-vitro release kinetics studies reveal that all formulations fits well with zero order kinetics and followed non-Fickian diffusion mechanism. **Conclusion:** Hence, it was concluded that the best formulation was suitable for all the evaluation parameters and can be permeated through human buccal mucosa.

**Keywords:** Mucoadhesive buccal tablets, Ex-vivo residence time, Swelling index, glimepiride

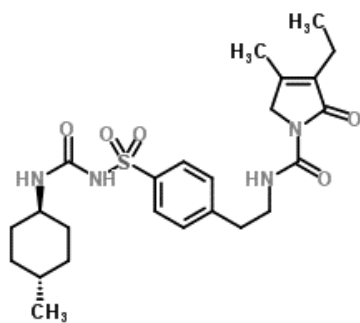
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### INTRODUCTION

Glimepiride is an oral antidiabetic drug which belongs to the sulfonylurea group and usually given as an oral antidiabetic therapy for patients with type 2 diabetes mellitus. Glimepiride acts to lower blood glucose by stimulating the release of insulin from pancreatic  $\beta$ -cells [1, 2].

It is used to lower blood sugar in patients with high blood sugar (diabetes) [3, 4]. Glimepiride is indicated to treat type 2 diabetes mellitus; its mode of action is to increase insulin production by the pancreas. It is not used for type 1

diabetes because in type 1 diabetes the pancreas is not able to produce insulin. The more common side effects that can occur with glimepiride include low blood sugar (hypoglycemia), trembling or shaking, nervousness or anxiety, irritability, sweating, lightheadedness or dizziness, headache, fast heart rate or palpitations, intense hunger, fatigue or tiredness, headache, nausea, dizziness, weakness, unexplained weight gain [5-7].



**Figure 1:** Chemical structure of glimepiride.

Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time [8]. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term “mucoadhesion” is used. Oral route is the most preferred route for the delivery of any drug. Drug delivery via the membranes of the oral cavity can be subdivided as 1. Sublingual delivery: This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, 2. Buccal delivery: This is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), 3. Local delivery: This is drug delivery into the oral cavity. Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the

bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Hydration of the polymer plays a very important role in bioadhesion. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs [9].

## **MATERIALS AND METHODS**

### **Chemicals and Reagents**

Glimepiride, Sodium Alginate, PVP, Lactose, MCC, Talc, Magnesium stearate

### **Preparation of Mucoadhesive 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 [10].

### **Evaluation of Mucoadhesive Buccal Tablets**

#### *Drug content*

The drug content of glimepiride prepared tablet of each batch of the formulation was determined. Ten tablets weighted and finely powdered. An amount of powder equivalent to 4 mg of powder was accurately weighted and dissolved in 6.8 phosphate buffer. The resulting solution was suitably diluted and analyzed on UV spectrophotometer at 276 nm [11].

#### *Hardness*

The hardness of tablets is directly proportional to friability loss and convenient in handling the tablets. Breaking under the condition of storage, transportation, and handling before the uses

depends on its hardness. Monsanto hardness tester was used to measure the hardness of tablets of each batch. The hardness expressed in terms of kg/cm<sup>2</sup> [12].

#### *Friability*

A friability test was conducted on the glimepiride buccal tablets using Friabilator. Approximately around twenty tablets were taken from each batch weighed for the initial weight (W1) and kept in friability machine at the speed of 100 rpm for a time of 2 minutes. After the specific time the tablets were collected and removed any loose dust was with the help of a soft brush before weighing. The tablets were weighed again as final weight (W2). The percentage friability was then calculated by,  $F = [(W1 - W2) / W1] \times 100$ .

Percentage Friability of tablets less than 1% is considered acceptable.

#### *Thickness*

The thickness of the tablets was determined using a thickness screw gauge. Five tablets from each batch were used and average values were calculated.

#### *Uniformity of weight*

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

#### *Surface pH*

The objective of study of surface pH of buccal tablet was to know whether the tablet causes any irritation to mucus membrane of buccal region. The buccal tablets were allowed to swell at 37 ± 1 °C for 2 hrs in 50 ml phosphate buffer (pH 6.8). The surface pH of swollen buccal tablets was measured by using pH paper [13].

#### *Swelling index study*

Swelling study of buccal tablets was done on 1% agar gel plates. Ten tablets of all the formulations are weighed and average weight of each tablets were calculated. The tablets were placed on the gel surface in Petri dishes, which

were placed in an incubator at 37 °C. The tablets were removed at time intervals of 1, 2, 3, 4, 5 and 6 hrs, excess water from the surface was carefully soaked using filter paper, and swollen tablets were weighed. The swelling index was calculated by using formula,

% Swelling index (S.I) =

$$\frac{\text{tablet wet weight} - \text{tablet dry weight}}{\text{tablet wet weight}} \times 100$$

#### *Ex Vivo residence time*

In vitro residence time for tablets was determined using USP disintegration apparatus. The disintegration medium was composed of 800 ml of phosphate buffer of pH 6.8 maintained at 37°C. A segment of rabbit buccal mucosa 3 cm length was glued to glass slab. The tablet surface was hydrated using 15 ml pH 6.8 and then hydrated surface brought into contact with the mucosal membrane. The tablets were fixed to glass slab and the slab was completely immersed in the buffer solution at lowest and wash out at highest point. The time necessary for complete erosion or detachment of tablets from mucosal surface was determined [13].

#### *In vitro release dissolution*

The in vitro dissolution tests were performed using the basket method of USP 24. With the aid of a dissolution apparatus (TDT 08L Dissolution Tester Electro Lab) rotating at 100 rpm. The dissolution medium was 900 ml phosphate buffer (pH 6.8) and the temperature maintained was at 37 ± 1 °C. Samples of the dissolution solution were withdrawn at definite time intervals. The dissolution media was then replaced by fresh dissolution fluid to maintain a constant volume. The solution was filtered to remove any undissolved solid particles. Then the concentration of in solution was measured with an Ultraviolet-Visible spectrophotometer at a wavelength of 276 nm [13].

## RESULTS AND DISCUSSION

### Hardness Test

The adequate tablet hardness is necessary requisite for consumer acceptance and handling. The measured hardness of the tablets of batch was ranged between  $4.0 \pm 0.09$  to  $4.6 \pm 0.05$  Kg/cm<sup>2</sup>. This ensures good handling.

### Thickness

The thickness of the tablets was found to be almost uniform in all formulation of batch. The thickness was found to be in the range of  $3.26 \pm 0.057$  to  $3.73 \pm 0.010$  mm (Fig. 2). None of the formulations showed a deviation. Hence, it is concluded that all the formulations complied the thickness test.

### Weight Variation

The weight variation test was conducted for each batch of all formulation as per Pharmacopoeia. The weight variation test for all the formulations complies with the limit ( $\pm 10\%$ ). The weight variations for formulation were ranged between  $149.0 \pm 0.20$  to  $151.1 \pm 0.48$  mg.

### Friability Test

The friability test for all the formulations was done as per the standard procedure. The results of the friability test were ranged between  $0.132 \pm 0.05$  to  $0.533 \pm 0.04\%$ . The data indicates that the friability was less than 1% in all formulations ensuring that the tablets were mechanically stable.

### Surface pH

Surface pH of all the formulations was found to be  $6.22 \pm 0.08$  to  $6.87 \pm 0.02$  (Fig. 2), which is well within the limit of acceptable salivary pH range of 5.6 to 7.1. Hence, it was concluded that all formulations could not produce any local irritation to the mucosal surface [14].

### Drug Content

The drug content of each batch of all the formulations was evaluated as per the standard protocol. The results indicate that the percentage of drug content was found to be  $95.28 \pm 0.18\%$  to  $104.12 \pm 0.65\%$ . Hence it is concluded that all the

formulations are following acceptable limits as per Indian Pharmacopoeia i.e.  $\pm 5\%$ .

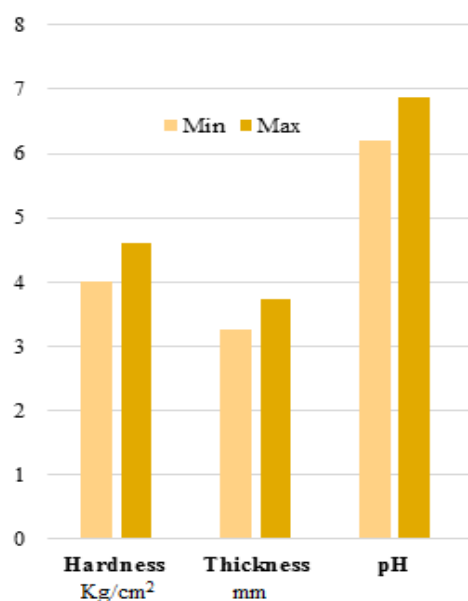


Figure 2: Parameters of mucoadhesive tablets.

### Ex-vivo Residence Time

The ex-vivo residence time is one of the important physical parameter of buccal mucoadhesive tablets. The Ex-vivo residence time was determined by using specially designed dissolution apparatus. The ex-vivo residence time found to be in the range of 230 minutes to 235 minutes (Fig 3).

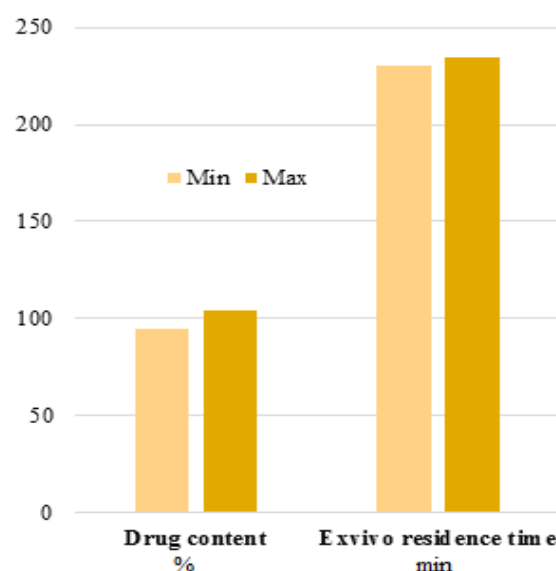


Figure 3: Drug content and ex vivo residence time of mucoadhesive tablets.

### Swelling Study

The swelling studies were conducted for all formulation. Tablets were hydrated generally by keeping the tablets in contact with water for 1 h to 12 h. The highest hydration (swelling) i.e.  $289.8 \pm 0.41\%$  was observed.

### In-vitro Dissolution Studies

In-vitro dissolution studies were designed to carry out in such a way that they simulate in-vivo conditions. The purpose of in-vitro release study was to provide a fast, easily performed and in-expensive method that correlates with the performance of dosage form in human subjects. The conditions of in-vitro dissolution test were well defined, standardized and enable comparison among various results. For in-vitro dissolution study, it was decided to carry out the dissolution in pH 6.8 phosphate buffer. The in-vitro drug release profile of formulation was  $90.77 \pm 0.6\%$ . During the study, it was observed that initially tablets were swollen and non-erodible over the period of 6 hours [15, 16].

### CONCLUSION

Glimepiride mucoadhesive buccal tablets were formulated. The formulation was evaluated for physicochemical parameters i.e. hardness, thickness, weight variation, friability, in vitro dissolution and disintegration studies. Friability test of glimepiride showed that the formulation is suitable for transport and storage. There was minimum loss of drug during transportation. Hardness test indicates that the tablets are hard enough and are not fragile. They possess the hardness that makes them suitable as a mucoadhesive dosage form. From the weight variation tests, we conclude that all the tablets formulated falls within the weight variations given by USP. This showed that we can have an estimate that these tablets contain almost equal. These tests indicated that the tablets formed are upto standards and are formulated accurately. Dissolution and disintegration studies were performed and estimated times are recorded.

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