JOURNAL OF DRUG DELIVERY RESEARCH

eISSN 2319-1074

RESEARCH ARTICLE

Formulation and Evaluation of Mucoadhesive Buccal Tablets of Glipizide

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Publication history: Received on 18.3.2017 , Published online on 22.5.2017

ABSTRACT

Glipizide is a second generation sulphonyl urea compound which is used as a drug of choice in maturity onset diabetes. There are certain inherent drawbacks associated with this drug like it undergoes first pass hepatic effect, poor bioavailability etc., hence this drug warrants an alternative drug delivery system to conventional formulations. Buccal mucoadhesive tablet of Glipizide were prepared using mucoadhesive natural polymers. The surface pH of tablets was from 6.02 to 6.83 and all tablet showed in vitro residence time of 3.50 to 8.50 hr indicate good adhesive capacity of tablet. Buccal tablet showed good swelling of >60 % up to 8 hr maintaining integrity of polymer. The in-vitro release of drug was extended 4-6 hr and the % cumulative drug release was approx 90%. The present study demonstrated the possibility of designing a transmucosal drug delivery system for this antidiabetic drug which will be more bioavailable, efficacious than the conventional delivery and could be a drug delivery system of choice in treatment of maturity onset diabetes.

Keywords: Buccal mucoadhesive, Glipizide, Antidiabetic, Bioadhesion.

INTRODUCTION

The delivery of drugs through the buccal mucosa has attracted much research interest over the past two decades and has been developed in an attempt to deliver a variety of pharmaceutical compounds via the buccal route[1]. Since the early 1980s there has been renewed interest in the use of bioadhesive polymer to prolong contact time in the various mucosal routes of drug administration. Per oral drug delivery has been most widely utilized route of administration for the systemic delivery of drug. The lack of efficacy of certain drugs due to decreased bioavailability, GI intolerance, unpredictable, erratic absorption and pre-systemic elimination of other potential route for administration. The recent development in the drug delivery has intensified investigation of mucosal delivery of drug such route includes oral, buccal, ocular, nasal and pulmonary routes etc[2]. Buccal mucosa is a potential site for the delivery of drugs to the systemic circulation. A drug administered through the buccal mucosa enters directly the systemic circulation, thereby minimizing the first-pass hepatic metabolism and adverse gastro-intestinal effect[3]. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of

eISSN 2319-1074

low oral bioavailability are attributed to poor solubility and low permeability. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption[4]. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs with slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist [5].

The aim and objective of the present work is to formulate and evaluate glipizide buccal tablets and to enhance the solubility and permeability of drug. It is also focused on the selection of bioadhesive polymers and its activity in various combinations and ratios. The first approach is to improve the drug solubility by solid dispersion technique [6]. The optimized solid dispersion containing is selected for the formulation of buccal tablets using bioadhesive polymers i.e., sodium carboxy methyl cellulose, HPMC and carbopol 934P.

EXPERIMENTAL

Materials

Glipizide was received as a gift sample from Micro Advanced Research Center (Bangalore), India. Carbopol was obtained from SD Fine Chemical Ltd. and HPMC was obtained from Merck India Pvt Ltd. Guar Gum and Chitosan samples were obtained from Akums, Haridwar. All other chemicals were of analytical grade purchased from local suppliers.

Methods

Preparation of Mucoadhesive tablets of Glipizide [7]

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Carbopol 934, chitosan, guargum, HPMC K15M are the mucoadhesive and biodegradable polymers used in this preparation of buccal mucoadhesive drug delivery systems.

Glipizide was mixed manually with different ratios of carbopol 934, chitosan, guargum, HPMC K15M and mannitol as diluent for 10 min. The blend was mixed with talc and magnesium stearate for 3-5 min. Then the powder blend was compressed into tablets by the direct compression method using 6 mm flat faced punches. The tablets were compressed using 10 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 Formulation Table.

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Table 1 Composition of Formulation F1 to F12 for one tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Glipizide	5	5	5	5	5	5	5	5	5	5	5	5
Carbopol 934	24	48	36									
Chitosan				24	48	36						
Guargum							24	48	36			
HPMC K15M										24	48	36
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total	120	120	120	120	120	120	120	120	120	120	120	120

Evaluation of prepared buccal tablet: Prepared buccal tablets were evaluated by following tests:-

Physical parameter

a) Weight variation

20 tablets from each formulation (F1 to F12) were weighed using an electronic balance and the average weight was calculated.

b) Hardness

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean were calculated.

c) 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 friability was determined by using following formula-

$$\frac{\text{Initial weight - final weight}}{\text{Initial weight}} \times 100$$

d) Thickness

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

e) Surface pH [8,9]

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 was used to determine the surface pH of the tablet. 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 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.

f) Swelling study [10]

Five 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 and 8 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 was calculated using the following formula

$$\text{Percentage hydration} = [(W2-W1)/ W1] \times 100$$

Performance Parameter:

a) Content uniformity

One tablet from each formulation was taken, crushed and mixed. Then it was mixed in 100 mL of pH 6.8 phosphate buffer and sonicated for 30 min. The amount of drug present in each extract was determined using UV spectrophotometer at 224 nm. This procedure was repeated thrice and this average was chosen.

b) In-vitro Dissolution Study [11, 12]

Release experiments were conducted in a paddle dissolution apparatus (Apparatus II, USP). The tablets were posed with the inferior layer attached to the bottom of the vessel. A volume of 900 ml of dissolution medium consisting of phosphate buffer pH 6.8 at agitation rate of 50 rpm at 37ºC±0.5 temperature. Sampling was done by taken 5 ml dissolution medium and addition of 5 ml of pH 6.8 buffer solution was necessary in order to maintain sink conditions for the release of Glipizide. Taken sample was diluted 10 times in volumetric flask and Glipizide concentrations were determined spectrophotometrically at 224 nm.

Stability study

The physical and chemical stability of the final formulation was evaluated by long term testing conducted at 25± 2 ºC, 60± 5% relative humidity and accelerated testing conducted at 40± 2 ºC, 75± 5% relative humidity for one month.

RESULT AND DISCUSSION

Preparation of Mucoadhesive tablets of Glipizide

The tablets were prepared according to the formulation table.

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Evaluation of prepared mucoadhesive buccal tablet

Prepared mucoadhesive buccal tablet evaluated for following parameter.

Physical Parameter

a) Weight Variation

Twenty tablets of each formulation (F1-F12) were subjected to weight variation test as per USP specifications. The average weight of each formulation is recorded in table 2. The value obtained indicates that all the tablets of different formulations were within the Pharmacopoeia specification of percentage deviation of ± 7.5%. Because the standard limit value is >80 and <250 mg for ± 7.5 % deviation

b) Friability

Friability values for each formulation were recorded in table 2. Percentage friability was less than 0.98% for all formulations. These valves are with-in the acceptable limits because not exceed 1% friability, implying good compactness and strength. It also implies the ability of tablets to withstand physical and mechanical stress conditions.

c) Hardness

Three tablets of each formulation were evaluated and mean hardness values were recorded in table 2.The values were found to be in range of 3.4 –4.5 kg /cm^2. The values revealed that the tablets were having good mechanical strength.

d) Thickness

Thickness values for each formulation were recorded in table 2. Thickness values ranges from 2.23-2.51 mm.

Table 2 Evaluation of physical parameter of different buccoadhesive tablet of Glipizide

Formulation Code	Weight variation test		Percent friability (mean)	Hardness (kg/cm2) ± sd.	Thickness (mm) (mean) ± (sd)
	Average Weight(mg)(mean	U.S.P. Weight Variation Test			
F1	119.1	Pass	0.43	4.2±0.7	2.23±0.010
F2	120.22	Pass	0.513	4.4±0.3	2.29±0.020
F3	122.43	Pass	0.489	4.5±0.3	2.43±0.030
F4	123.54	Pass	0.536	4.1±0.5	2.53±0.041
F5	119.32	Pass	0.433	4.6±0.2	2.27±0.057
F6	118.2	Pass	0.422	4.3±0.4	2.25±0.061
F7	123.33	Pass	0.521	4.8±0.6	2.36±0.010
F8	120.65	Pass	0.464	4.9±0.3	2.59±0.042
F9	122.14	Pass	0.423	5±0.1	2.41±0.052
F10	119.21	Pass	0.389	3.9±0.3	2.58±0.068
F11	119.18	Pass	0.498	3.8±0.6	2.71±0.052
F12	121.17	Pass	0.521	4±0.2	2.65±0.028

e) Surface pH

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Table 3 shows the results of surface pH values for all formulations. They were found to be 6.12, 6.44, 6.29, 6.52, 6.50, 6.62, 6.74, 6.67, 6.56, 6.57, and 6.53 for the formulations F1 to F11 respectively and 4.62 for formulation F12. The surface pH of all formulations (except F12) was almost with-in the range of salivary pH. Hence F1-F11 should not cause irritation and the tablets should have good patient acceptance. There was no considerable difference in surface pH of tablets.

f) Swelling Study

Swelling study describe the amount of water that contained with-in the hydrogel at equilibrium and is the function of network structure, hydrophilicity and ionization of functional group. Swelling study were performed for all formulation .The swelling index of all formulation was in range of 44.33 % to 97.66 % at 8 hr. Maximum swelling was seen with the formulations (F12, F4, F5, F6, F7, F8, F9) containing Carbopol 934P alone and in combination with NaCMC and HPMC 50 cps than remaining formulations. The swelling index was decreased as the concentration of secondary polymer (HPMC K4M, HPMC-50cps and NaCMC) increased in formulation.

Table 3 Evaluation of surface pH and swelling study of all formulations

S.No.	Formulation Code	Surface pH (mean)± (sd.)	% Swelling index (mean)±(sd.)
1	F1	6.11±0.5	62.35±0.5
2	F2	6.02±0.4	53.45±0.5
3	F3	6.29±0.7	34.13±1.1
4	F4	6.46±0.3	74.66±0.5
5	F5	6.47±0.5	74.34±0.5
6	F6	6.81±0.1	95.66±1.5
7	F7	6.69±0.1	92.33±1.1
8	F8	6.65±0.2	81.12±1.1
9	F9	6.83±0.1	94.66±0.1
10	F10	6.50±0.3	59.15±0.2
11	F11	6.53±0.7	69.43±0.5
12	F12	6.63±0.2	95.46±0.5

Performance Parameters-

a) Content Uniformity

The % drug content of all formulations was ranges from 98.85 to 99.44 %. All % drug content values are given in table 4.

In vitro Dissolution Study

eISSN 2319-1074

The in-vitro dissolution was studied in phosphate buffer pH 6.8. The in-vitro dissolution studies were carried out in triplicate and the results of all formulations are shown in the table 5 and table 6 and the cumulative drug release data v/s time plots are shown in Fig. 1 to Fig. 2

Table 4 % Drug content of all Formulations

S.No.	Formulation Code	%drug content (mean)± (sd)
1	F1	99.12±0.22
2	F2	99.09±0.70
3	F3	99.26±0.58
4	F4	98.85±0.06
5	F5	99.28±0.46
6	F6	99.2±0.43
7	F7	98.23±0.48
8	F8	99.44±0.48
9	F9	99.11±0.49
10	F10	99.44±0.39
11	F11	99.22±0.68
12	F12	99.11±0.48

it was evident that Chitosan in the concentration of 36mg (F6), is showing better result 99.96% drug release when compared with other two concentrations (F7 & F8). It was evident that Guargum in the concentration of 36 mg (F9), is showing better result 99.88% drug release when compared with other two ratios (F10 & F11).

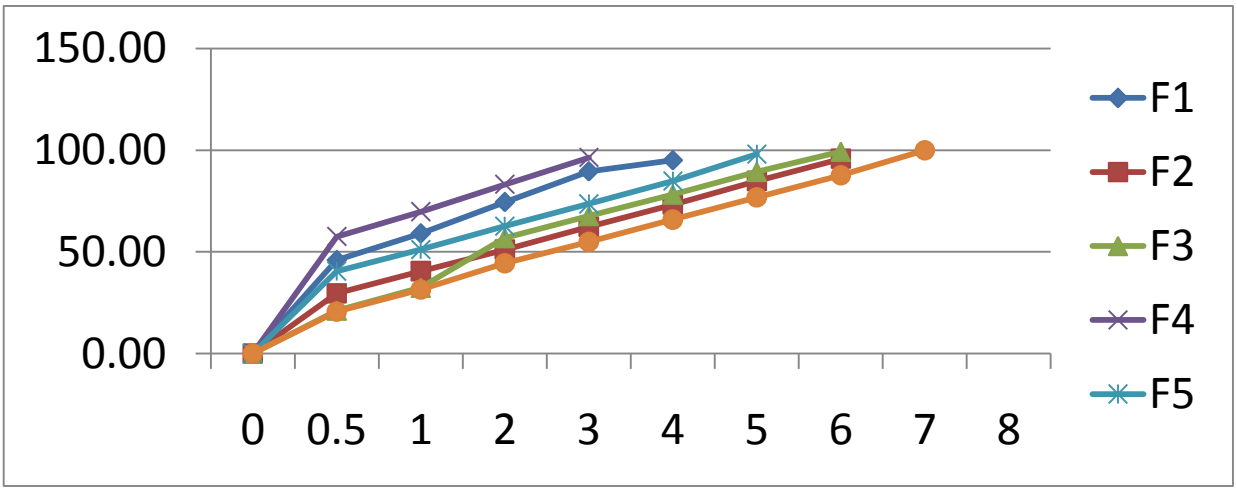

Fig 1 % cumulative drug release v/s time curve of F1-F6

eISSN 2319-1074

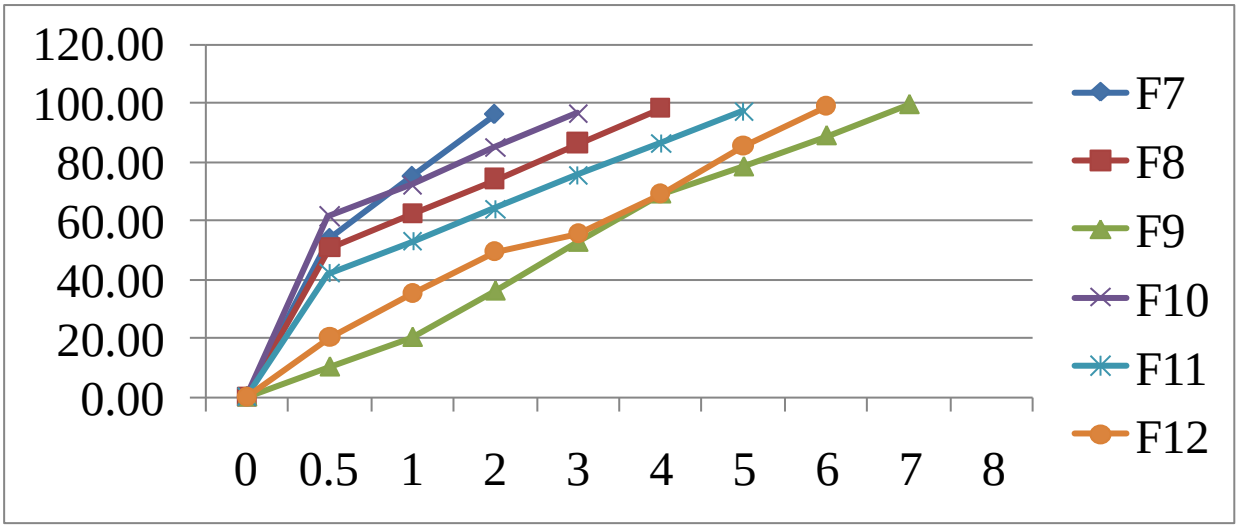

Fig 2 % cumulative drug release v/s Time curve of F6- F12

Table 5 % cumulative drug release V/s time for F1- F6

S. No.	Time (hr)	Formulation Code % cumulative drug release ± S.D. F1	F2	F3	F4	F5	F6
1	0.5	43.35±2.5	27.89±1.9	16.39±1.4	32.07±1.8	25.12±1.3	11.54±2.4
2	1	54.18±3.7	44.43±1.6	40.73±1.2	42.76±2.3	36.88±2.6	30.35±1.4
3	2	95.51±1.5	74.72±1.5	50±3.2	50.52±1.4	44.55±2.5	37.76±1.9
4	4	99.47±1.9	98.33±2.2	84.23±1.2	76.06±2.0	60.19±2	49.52±1.5
5	6	99.69±3.8	98.51±1.7	98.84±1.3	94.95±1.9	82.92±2.6	78.83±2.5
6	8	99.81±1.8	98.55±2.4	98.92±1.4	94.44±1.5	98.12±2.2	98.92±1.0

Table 6 % cumulative drug release V/s time for F7- F12

S. No.	Time (hr)	Formulation Code % cumulative drug release ± S.D. F7	F8	F9	F10	F11	F12
1	1	7.4±1.6	10.87±1.5	15.62±0.8	45.33±1.5	37.46±1.9	25.66±0.6
2	2	12.42±1.4	43.65±1.6	45.73±2.1	55.81±1.0	46.47±1.4	34.01±1.5
3	3	21.35±1.2	49.63±0.6	52.69±0.8	64.67±0.7	61.08±2.0	36.89±1.5
4	4	33.08±1.8	56.47±1.5	58.77±0.8	78±1.2	71.23±0.9	41.62±0.8
5	5	42.9±0.9	58.29±1.2	85.43±1.2	89.85±0.9	77.42±1.4	52.97±1.7
6	6	46.85±0.9	64.62±1.1	99.85±1.4	97.85±2.1	86.72±0.7	67.89±2.0

eISSN 2319-1074

Stability study

Randomly selected tablet from formulation F6 and F9 (one from each) were subjected to stability studies conducted at 25 ^{o}C ± 2^{0}C , 60±5% relative humidity and 40^{o}C ± 2^{0}C with 75% ± 5% relative humidity for a period of one month, and evaluated for percent drug content. The observations are shown in table 13 and 14 respectively. Both formulations showed slight decrease in drug content at 25 ^{o}C and at 40^{o}C after 30 days of So from this study it is cleared that mucoadhesive buccal tablet of Glipizide is most stable in room temperature and at 40^{o}C temperature.

Table 7 Stability study of Formulation F6

Storage Condition	Percent Drug Content(mean)±(sd)		
	7 days	15 days	30 days
25 ^{o}C±2^{o}C/60±5% RH	98.78%±0.89	98.14%±0.67	98.13%±0.90
40^{o}C±2^{o}C/75±5% RH	99.13%±0.95	98.98%±0.78	98.96%±0.79

Table No. 8 Stability study of Formulation F9

Storage Condition	Percent Drug Content(mean)±(sd)		
	7 days	15 days	30 days
25 ^{o}C±2^{o}C/60±5% RH	98.98%±0.80	98.92%±0.70	98.73%±0.80
40^{o}C±2^{o}C/75±5% RH	99.26%±0.93	98.89%±0.69	98.75%±0.45

CONCLUSION

The formulations prepared with Guar gum in the concentration of 36mg (F9) was showing better result 99.88% drug release and is thus optimized. The swelling studies were performed for the formulations which were shown desired drug release and the value was found to be 95.66 % in 8 hours, and for F9 94.66 % surface pH, values for selected formulations of F6 is 6.32 and F9 is 6.83 were found to be good.

The precompression blend of Glipizide Buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio and all the results indicated that the blend was having good flow nature and better compression properties.

Our work established and compared several novel, easy to prepare formulations of glipizide with better drug solubility due to solid dispersions and probably improved bioavailability.

ACKNOWLEDGEMENT

I am very much thankful to my guide Mr. Singh Shekhar Gautam and Shambhunath Institute of Pharmacy, Allahabd(UP) for providing best lab facilities necessary for completion of research project. I am highly obliged to Akums Research Lab and Micro Reseacrh labs for providing gift samples.

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