FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF GLIPIZIDE

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ABSTRACT

Mucoadhesive tablets of Glipizide were prepared by using Tragacanth, Xanthan gum and Tamarind Gum as mucoadhesive polymers. Nine formulations were developed with varying concentrations of polymers. G1 to G9 formulations were composed of Tragacanth, Xanthan gum and Tamarind Gum in ratios of 1:1, 1:2 and 1:3. The formulated mucoadhesive buccal tablets were assessed for quality attributes like weight variation, hardness, thickness, friability, drug content, moisture absorption, surface pH and *in vitro* drug release studies. Optimized formulation G4 showed maximum release of the drug (99.61%). The FTIR results showed no evidence of interaction between the drug and polymers. All the evaluation parameters given the positive result and comply with the standards. The results indicated that the mucoadhesive buccal tablets of Glipizide may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in bioavailability of Glipizide through buccal mucosa.

Key words: Glipizide, Tragacanth, Xanthan gum, Tamarind Gum and Buccal tablets.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing .Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) A vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and (c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promote the residence time and act as controlled release dosage forms.

The use of many hydrophilic macromolecular drugs as potential therapeutic agents is their in adequate and erratic oral absorption. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. Based on our current understanding, it can be said that many drugs can not be delivered effectively through the conventional oral route.

The main reasons for the poor bio-availability of many drugs through conventional oral route are:

- ✓ Pre-systemic clearance of drugs.
- ✓ The sensitivity of drugs to the gastric acidic environment which leads to gastric irritation. Limitations associated with gastro intestinal tract like variable absorption characteristics.

Buccal mucosa composed of several layers of different cells. The Epithelium is similar to stratified squamous epithelia found in rest of the at least one of which is biological nature are held together by means of interfacial forces.[1]

Buccal drug delivery is a type of bioadhesive drug delivery especially it is a mucoadhesive drug delivery system is adhered to buccal mucosa.

- The term bioadhesion is commonly defined as an adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesive drug delivery systems, bioadhesion often refers to the adhesion between the excipients of the formulation (i.e. the inactive media) and the biological tissue.
- The term mucoadhesion can be considered to refer to a sub group of bioadhesion and, more specifically, to the case when the formulation interacts with the mucous layer that covers a mucosal tissue.

The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye. Hence mucoadhesive drug delivery system includes the following.

1. Buccal delivery system

2. Oral delivery system

3. Ocular delivery system

4. Vaginal delivery system

5. Rectal delivery system

6. Nasal delivery system[2]

Overview of the Oral Mucosa Structure The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer18, 19 can be seen in figure 1. The epithelium of the buccal mucosa is about 40- 50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days[3], and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress

(the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized[4]. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, nonkeratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide [5-7]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

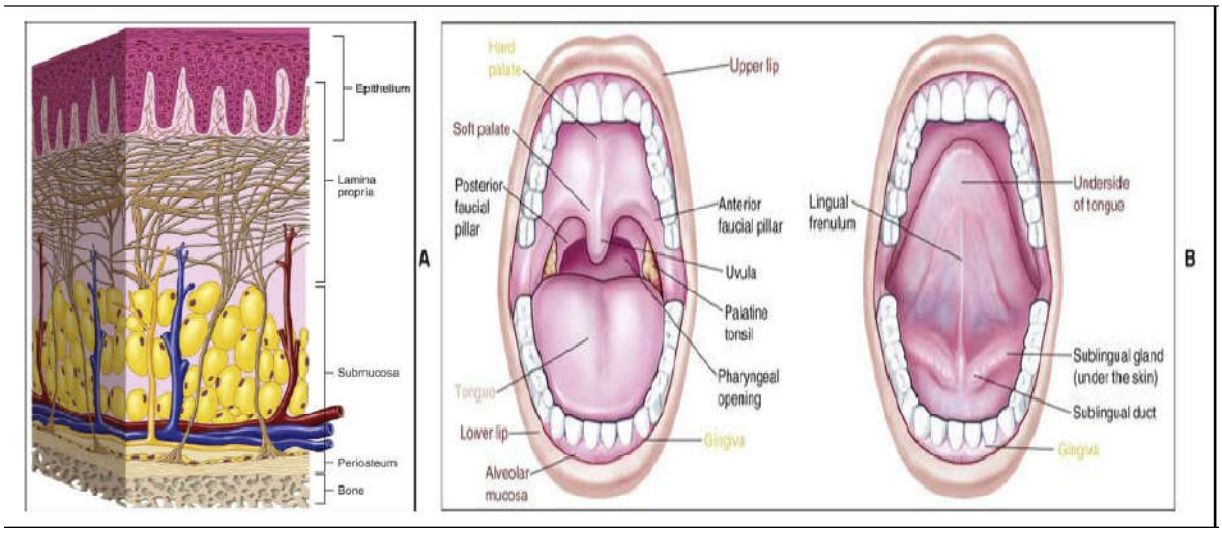

Figure 1: Anatomy of Oral Mucosa

MATERIALS AND METHODS

Glipizide Provided by SURA LABS, Dilsukhnagar, Hyderabad. Tragacanth from Zydus Cadila, Ahmedabad Xanthan gum from Acurate Pharma. Tamarind Gum from Sd fine Chem.Ltd. Mumbai. MCC from Chemdie Corporation. Magnesium stearate from Chemdie Corporation. Talc from Sd fine Chem.Ltd. Mumbai. Saccharin sodium from Sd fine Chem.Ltd. Mumbai.

METHODOLOGY

Preformulation studies

Analytical method used in the determination of Glipizide

Preparation of 0.1N HCl

Diluted 8.5mL of Concentrated Hydrochloric acid to 1000mL of Purified water and mixed

Preparation of 0.2M NaOH Solution

Dissolved 4g of Sodium hydroxide pellets in to 1000mL of Purified water and mixed

Preparation of pH 6.8 Phosphate buffer

Dissolved 6.805 g of Potassium dihydrogen phosphate in to 800mL of purified water and mixed added 112mL of 0.2M NaOH solution and mixed. Diluted to volume 1000mL with purified water and mixed. Than adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

Preparation of pH 7.4 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 195.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Preparation of standard graph in phosphate buffer pH 6.8

100 mg of Pure drug was dissolved in small amount of DMSO (5-10 ml), allowed to shake for few minutes and then the volume was made up to 100ml with phosphate buffer pH 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 6.8. From this secondary stock 0.5, 1, 1.5, 2, 2.5, ml was taken separately and made up to 10 ml with phosphate buffer pH 6.8 to produce 5, 10, 15, 20, 25 µg/ml respectively. The absorbance was measured at 227 nm using a UV spectrophotometer. Standard calibration curve values were shown in Table (3). The standard calibration curve of Glipizide in phosphate buffer pH 6.8 was shown in fig 2.

Preparation of standard graph in phosphate buffer pH 7.4

100 mg of drug was dissolved in small amount of DMSO and sonicated to dissolve and make the volume up to 100ml with phosphate buffer pH 7.4, from this primary stock(1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 7.4. From this secondary stock 0.5, 1, 1.5, 2, 2.5 ml were taken separately and made up to 10 ml with phosphate buffer pH 7.4, to produce 5, 10, 15, 20, 25 µg/ml respectively. The absorbance was measured at 230 nm using a UV spectrophotometer. Standard calibration curve values were shown in Table (4). The standard calibration curve of Glipizide in phosphate buffer pH 7.4 was shown in fig 3.

Solubility Studies

The solubility of Glipizide in phosphate buffer solution pH 6.8 was determined by phase equilibrium method. An excess amount of drug was taken into 20 ml vials containing 10 ml of phosphate buffers (pH 6.8). Vials were closed with rubber caps and constantly agitated at room

temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm Whattman's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 227 nm using a UV spectrophotometer.

The standard curves for Glipizide were established in phosphate buffers (pH 6.8) and from the slope of the straight line the solubility of Glipizide was calculated. The studies were repeated in triplicate (n = 3), and mean was calculated.

Evaluation of pre-compression blend:

The quality of tablet, once formulated, by rule is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characterization of blends produced. Prior to compression, granules were evaluated for their characteristic parameter such as Tapped density, Bulk density, Carr's index, Angle of repose, Hausner's ratio. Compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus. The various characteristics of blends tested are as given below:

Preparation of Tablets:

Then the powder blend was compressed into tablets by the direct compression method using 6mm flat faced punches. The tablets were compressed using a sixteen station LAB PRESS rotary tablet-punching machine. The weight of the tablets was determined using a digital balance and thickness with digital screw gauge. Composition of the prepared bioadhesive buccal tablet formulations of Glipizide were given in Table 1.

Table 1: Formulation Chart

INGREDIENTS (MG)	FORMULATION CODES								
	G1	G2	G3	G4	G5	G6	G7	G8	G9
Glipizide	5	5	5	5	5	5	5	5	5
Tragacanth	10	20	30	-	-	-	-	-	-
Xanthan gum	-	-	-	10	20	30	-	-	-

Tamarind Gum	-	-	-	-	-	-	10	20	30
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Saccharin sodium	10	10	10	10	10	10	10	10	10
Total weight	80	80	80	80	80	80	80	80	80

RESULTS AND DISCUSSION

Solubility Studies:

Table 2: Solubility studies

S.No	Medium	Amount present (µg/mL)
1	Phosphate pH 6.8 buffer	98.10
2	Phosphate pH 7.4 buffer	96.54

Saturation solubility of Glipizide in various buffers were studied and shown in the Table 2. The results revealed that the solubility of the Glipizide was increased from pH 6.8 to 7.4. The solubility of the Glipizide in phosphate buffer pH 6.8 is 98.10µg/mL and it was selected as the suitable media for the release studies because the pH of the phosphate buffer pH 6.8 is nearer to that of buccal mucosa pH.

Standard graph in phosphate buffer pH 6.8 (λ_{max} 227 nm)

Standard graph of Glipizide was plotted as per the procedure in experimental method and its linearity is shown in Table 3 and Fig 2**.** The standard graph of Glipizide showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Table 3: Standard graph values of Glipizide in pH 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
5	0.127
10	0.227
15	0.314
20	0.422
30	0.617

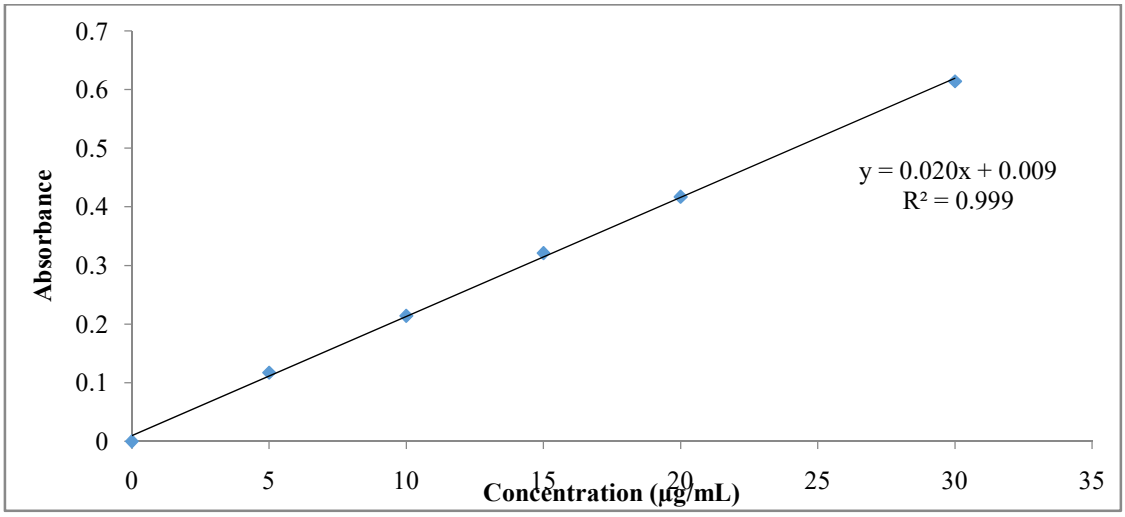

Fig 2: Standard graph of Glipizide in pH 6.8 phosphate buffer

Standard graph in phosphate buffer pH 7.4 (λ_{max} 230 nm)

Standard graph of Glipizide was plotted as per the procedure in experimental method and its linearity is shown in Table 4 and Fig 3. The standard graph of Glipizide showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Table 4: Standard graph values of Glipizide in pH 7.4 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
5	0.117
10	0.214
15	0.321
20	0.417
30	0.614

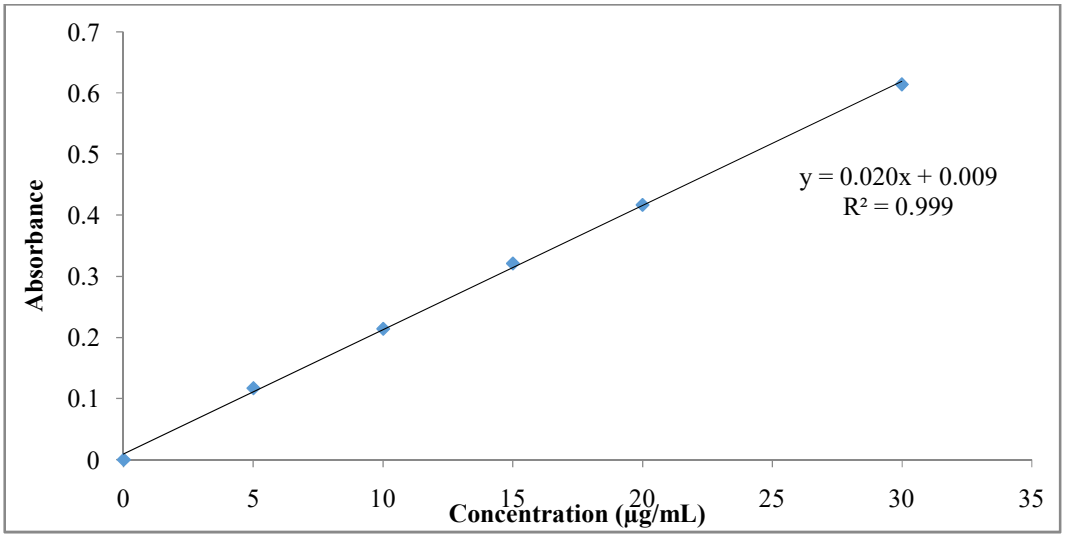

Fig 3: Standard graph of Glipizide in pH 7.4 phosphate buffer

Evaluation:

Characterization of pre-compression blend:

Table 5: Physical properties of pre-compression blend

Formulation Code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
G1	24.72 ± 0.01	0.345 ± 0.018	0.401 ± 0.012	13.97 ± 0.01	1.16 ± 0.02
G2	19.66 ± 0.02	0.332 ± 0.002	0.375 ± 0.015	11.46 ± 0.01	1.13 ± 0.01
G3	20.16 ± 0.015	0.465 ± 0.015	0.532 ± 0.001	12.59 ± 0.01	1.14 ± 0.01
G4	21.41 ± 0.01	0.421 ± 0.002	0.492 ± 0.002	14.43 ± 0.02	1.17 ± 0.02
G5	20.60 ± 0.015	0.382 ± 0.001	0.439 ± 0.002	12.98 ± 0.01	1.15 ± 0.01
G6	20.36 ± 0.015	0.523 ± 0.002	0.604 ± 0.017	13.41 ± 0.02	1.15 ± 0.01
G7	19.98 ± 0.01	0.348 ±0.001	0.401 ± 0.001	13.22 ± 0.01	1.15 ± 0.01
G8	40.13 ± 0.01	0.412 ±0.015	0.530 ±0.021	22.23 ± 0.01	1.29 ± 0.01
G9	39.90 ± 0.01	0.424 ± 0.001	0.517 ± 0.01	18.00 ± 0.01	1.21 ± 0.01

All the values represent n=3

Tablet powder blend was subjected to various preformulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be 11.46 to 22.23 which show that the powder has good flow properties. All the formulations has shown the hausner ratio 1.13 to 1.29 indicating the powder has good flow properties.

Evaluation of buccal tablets:

Physical evaluation of Glipizide buccal tablets: The results of the weight variation, hardness, thickness, friability and drug content of the tablets are given in Table 6. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.0 to 4.6 kg/cm^2 and the friability values were less than 0.61 % indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 1.01 – 1.92 mm. All the formulations satisfied the content of the drug as they contained 97.87-100.02 % of Glipizide. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Table 6: Physical evaluation of Glipizide buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
G1	78.47	1.01	3.9	0.54	98.24
G2	76.92	1.92	3.0	0.42	99.46
G3	79.30	1.35	4.3	0.36	100.02
G4	77.12	1.87	3.1	0.61	97.64
G5	80.12	1.28	4.2	0.50	98.99
G6	79.27	1.13	4.6	0.46	99.06
G7	80.04	1.79	3.1	0.40	98.42
G8	80.25	1.35	4.0	0.37	97.87
G9	77.80	1.60	3.8	0.29	98.31

***In vitro* release studies:**

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Glipizide from different formulations varies with characteristics and composition of matrix forming polymers.

Table 7: *In vitro* dissolution data for formulations L1 – L9

TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE								
	G1	G2	G3	G4	G5	G6	G7	G8	G9
0	0	0	0	0	0	0	0	0	0
0.5	21.59	17.19	20.14	31.06	25.39	20.92	18.82	15.10	11.58
1	26.34	36.30	23.39	38.26	31.19	28.03	22.09	17.49	20.16
2	37.20	45.11	30.92	46.17	37.24	32.51	31.99	27.60	26.09
3	52.87	62.24	35.57	50.96	46.08	40.99	38.46	35.18	34.10
4	68.46	69.97	44.26	56.32	57.77	45.42	50.06	44.82	53.23
5	79.22	74.43	56.41	68.24	64.69	54.60	56.33	53.99	57.42
6	86.97	81.19	62.14	74.12	71.53	60.17	78.10	65.76	65.99
7	97.17	87.13	74.06	89.03	76.11	77.96	86.71	78.14	76.37
8		91.06	87.79	99.61	90.72	85.12	94.13	88.34	81.83

Table 8: Moisture absorption, surface pH of selected formulations

Formulation Code	Moisture absorption	Surface pH
G2	83	5.82

G4	97	5.05
G7	92	6.10

The moisture absorption studies give important information of the relative moisture absorption capacities of polymers and it also give information regarding whether the formulations maintain the integrity or not. Among the selected formulations G4 formulation shown good moisture absorption.

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects. 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 surface pH of the selected formulations was found to be 5.05 to 6.10 and the pH was near to the neutral. These results suggested that the polymeric blend identified was suitable for oral application and formulations were not irritant to the buccal mucosa.

Release kinetics:

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Glipizide release from buccal tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table 9: Release kinetics and correlation coefficients (R^2)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
31.06	0.5	0.707	1.492	-0.301	1.838	62.120	0.0322	-0.508	68.94	4.642	4.100	0.541
38.26	1	1.000	1.583	0.000	1.791	38.260	0.0261	-0.417	61.74	4.642	3.952	0.689
46.17	2	1.414	1.664	0.301	1.731	23.085	0.0217	-0.336	53.83	4.642	3.776	0.866
50.96	3	1.732	1.707	0.477	1.691	16.987	0.0196	-0.293	49.04	4.642	3.660	0.981
56.32	4	2.000	1.751	0.602	1.640	14.080	0.0178	-0.249	43.68	4.642	3.522	1.120
68.24	5	2.236	1.834	0.699	1.502	13.648	0.0147	-0.166	31.76	4.642	3.167	1.475
74.12	6	2.449	1.870	0.778	1.413	12.353	0.0135	-0.130	25.88	4.642	2.958	1.684
89.03	7	2.646	1.950	0.845	1.040	12.719	0.0112	-0.050	10.97	4.642	2.222	2.420

99.61	8	2.828	1.998	0.903	-0.409	12.451	0.0100	-0.002	0.39	4.642	0.731	3.911

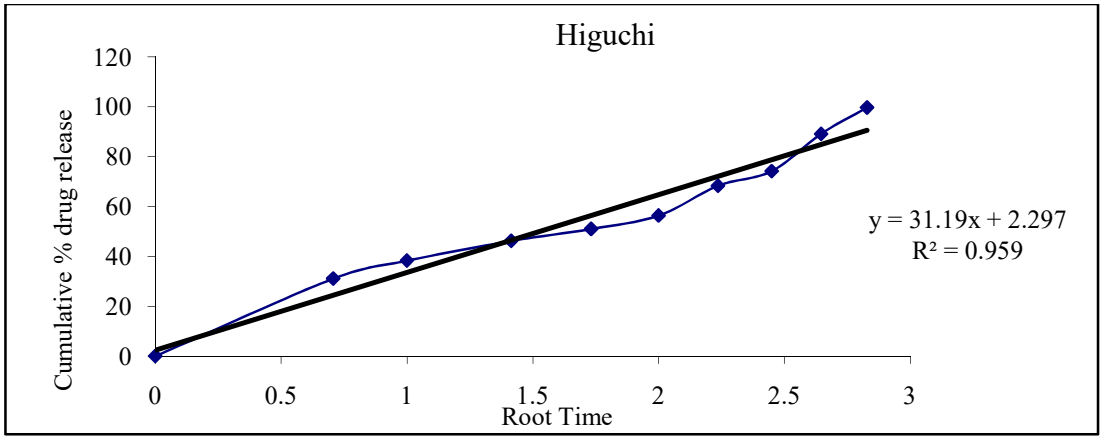

Fig 4: Higuchi plot of optimized formulation

This formulation was following Higuchi release mechanism with regression value of 0.959.

Drug – excipient compatibility studies by physical observation:

Glipizide was mixed with various proportions of excipients showed no color change at the end of two months, proving no drug-excipient interactions.

FTIR

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra of pure Glipizide drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Glipizide are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

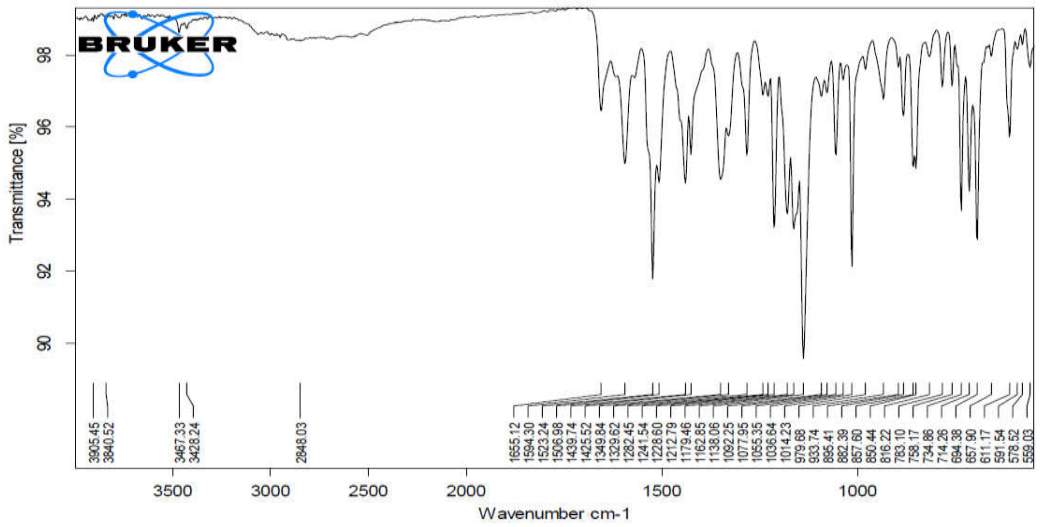

Fig 5: FTIR Peak of pure drug Glipizide

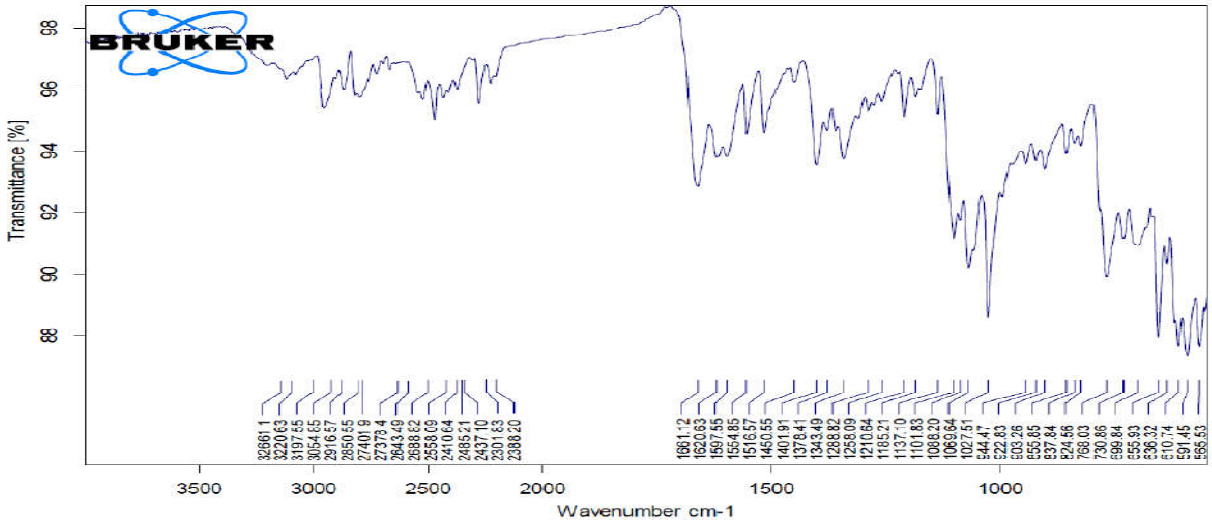

Fig 6: FTIR Peak of Optimised formulation

CONCLUSION

The present research was carried out to develop mucoadhesive buccal tablets of Glipizide using various polymers. The preparation process was simple, reliable and inexpensive. All the prepared tablet formulations were found to be good without capping and chipping. The mucoadhesive buccal tablets of Glipizide could be prepared using Tragacanth, Xanthan gum and Tamarind Gum polymers by using direct compression method. The prepared mucoadhesive buccal tablets subjected to infrared spectrum study suggested that there was no drug -polymer

interaction. All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeial specification. The surface pH of prepared buccal tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation. The *in-vitro* release of Glipizide was extended for 8h. Formulations G4 batch shows good *in vitro* drug release 99.61%. From the results of present investigation it can be concluded that Glipizide can certainly be administered through the oral mucosa and Xanthan gum is suitable for development of buccoadhesive system.

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