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Formulation and Evaluation of Mucoadhesive Tablets of Linagliptin

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ABSTRACT

The present study involves formulation and evaluation of buccal tablets of Linagliptin, an antidiabetic drug belonging to class of drugs that inhibit the enzyme, dipeptidyl peptidase-4 (DPP-4) and has high first pass metabolism. Buccal drug delivery has been considered an alternative to the oral dosing for compound subjected to degradation in the gastrointestinal tract or to first pass metabolism. Here in an attempt has been made to develop mucoadhesive buccal tablets comprising of drug, mucoadhesive layers and drug free backing layer of ethyl cellulose to release the drug for extended period of time while reducing the dosing frequency, dose related side effects and improving the bioavailability of drug. Tablets of Linagliptin were prepared by direct compression using mucoadhesive polymers Carbopol 934-P and HPMC K4M, Hydroxy ethyl cellulose. Buccal tablets were evaluated by different parameters such as thickness, hardness, and weight uniformity, content uniformity, swelling index, surface pH, *in vitro* drug release, *in vitro* drug permeation and FTIR studies. All the formulations followed Fickian release mechanism. The overall results indicated that the polymers API and Carbopol 934 in the ratio of 1: 6 showed satisfactory mucoadhesive properties. The optimized formulation also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability in human saliva.

INTRODUCTION

The recent development of a large number of peptides as drugs has intensified investigation of mucosal delivery of drugs. Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion 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 period of time. Bioadhesion is an integral phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces. In the case of polymer attached to mucin layer of a mucosal tissue, the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye.

Mucoadhesive buccal drug delivery systems:

Drug delivery via membranes of the oral cavity can be subdivided as Sub lingual delivery, buccal delivery and local delivery.

Because of easy accessibility it permits localization of the system.

- Since the patients are well accustomed to oral administration of drugs in general, patient recognition and compliance is expected to be good.

Its ability to convalesce after local treatment is evident and hence allows a wide range of formulations to be used e.g. bioadhesive patches and ointments

MATERIALS AND METHODS

Table 1: List of Materials used

S. No.	Ingredients	Supplier
1	Linagliptin	Laboratories Pvt. Ltd., Mumbai.
2	Carbopol-934P	Loba chemie, Mumbai.
3	Hydoxy ethyl cellulose	Ranbaxy Research Laboratories, Gurgaon.
4	HPMC K4M	Griffon laboratories Pvt. Ltd., Mumbai.
5	Lactose	S D Fine-Chem Limited, Mumbai.
6	Aspertane	Qualigens Fine Chemicals, Mumbai.
7	(SSF) Sodium steryl fumarate	S D Fine-Chem Limited, Mumbai.
8	Talc	Otto chemicals

Table 2: List of Equipments used

S. No	Equipments	Model/ Make
1	Electronic balance	Shimadzu BL-220H,Mumbai
2	Bulk density apparatus	Indolab VTAP/MATIC-II
3	Standard sieve (20 and 40#)	Jayant scientific, India
4	Hot air oven	Chemi Equipments, Chennai
5	16 punch tablet compression machine	Cadmach, Ahemdabad, india
6	Varnier caliper	Veego scientific VFT-DV
7	Hardness tester	Monsanto,Chennai
8	Friability apparatus	Indolab, Mitutoyo.
9	USP tablet dissolution apparatus Type I	Veego scientific VDA-8DR, Chennai
10	UV spectrophotometer	Shimadzu-1700 Pharmaspec UV-Visible spectrophotometer, Chennai
11	FTIR spectrophotometer	Perkin Elmer-Pharmaspec-1, Chennai

Formulation of buccal tablets

Table 3: Composition of Buccoadhesive Tablets of Linagliptin

Ingredients (mg/tab)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Linagliptin	5	5	5	5	5	5	5	5	5
Lactose	82	72	62	82	72	62	82	72	62
HPMC K4M	10	20	30	-	-	-	-	-	-
Carbopol 934p	-	-	-	10	20	30	-	-	-
Hydroxy ethyl cellulose	-	-	-	-	-	-	10	20	30
Aspertane	1	1	1	1	1	1	1	1	1
SSF (Sodium steryl fumarate)	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total (mg/tab)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Preparation of buccoadhesive tablets

The buccoadhesive tablets were prepared by direct compression method. All the ingredients were mixed in formulated proportion followed by addition of lubricants and punched using 16 station multi punch tablet compression machine. Each tablet contained 100 mg of Linagliptin the batch size for each formulation was 50 tablets.

***In- Vitro* Swelling Study**

Three tablets were used from each formulation for the test. After recording the initial weights the tablets were placed over a 10 cm diameter wet filter paper disc soaked in purified water in a petri dish at room temp. After the time interval of 1, 2, 4, 6 and 8 h., the tablets were removed and weighed individually. The percent water sorption was calculated using following formula:

$$\% \text{ Swelling index} = [(w_2-w_1)/w_1] \times 100$$

Where, W_2- weight of tablet after particular time interval

W_1- initial weight of tablet

***In- Vitro* Bioadhesion Study**

a) Fabrication of the Test Assembly

For *in-vitro* study, an apparatus designed for the determination of mucoadhesive bond force was used. Bioadhesion test assembly is shown in figure 3. For the designing of the apparatus, two pan weighing balance was used. The pan from the left side was replaced with a glass vial hanged with the thread. Another glass vial inside the glass bottle was placed below this vial in such a way that both (upper and lower) vials just touch each other. The two sides were balanced so that the right side weighs exactly 2 gm heavier than left side by placing appropriate weight in right side pans.

Using this bioadhesion test assembly, the bioadhesion strength expressed in weight (g) required for detachment of the tablet from mucosa was determined.

b) Measurement of Adhesion Force

Measurement of adhesion force was determined by using bovine buccal mucosa which was obtained from slaughter house. The underlying tissues were separated and washed thoroughly with phosphate buffer solution (pH 6.8). The membrane was then tied to the bottom of the lower vial using rubber band. The vial was kept in glass bottle which was filled with phosphate buffer solution at 37 ± 1 ^{0}C in such way that buffer just reaches the surface of mucosal membrane and kept it moist. The tablet to be tested was stuck on the lower side of the hanging Glass vial by using adhesive tape and the weight (2 gm) on the right pan was removed.

Fig. 1: Bioadhesion test assembly

This lowered the left side of the pan along with tablet over the mucosa. It was kept undisturbed for three minutes and the weights were added on right side of pan till the tablet just separated from the membrane surface. The excess weight on the right pan i.e. total weight minus 2 gm was taken as measure of bioadhesive strength. Bioadhesive force was calculated by using following equation.

$$\textbf{Bioadhesive force} = \frac{\textbf{Bioadhesive Strength} \times \textbf{9.81}}{\textbf{100}}$$

Ex-Vivo Mucoadhesion Time

The *ex-vivo* mucoadhesion time was examined after application of the buccal tablet on freshly cut bovine buccal mucosa. The fresh bovine buccal mucosa was tied on the glass slide and a mucoadhesive core side of each tablet was wet with 1 drop of phosphate buffer (pH 6.8) and pasted to the bovine buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer and kept at 37 ^{0}C± 1 ^{0}C. After 2 minutes, a slow stirring rate was applied to stimulate the buccal cavity environment and tablet adhesion was monitored for 20 hours. The time for the tablet to detach from the bovine buccal mucosa was recorded as the mucoadhesion time.

In- Vitro Drug Release Study

The influence of technologically defined condition and difficulty in simulating *in- vivo* conditions has led to the development of a number of *in- vitro* release methods for buccal formulations, however, no standard method has yet been developed. *In-vitro* release rate of buccoadhesive tablets of Linagliptin was carried out using rotating basket apparatus (USP Type I). The dissolution medium consisted of 500 ml of phosphate buffer (pH 6.8). The release study was performed at 37 ^{0}C ± 0.5 ^{0}C with a rotation speed of 50 rpm. The sample (5 ml) was withdrawn at time interval of 30, 60 and 90 minutes up to 10 h and replaced with 5 ml of dissolution media. The amount of Linagliptin released was determined spectrophotometrically at 262 nm.

Table 4: Parameters were used for the dissolution study

Apparatus	**USP Dissolution apparatus (Type I)**
Dissolution medium	Phosphate buffer (pH 6.8)
Temperature	37±0.5 °C
Volume	500 ml
Speed	50 rpm
Sample withdrawn	5 ml
Running Time	8 hrs

Stability Study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

Formulations were selected for stability on the basis of the *in-vitro* drug release profile. The formulations were subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines i.e. 25^0C/60% RH and 40^0C/75% RH in air tight high density ethylene bottles for 2 months in thermostated ovens. Tablets were evaluated for the different physicochemical parameters i.e. content uniformity, weight variation, bioadhesive strength, surface pH, swelling study, and percentage of drug release.

RESULTS AND DISCUSSION

Table 5: Organoleptic Properties of drug

Colour	**White**
Odour	Odorless
Taste	Tasteless
Appearance	Crystalline powder

Calibration Curve of Linagliptin

Table 6: Data of concentration and absorbance for Linagliptin in Phosphate buffer pH 6.8

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	20	0.0674
3	40	0.1245
4	60	0.1898
5	80	0.2492
6	100	0.3097

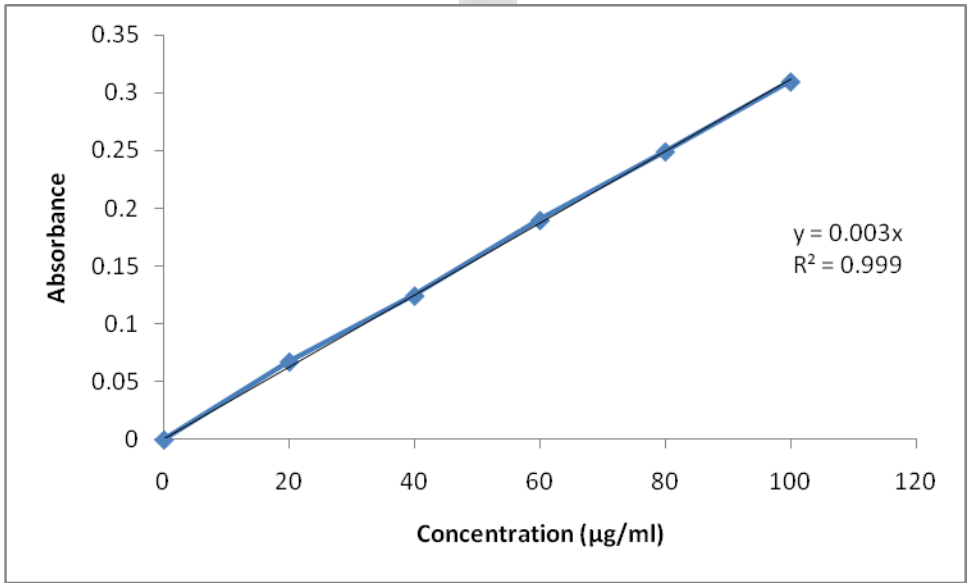

Fig. 2: Standard graph of Linagliptin in Phosphate buffer pH 6.8

Table 7: Data for Calibration Curve Parameters

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.996
2	Slope	0.022
3	Intercept	0.006

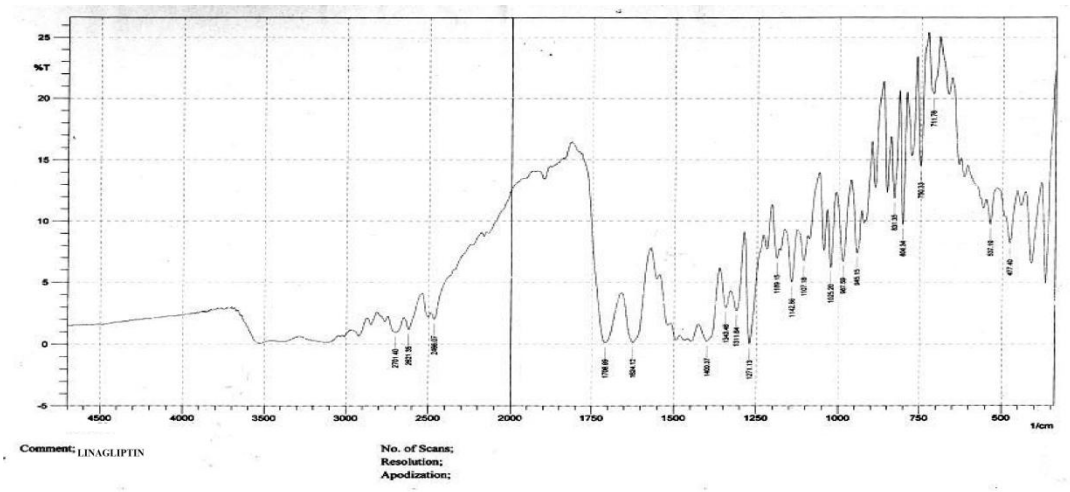

Fig. 3: FT-IR spectra of Linagliptin

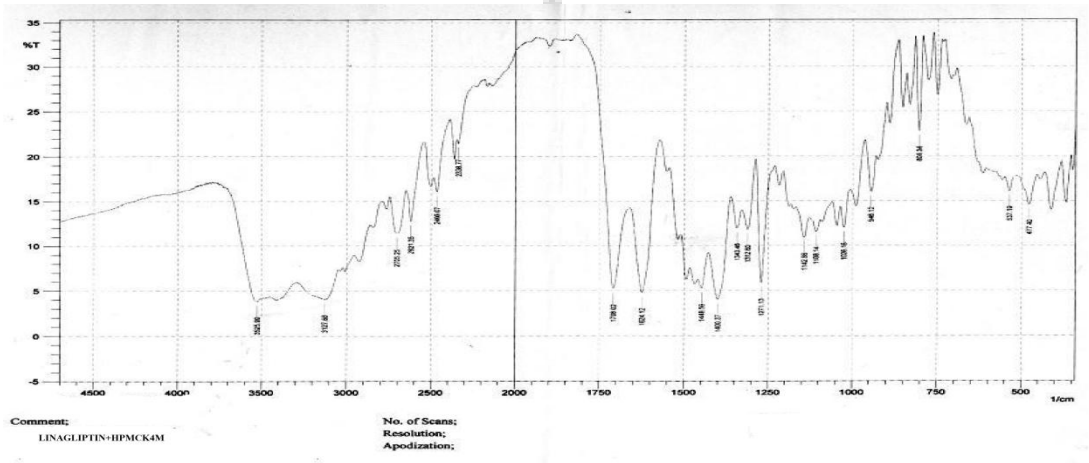

Fig. 4: FT-IR spectra of Linagliptin + HPMC K 4M

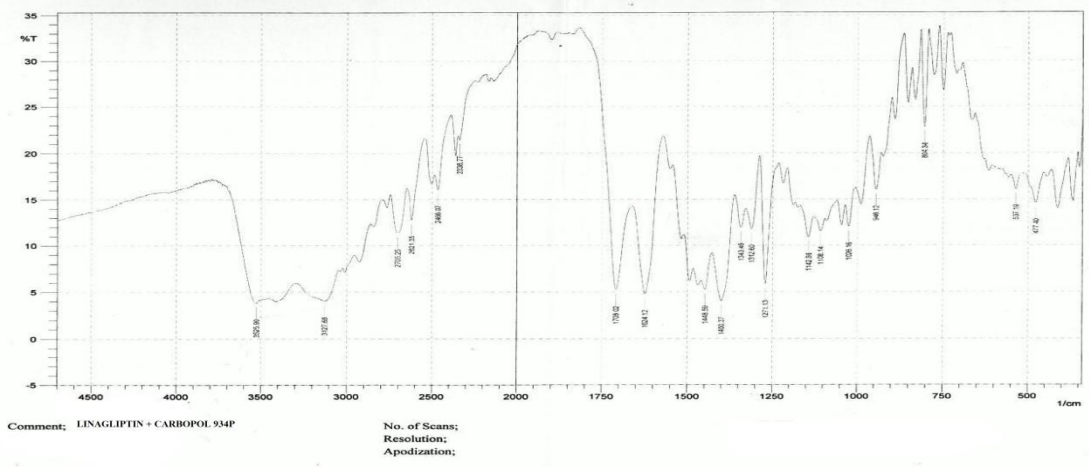

Fig. 5: FT-IR spectra of Linagliptin + Carbapol 934p

Table 8: Interpretation of FTIR spectra of Linagliptin

S. no.	Wave number (cm^{-1})	Function group	Peaks Observed (Yes/No)		
			(cm^{-1})	Drug	Drug+ Placebo
1	1400	C-N	1417	Yes	Yes
2	1540	N-H	1539	Yes	Yes
3	1780-1540	C=0	1632	Yes	Yes
4	1275-1200	C-O-C	1270	Yes	Yes
5	850-550	C-Cl	800	Yes	Yes
6	900-675	C-H	847	Yes	Yes
7	1500-1400	C-C	1500	Yes	Yes

Table 9: Micromeritic Properties of Powder Blend

Material	Angle of repose (degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausners ratio
API (Linagliptin)	23.92°	0.4526	0.4124	8.88	1.097
F1	25.23°	0.4269	0.4981	14.28	1.166
F2	26.46°	0.3737	0.4983	25.00	1.33
F3	22.36°	0.4250	0.4958	14.28	1.16
F4	22.21°	0.3319	0.3734	11.11	1.12
F5	24.56°	0.3726	0.4258	12.5	1.14
F6	25.62°	0.498	0.598	16.6	1.20
F7	24.35°	0.3775	0.4314	12.50	1.14
F8	26.5°	0.3732	0.4265	12.50	1.14
F9	25.32°	0.3341	0.3758	11.1	1.12

Table 10: Evaluation studies of Linagliptin tablets

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation	Fraibility(%)	Drug content (%)
F1	6.3±0.60	2.55±0.03	100.74±0.61	0.38	99±0.05
F2	6.8±0.16	2.54±0.02	100.38±0.71	0.15	99±0.01
F3	7.0±0.30	2.51±0.02	100.45±0.64	0.15	98±0.01
F4	6.8±0.16	2.31±0.01	99.91±1.01	0.25	100±0.06
F5	6.3±0.12	2.35±0.03	99.98±0.82	0.15	97±0.12
F6	7.1±0.02	2.12±0.01	100.42±0.61	0.31	98±0.56
F7	6.3±0.17	2.54±0.03	99.98±1.01	0.24	98±0.14
F8	6.8±0.13	2.42±0.01	100.74±0.75	0.43	99±0.25
F9	6.1±0.10	2.51±0.06	100.38±0.71	0.08	99±0.31

Where, All values are mean ±S.D, n=20.

Table 11: Swelling Index of Linagliptin Mucoadhesive buccal tablets

Time (hrs)	Swelling Index (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	52.12	36.23	26.35	46.27	35.06	36.55	36.5	33.68	35.21
2	63.52	46.61	35.62	63.51	49.18	45.92	43.1	56.33	49.35
3	71.32	53.24	33.21	76.81	53.34	69.37	62.6	75.92	72.31
4	83.61	63.53	46.41	83.56	66.29	79.11	72.8	83.29	86.35
5	86.15	76.62	56.10	84.17	79.14	86.54	86.3	86.16	78.03
6	66.24	58.8	48.23	60.43	55.55	78.44	72.1	70.13	68.32
7	36.32	34.14	42.11	33.98	46.18	52.15	62.35	56.24	52.42
8	19.25	23.23	36.87	14.26	22.46	32.29	25.6	27.35	24.35

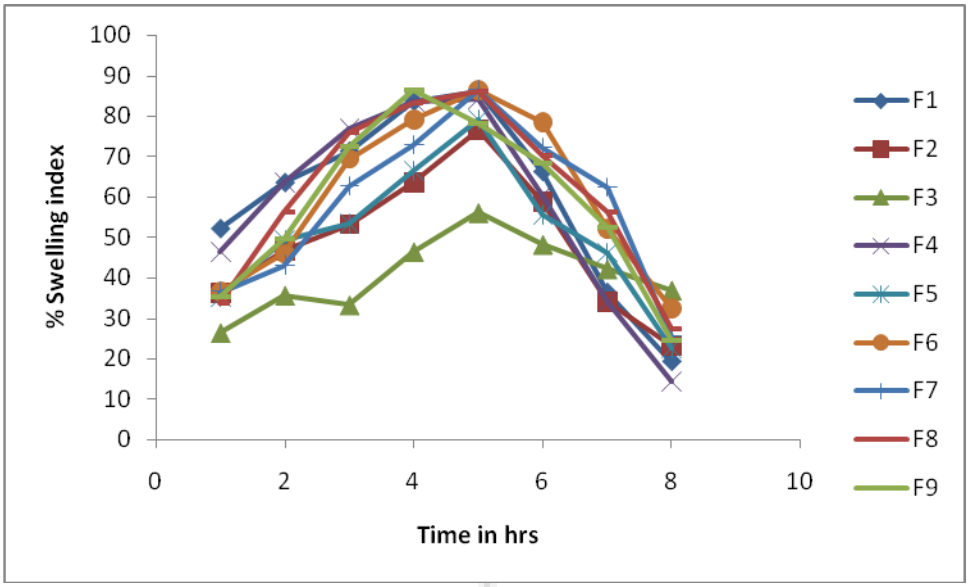

Fig. 6: Swelling index of linagliptin mucoadhesive buccal tablets

Table 12: Evaluation tests of linagliptin Mucoadhesive buccal tablets surface pH & Mucoadhesive strength

Formulation code	Surface PH	Mucoadhesive strength	*Ex-vivo* residance time
F1	6.82±0.31	18.65±0.36	5hr 15min
F2	6.71±0.2	18.12±0.15	6hr 30min
F3	6.03±0.1	17.95±0.40	7hr 15min
F4	6.82±0.4	16.41±0.37	7hr 45min
F5	6.1±0.2	16.15±0.30	Above 8hrs
F6	6.5±0.21	13.13±0.31	Above 8hrs
F7	6.2±0.35	11.23±0.26	Above 8hrs
F8	6.3±0.3	10.32±0.30	3hr 15min
F9	5.7±0.25	12.41±0.25	4hr 45min

Table 13: *In vitro* Drug release of Linagliptin Mucoadhesive Buccal Tablets Formulations

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	22	27	31	28	32	35	24	29	30
2	28	31	38	42	44	46	39	48	50
4	40	46	53	54	58	63	59	63	67
6	50	55	61	73	76	72	66	75	76
7	61	65	71	82	85	81	78	82	85
8	69	76	81	88	90	94	83	85	87

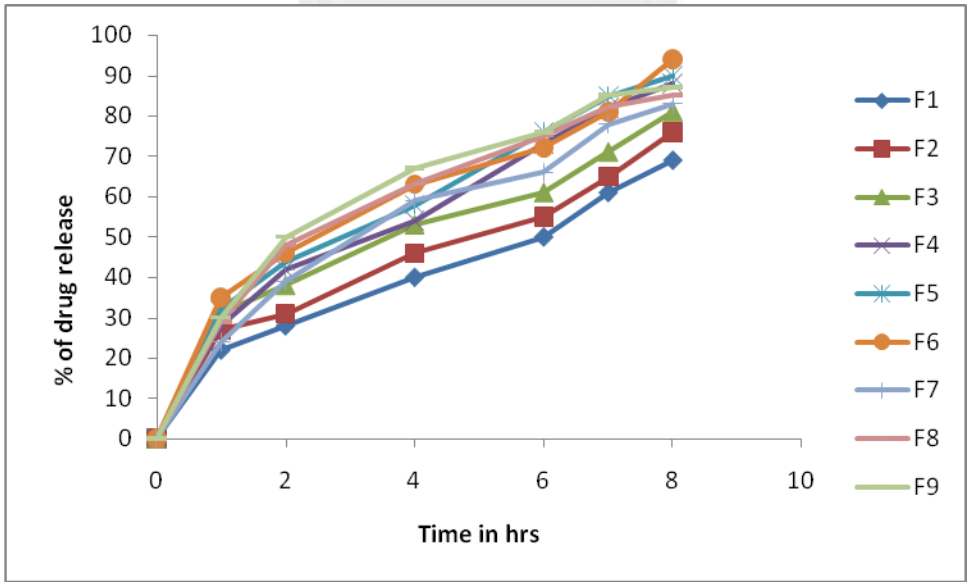

Fig. 7: (%) of drug release *in-vitro* characterization of linagliptin Mucoadhesive buccal tablets formulations

Table 14: Drug Release Kinetics of Batch (F6) Linagliptin Mucoadhesive buccal Tablets Mathematical modeling and drug release kinetics of F6 optimized formulation

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative % Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
0	0	1	-	-	100	2
1	1	0	35	1.544068	65	1.812913357
2	1.414214	0.30103	46	1.6627578	54	1.73239376
4	2	0.60206	63	1.7993405	37	1.568201724
5	2.44949	0.778151	72	1.8573325	28	1.447158031
6	2.645751	0.845098	81	1.908485	19	1.278753601
7	2.828427	0.90309	94	1.9731279	6	0.77815125

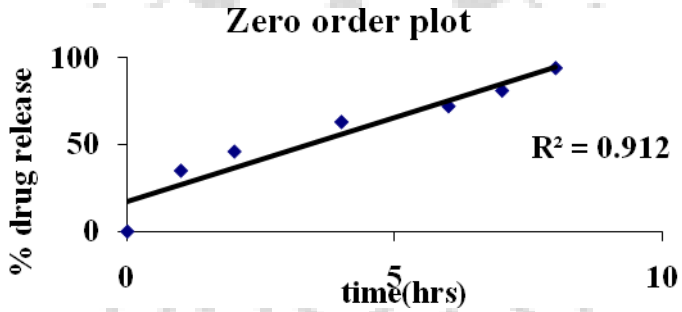

Fig. 8: Zero Order Graph of Optimized formulation F6

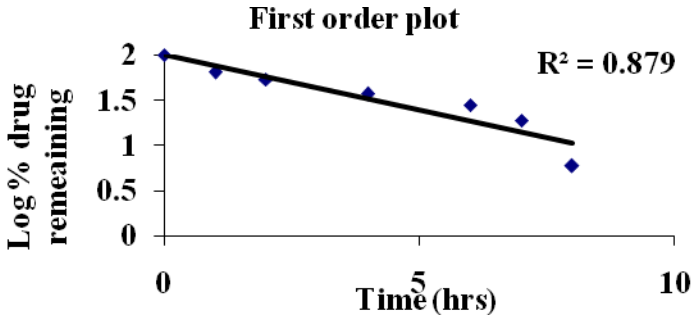

Fig. 9: First Order Graph of Optimized formulation F6

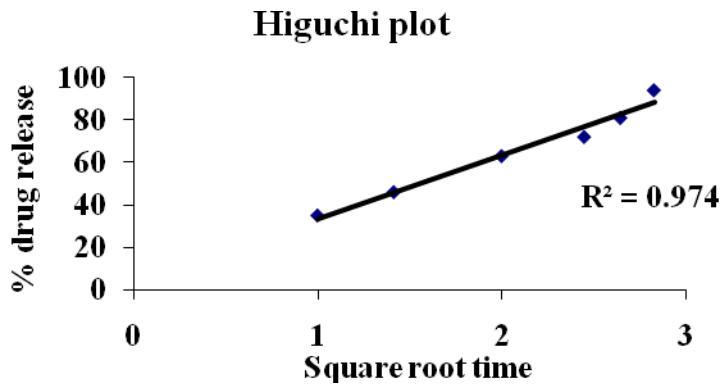

Fig. 10: Higuchi Plot of Optimized formulation F6

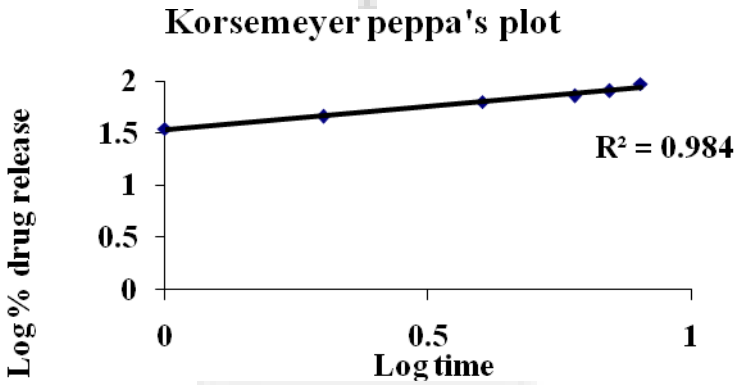

Fig. 11: Korsmeyer-Peppas plot for Optimized formulation F6

Table 15: Stability studies of tablets

Characteristic	**Initials**	**1 Month**	**2 Month**	**3 Month**
Hardness (kg/cm^2)*	7.1±0.02	6.9±0.19	6.9±0.20	6.8±0.21
Drug content (mg/tablet)*	98.±0.56	98±0.52	97.74±0.35	96.97±0.20
Bioadhesive Force (N)*	13.13±0.31	13.10±0.04	13.10±0.05	12.73±0.03
In-vitro* drug release at 8 hour	94	93.5	93.5	93.01

*All the values are expressed as mean± SD, n=3.

The tablets showed satisfactory physical stability at 40^{0}C at 75 % RH

DISCUSSION

An attempt was made to formulate Linagliptin using synthetic polymers viz. HPMC K4M, Carbopol 934 p, Hydroxy ethyl cellulose.

Literature review on polymers indicated that polymers selected for the present study has controlled release properties. Various formulations of Mucoadhesive buccal tablets of Linagliptin were prepared using HPMC K4M, Carbopol 934 p, Hydroxy ethyl cellulose polymers in different proportions and combinations.

The initial part of work was started from the identification of drug. Identification of drug was determined by melting point and solubility. The drug polymer interaction study was carried out by FTIR study. From the report it was concluded that there was no interaction between drug and polymers used in the formulations. Pre-formulation study was carried out for powder blends and it was evaluated to determine the flow characteristics by bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose. The results obtained from these studies indicated that the powder blend had good flow properties. The Mucoadhesive buccal tablets were prepared with different ratios of polymers by direct compression method. The formulated tablets were evaluated for physical characterization like thickness, hardness, friability, weight variation and drug content, swelling index, bioadhesive strength, *ex-vivo* retention time, dissolution. All the physical parameters of prepared Mucoadhesive buccal tablets comply with IP specifications.

The formulated tablets were evaluated for drug content and it was found to be in the range of 94 % w/w. Thus, all formulation of Linagliptin was found to be within the acceptable range.

The optimized formulation (F6) had shown the satisfactory release of drug.

CONCLUSION

The overall results indicated that the API and Carbopol 934 in the ratio of 1: 6 showed satisfactory mucoadhesive properties. Among all the formulations, the F6 formulation using these polymers in the above ratio with drug exhibited significant moisture absorption properties with optimum release profile. The optimized formulation F6 also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability in human saliva. Hence it can be concluded that the formulation F6 will be useful for buccal administration of Linagliptin. So, the mucoadhesive buccal tablets of Linagliptin may be a good choice to bypass the hepatic first pass metabolism with an improvement in the bioavailability of Linagliptin through Buccal mucosa. Further work is recommended to support its efficacy claims by pharmacodynamics and pharmacokinetics studies in human beings.

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