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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF GLIPIZIDE

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Abstract:

Glipizide is a medication used in the treatment of type 2 diabetes. The Mucoadhesive buccal tablets were prepared by direct compression method using Sodium Alginate, HPMC K4M and SCMC as mucoadhesive polymer. The compatibility studies of drug and excipients were performed by FT-IR spectroscopy. After examining the flow properties of the powder blends the results are found to be within prescribed limits and indicated good flowing property, hence it was subjected to tablet compression. The tablets were evaluated for post compression parameters like weight variation, hardness, thickness, friability, drug content uniformity, Surface pH, in-vitro studies like drug release. Formulation (F4) containing HPMC K4M in the ratio of (1:1) showed maximum drug release of 99.46% in 8 hrs. The drug content of shown highest of 99.24 %, Surface pH was found to be 6.12. All the evaluation parameters given the positive results and comply with the standards. The results indicate that the mucoadhesive buccal tablets of Glipizide may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Glipizide through buccal mucosa.

Key words: *Glipizide, Sodium Alginate, HPMC K4M, SCMC and Buccal tablets.*

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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. 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.

Permeability:

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin[8]. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

Mechanism of mucoadhasive:

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. Subsequently low chemical bonds can become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density.

MATERIALS:

Glipizide-Provided by SURA LABS, Dilsukhnagar, Hyderabad, Sodium Alginate Zydus -Cadila, Ahmedabad, HPMC K4M-Acurate Pharma, SCMC-Sd fine Chem.Ltd. Mumbai, MCC- Chemdie Corporation, Magnesium stearate-Chemdie Corporation,Talc-Sd fine Chem.Ltd. Mumbai, Saccharin sodium-Sd fine Chem.Ltd. Mumbai**.**

METHODOLOGY:

Preformulation studies

Analytical method used in the determination of Glipizide

Preparation of 0.2M Potassium Dihydrogen Orthophosphate Solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 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 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 Methanol (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 0.2, 0.4, 0.6, 0.8, 1 ml was taken separately and made up to 10 ml with phosphate buffer pH 6.8 to produce 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 270 nm using a UV spectrophotometer. Standard calibration curve values were shown in Table (9.1). The standard calibration curve of Glipizide in phosphate buffer pH 6.8 was shown in fig 9.1.

Preparation of standard graph in phosphate buffer pH 7.4

100 mg of drug was dissolved in small amount of phosphate buffer 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 0.2, 0.4, 0.6, 0.8, 1 ml were taken separately and made up to 10 ml with phosphate buffer pH 7.4, to produce

2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 275 nm using a UV spectrophotometer.

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 ten 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 8.4.

Table : Formulation Chart

INGREDIENTS (MG)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glipizide	5	5	5	5	5	5	5	5	5
Sodium Alginate	10	20	30		-	-	-	-	-
HPMC K4M	-	-	-	10	20	30	-	-	-
SCMC	-	-	-	-	-	-	10	20	30
MCC	61	51	41	61	51	41	61	51	41
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Saccharin sodium	15	15	15	15	15	15	15	15	15
Total weight	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION:

Solubility Studies:

Table: Solubility studies

S.No	Medium	Amount present (µg/mL)
1	Phosphate pH 6.8 buffer	92.10
2	Phosphate pH 7.4 buffer	90.27

Saturation solubility of Glipizide in various buffers were studied and shown in the Table 9.1. 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 92.10µg/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} 304 nm):

The standard graph of Glipizide showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer-Lamberts" law.

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

Concentration (µg/mL)	Absorbance
0	0
2	0.145
4	0.255
6	0.368
8	0.482
10	0.593

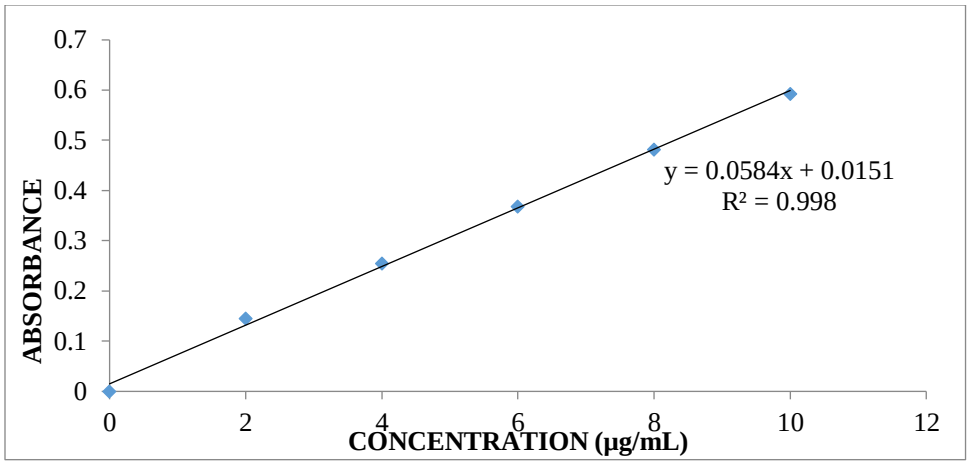

Fig: Standard graph of Glipizide in pH 6.8 phosphate buffer

Standard graph in phosphate buffer pH 7.4 (λ_{max} 304 nm) :

Standard graph of Glipizide was plotted as per the procedure in experimental method and its linearity is shown in Table 9.3 and Fig 9.2. The standard graph of Glipizide showed good linearity with R^2 of 0.997, which indicates that it obeys "Beer- Lamberts" law.

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

Concentration (µg/mL)	Absorbance
0	0
2	0.131
4	0.214
6	0.321
8	0.422
10	0.520

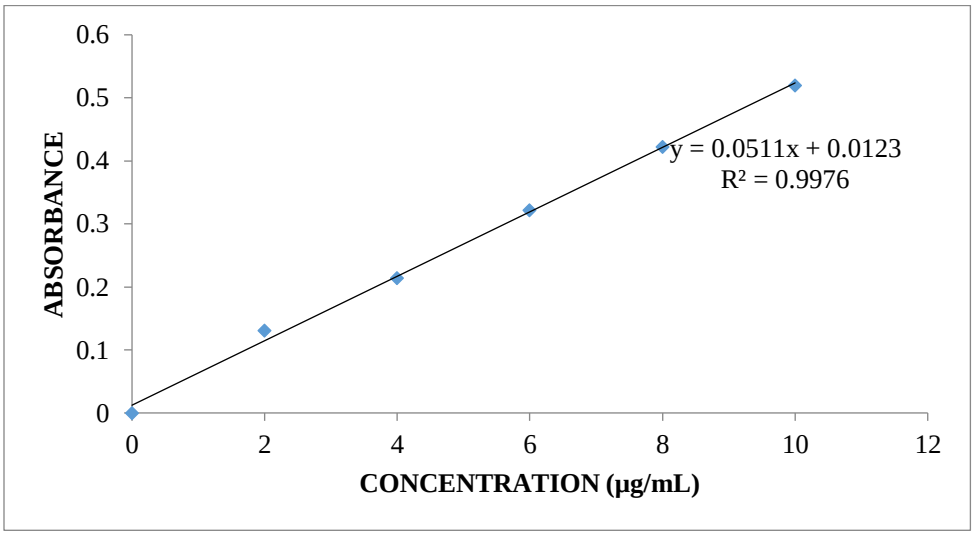

Fig : Standard graph of Glipizide in pH 7.4 phosphate buffer

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
F1	22.17±0.15	0.515±0.015	0.522±0.008	13.15±1.04	1.10±0.07
F2	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F3	25.71±0.13	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F4	23.31±0.13	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F5	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F6	25.71±0.13	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F7	23.31±0.13	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F8	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F9	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.16

Physical evaluation of Glipizide buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	99.68	2.69	5.1	0.32	97.32
F2	100.15	2.78	5.6	0.41	99.60
F3	97.36	2.35	5.9	0.29	98.31
F4	100.25	2.51	5.3	0.30	99.24
F5	99.77	2.49	5.0	0.54	99.31
F6	97.68	2.81	4.9	0.62	98.64
F7	98.38	2.29	5.3	0.44	97.24
F8	100.31	2.33	5.7	0.38	99.52
F9	99.53	2.57	5.2	0.61	97.24

***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: *In vitro* dissolution data for formulations F1 – F9

TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	30.92	30.05	25.14	32.36	23.01	20.47	23.36	16.59	13.58
1	43.21	36.11	31.36	41.12	36.63	26.62	30.41	21.93	17.16
2	50.02	48.92	36.41	46.91	40.14	31.05	35.56	32.62	28.09
3	56.64	65.16	42.00	52.46	51.20	38.20	41.42	39.17	36.10
4	70.22	71.01	51.16	58.78	57.15	50.19	53.05	48.81	54.23
5	75.29	79.60	63.98	70.92	71.34	56.27	60.36	53.96	61.42
6	90.16	82.14	70.24	78.36	76.81	66.45	78.19	70.72	67.99
7	95.24	86.39	77.14	84.22	81.99	72.98	86.24	76.15	75.37
8		93.25	89.34	99.46	87.32	77.31	95.16	89.05	81.83

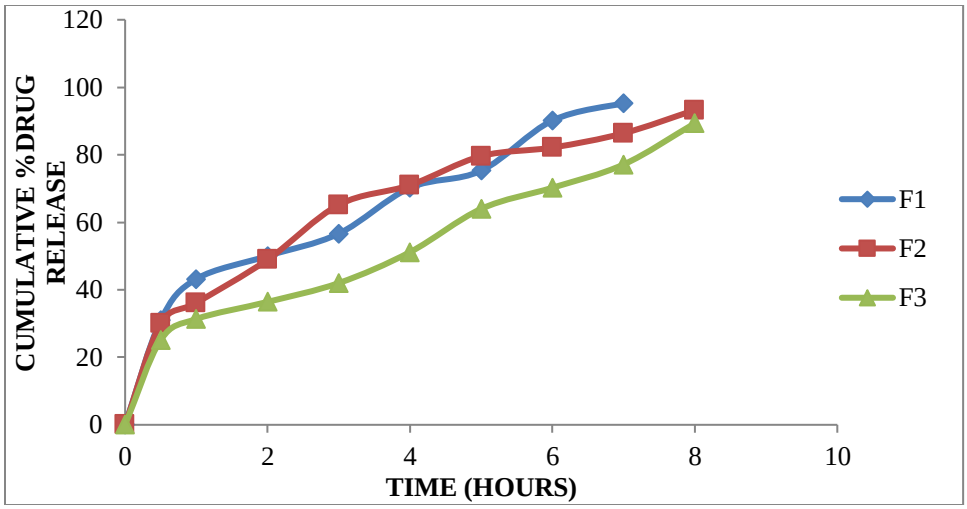

Fig : *In vitro* dissolution data for formulations F1 – F3 by using Sodium Alginate polymer

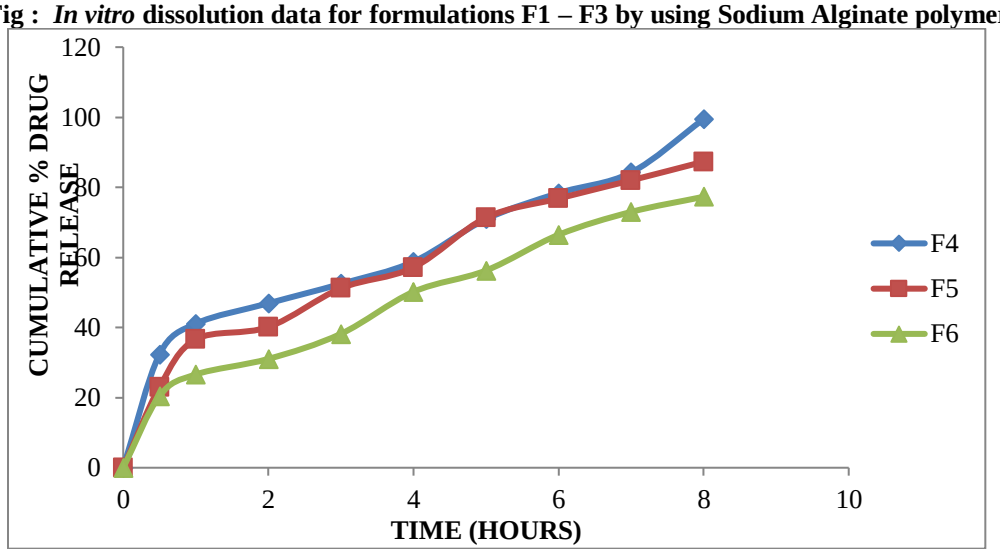

Fig : *In vitro* dissolution data for formulations F4 –F6 by using HPMC K4M polymer

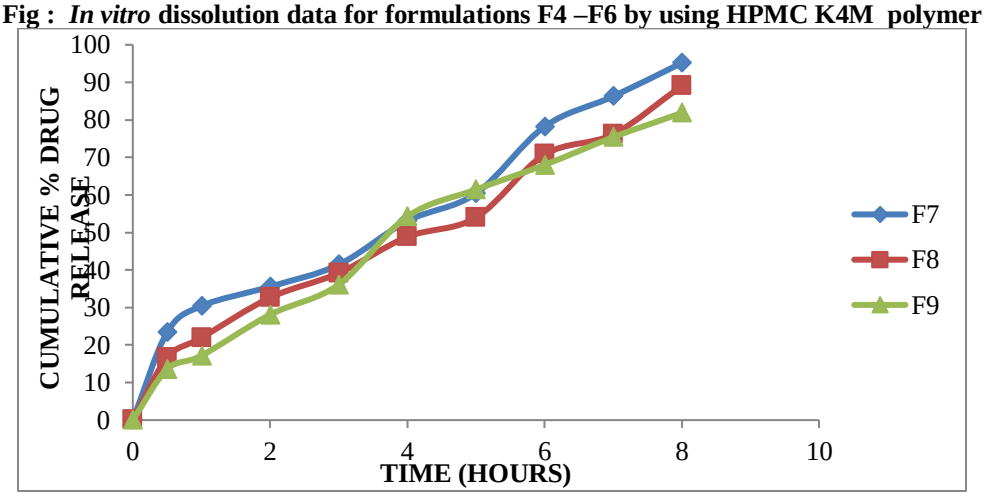

Fig : *In vitro* dissolution data for formulations F7- F9 by using SCMC polymer

From the above graphs it was evident that Sodium Alginate in the concentration of 20mg of polymer of the total tablet weight (F2) drug with other Two Formulations F1, F3. Where as in F2 formulation the quantity of polymer was less hence it showed more drug retardation with more drug release that is 93.25 % in 8 hrs.

From the above graphs it was evident that HPMC K4M in the Polymer concentration of 10mg (F4) is showing better result 99.46% drug release when compared with other two formulations F5, F6, as the concentration of polymer increases the retarding of drug release decreased.

From the above graphs it was evident that SCMC in the Polymer concentration 10mg formulation (F7) is showing better result 95.16% drug release when compared with other two formulations. Where as in F8, F9 formulations the concentration become high and the drug release was less.

Table: Moisture absorption, surface pH of selected formulations

Formulation Code	Moisture absorption	Surface pH
F2	86	5.01
F4	95	6.12
F7	90	6.20

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 F4 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 5.01 to 6.20 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 : 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
32.36	0.5	0.707	1.510	-0.301	1.830	64.720	0.0309	-0.490	67.64	4.642	4.074	0.567
41.12	1	1.000	1.614	0.000	1.770	41.120	0.0243	-0.386	58.88	4.642	3.890	0.751
46.91	2	1.414	1.671	0.301	1.725	23.455	0.0213	-0.329	53.09	4.642	3.758	0.883
52.46	3	1.732	1.720	0.477	1.677	17.487	0.0191	-0.280	47.54	4.642	3.623	1.019
58.78	4	2.000	1.769	0.602	1.615	14.695	0.0170	-0.231	41.22	4.642	3.454	1.187
70.92	5	2.236	1.851	0.699	1.464	14.184	0.0141	-0.149	29.08	4.642	3.075	1.566
78.36	6	2.449	1.894	0.778	1.335	13.060	0.0128	-0.106	21.64	4.642	2.787	1.855
84.22	7	2.646	1.925	0.845	1.198	12.031	0.0119	-0.075	15.78	4.642	2.508	2.133
99.46	8	2.828	1.998	0.903	-0.268	12.433	0.0101	-0.002	0.54	4.642	0.814	3.827

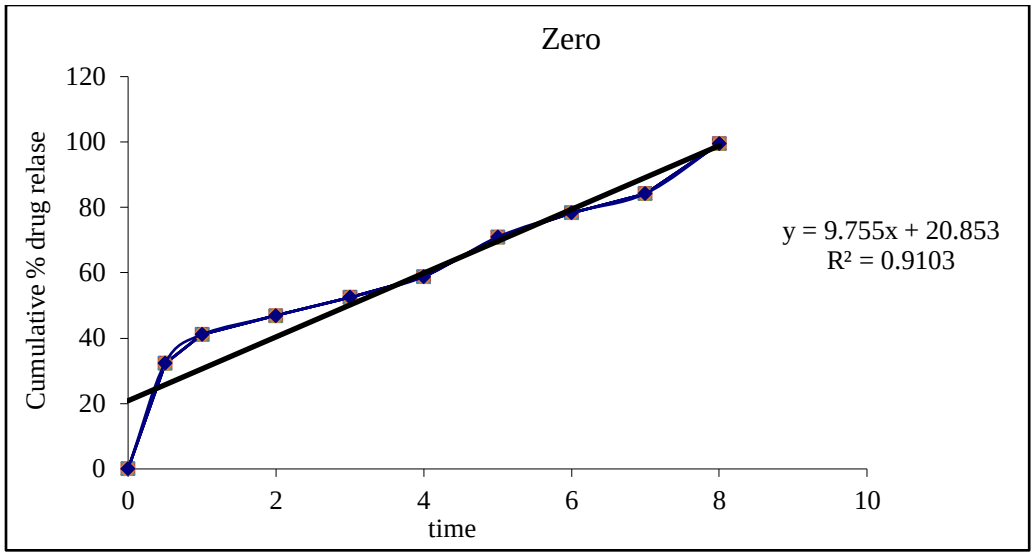

Fig : Zero order plot of optimized formulation

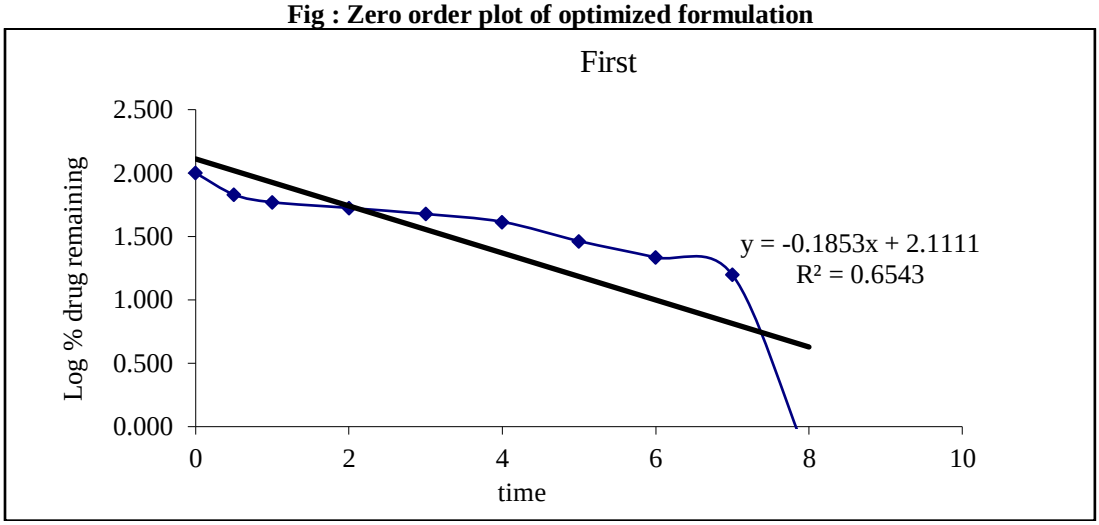

Fig: First order plot of optimized formulation

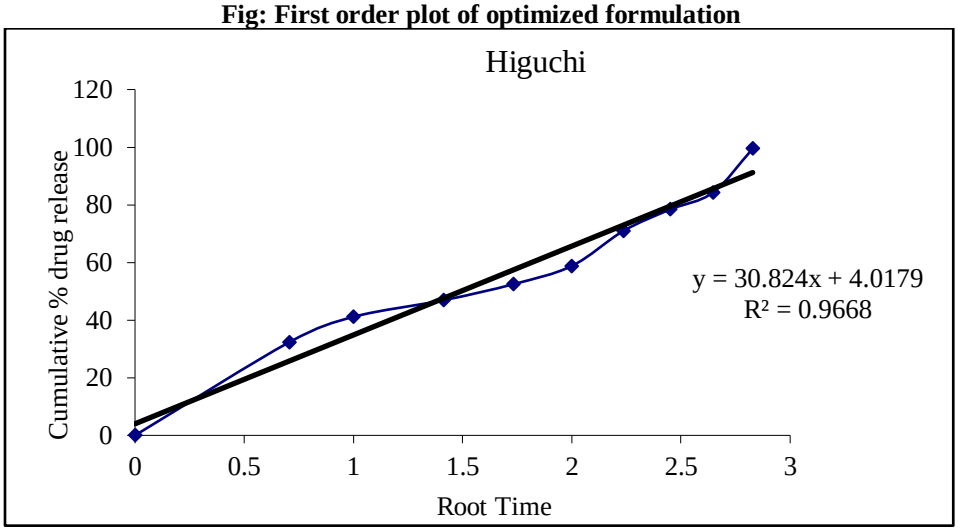

Fig: Higuchi plot of optimized formulation

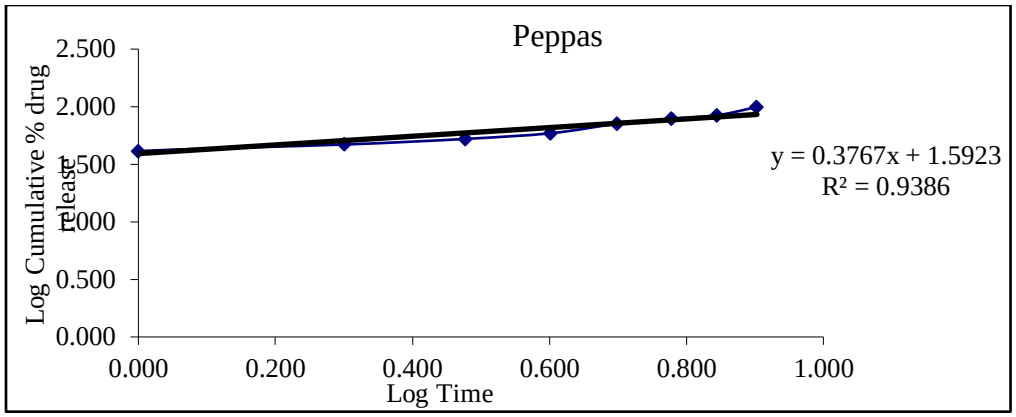

Fig: Koresmeyer-peppas plot of optimized formulation.

This formulation was following Higuchi release mechanism with regression value of 0.966.

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.

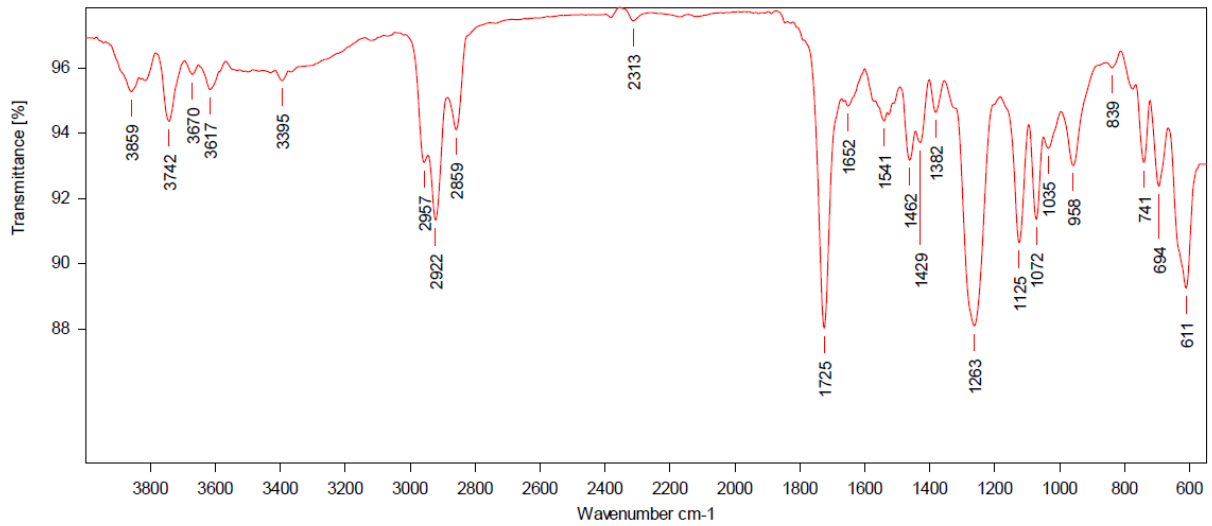

Fig : FTIR Peak of pure drug Glipizide

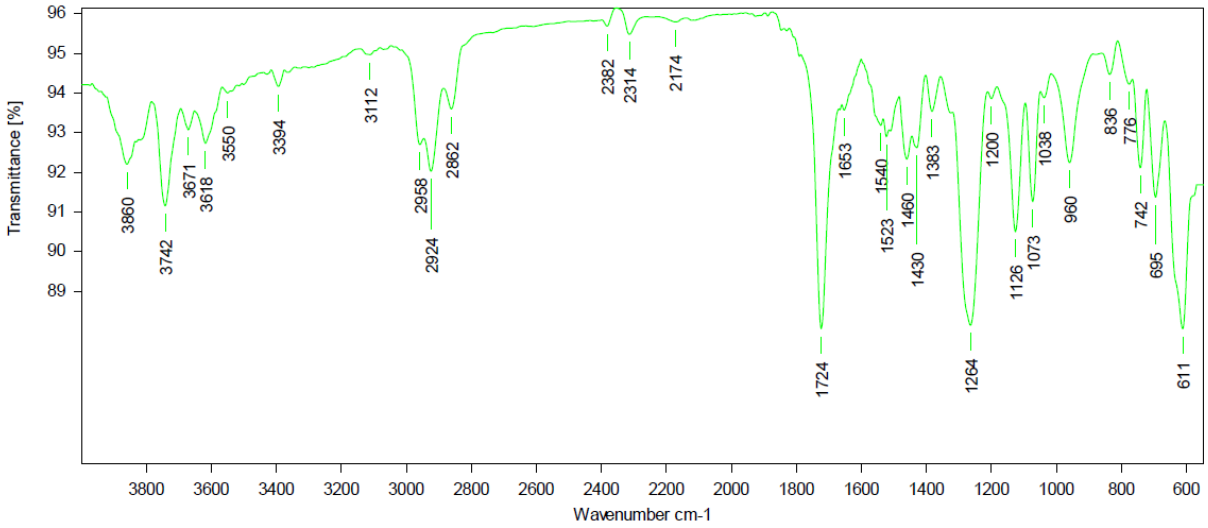

Fig : FTIR Peak of Optimised formulation

CONCLUSION:

The present research was carried out to develop mucoadhesive buccal tablets of Glipizide using different types of polymers Sodium Alginate, HPMC K4M and SCMC. 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 Sodium Alginate, HPMC K4M and SCMC 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.

Among the 9 formulations, the formulation F4 using these polymers in the above ratio with drug exhibited optimum release profile. Hence it can be concluded that the formulation F4 will be useful for buccal administration for the treatment of type 2 diabetes. Hence the mucoadhesive buccal tablets of Glipizide may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability through buccal mucosa. The release data was showed that the drug release follows Higuchi release kinetics.

REFERENCES:

1. V. T. Iswariya and A. Hari Om Prakash Rao. Buccal Tablets A Comprehensive Review. ejpmr, 2016,3(8), 252-262.
2. S.K.Gupta et al; Buccal adhesive drug delivery system: A review; Asian Journal Of Biochemical and pharmaceutical research, 2011;1(2): 105-114.
3. Reena Sheoran. Buccal Drug Delivery System: A Review. Int. J. Pharm. Sci. Rev. Res., 50(1), May - June 2018; Article No. 07, Pages: 40-46.
4. Wertz, P.W. and Squier, C.A., Cellular and molecular basis of barrier function in oral epithelium, Crit. Rev. Ther. Drug Carr. Sys, 8, 1991, 237-269.
5. Squier, C.A., Cox, P., and Wertz, P.W., Lipid content and water permeability of skin and oral mucosa, The J. Invest. Dermat, 96, 1991, 123-126.
6. Squier, C.A. and Wertz, P.W. Structure and function of the oral mucosa and implications for drug delivery, in eds. M.J. Rathbone, Oral Mucosal Drug Delivery, Marcel Dekker, Inc., New York, New York, 1996, 1-26.
7. Galey, W.R., Lonsdale, H.K., and Nacht, S., The in vitro permeability of skin and buccal mucosa to selected drugs and J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 1 (1), 1998, 15-30.
8. Gandhi, R.B. and Robinson, J.R., Oral cavity as a site for bioadhesive drug delivery, Adv. Drug Del. Rev., 13, 1994, 43-74.
9. Peppas, N.A. and Buri, P.A., Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues, J.Control. Rel., 2, 1985, 257-275.
10. Duchene D, Touchard F and Peppas N A Pharmaceutical and medical aspects of Bioadhesive system for drug administration. Drug Dev. Ind. Pharm.; 14, 1998, 283-381.
11. Parth S. Patel ,Ashish M. Parmar, Nilang S. Doshi, Hardik V. Patel, Raxit R. Patel, Chetan Nayee. Buccal Drug Delivery System: A Review.

12. Webster's Encyclopedic Unabridged Dictionary of the English Language. Thunder Bay Press, Avenel (NJ, USA), 2001.
13. Kaelbe D H and Moacanin J. A surface energy analysis of bioadhesion. Polym.; 18: 475-481, 1977.
14. Gu J M, Robinson J R and Leung S. binding of acrylic polymers to mucin/epithelial surfaces; Structure property-relationship. Crit. Rev. Ther. Drug Car. Sys.; 5, 21-67, 1998.
15. Duchene D, Touchard F and Peppas N A. Pharmaceutical and medical aspects of Bioadhesive system for drug administration. Drug Dev. Ind. Pharm.; 14, 283-381, 1998.