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Formulation and Development of Mucoadhesive Tablets by Anti-Ulcer Drug Esomeprazole

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Abstract

Esomeprazole is a medication used in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger–Ellison syndrome. It is also used to prevent upper gastrointestinal bleeding in people who are at high risk. The Mucoadhesive buccal tablets were prepared by direct compression method using Chitosan, HPMC K100 and Carbopol p934 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 K100 in the ratio of (1:1) showed maximum drug release of 99.54% in 8 hrs. The drug content of shown highest of 99.61 %, Surface pH was found to be 6.05. All the evaluation parameters given the positive results and comply with the standards. The results indicate that the mucoadhesive buccal tablets of Esomeprazole may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Esomeprazole through buccal mucosa.

Key words: Esomeprazole, Chitosan, HPMC K100, Carbopol p934and 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. 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.

ADVANTAGES

1) Bypass the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.

2) Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.

3) Sustained drug delivery.

4) A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.

5) Increased ease of drug administration.

DISADVANTAGES

1) Low permeability of the buccal membrane: specifically, when compared to the sublingual membrane.

2) Smaller surface area. The total surface area of membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane.

3) The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug.

4) Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form.

LIMITATIONS

1) Drugs which are unstable at buccal pH cannot be administered.

2) Eating and drinking may become restricted.

3) There is an ever-present possibility of the patient swallowing the dosage form.

4) Only drug with small dose requirement can be administered.

5) Only those drugs which are absorbed by passive diffusion can be administered by this route.

MATERIALS AND METHODS

S.No	Materials	Supplied by
1	Esomeprazole	Procured From Lark laboratories, Bhiwadi, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad.
2	Chitosan	CMR college of Pharmacy
3	HPMC K100	CMR college of Pharmacy
4	Carbopol p934	CMR college of Pharmacy

5	MCC	CMR college of Pharmacy
6	Magnesium stearate	CMR college of Pharmacy
7	Talc	CMR college of Pharmacy
8	Saccharin sodium	CMR college of Pharmacy

PREPARATION METHOD

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.

INGREDIENTS (MG)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Esomeprazole	20	20	20	20	20	20	20	20	20
Chitosan	20	40	60		-	-	-	-	-
HPMC K100	-	-	-	25	50	75	-	-	-
Carbopol p934	-	-	-	-	-	-	30	60	90
MCC	136	116	96	131	106	81	130	101	66
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	200	200	200	200	200	200	200	200	200

Table 2: Formulation code for ingredients

Characterization of tablets:

Assay:

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 304 nm using pH6.8 phosphate buffer.

In vitro release studies:

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore, an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution

of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analysed after appropriate dilution by using UV Spectrophotometer at 304nm.

Surface pH:

Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.8 phosphate buffers (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3).

Moisture absorption:

Agar (5% m/V) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture. They were then placed on the surface of the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

RESULTS AND DISCUSSION

Solubility Studies:

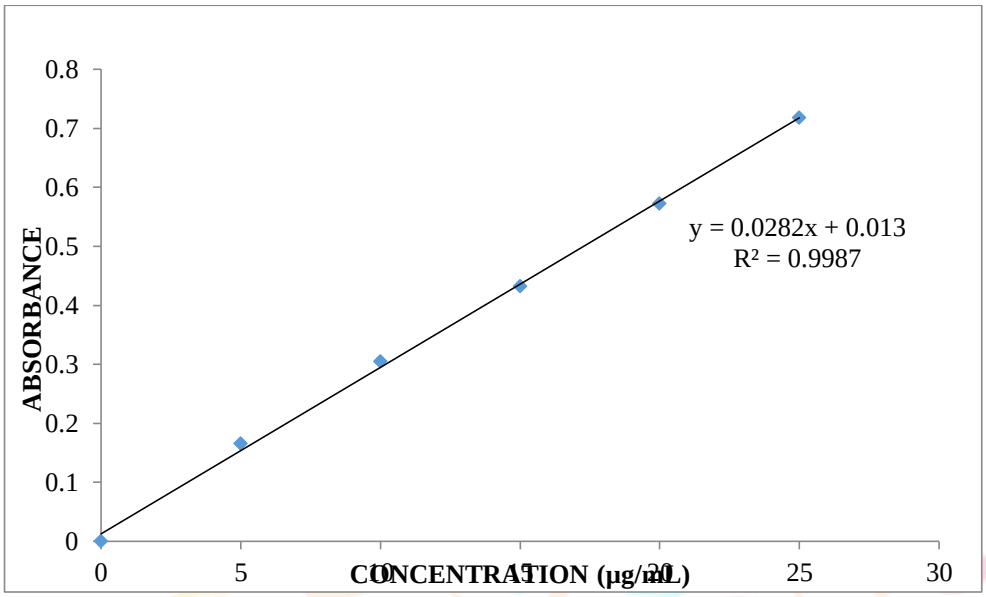
Saturation solubility of Esomeprazole in various buffers were studied and shown in the Table 9.1. The results revealed that the solubility of the Esomeprazole was increased from pH 6.8 to 7.4. The solubility of the Esomeprazole in phosphate buffer pH 6.8 is 98.69µg/mL and it was selected as the suitable media for the release studies because the pH of the phosphate buffer pH 6.8 is nearer to that of buccal mucosa pH.

S.No	Medium	Amount present (µg/mL)
1	Phosphate pH 6.8 buffer	97.52
2	Phosphate pH 7.4 buffer	98.69

Standard graph in phosphate buffer pH 6.8 (λ_{max} 304 nm)

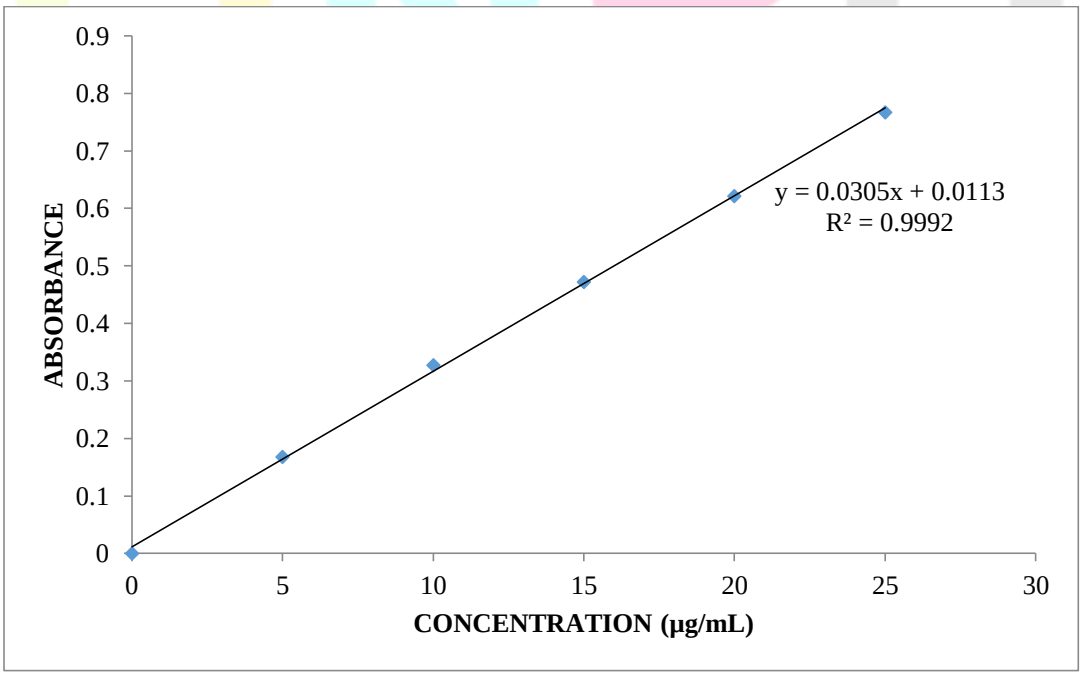
Concentration (µg/mL)	Absorbance
0	0
5	0.166
10	0.305

15	0.432
20	0.572
25	0.718



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

Concentration (µg/mL)	Absorbance
0	0
5	0.168
10	0.328
15	0.472
20	0.622
25	0.767



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	23.45 ±0.0002	0.55 ± 0.12	0.65 ± 0.89	12.2	1.21 ± 0.87
F2	19.65 ±0.0055	0.54 ± 0.31	0.62 ± 0.78	12.2	1.22 ± 0.67
F3	22.35 ±0.0063	0.56 ± 0.41	0.64 ± 0.65	14.5	1.23 ± 0.45
F4	20.69 ±0.0074	0.54 ± 0.54	0.63 ± 0.51	14.1	1.24 ± 0.39
F5	20.82 ±0.0041	0.50 ± 0.84	0.64 ± 0.45	12.3	1.22 ± 0.59
F6	20.72±0.0056	0.53 ± 0.78	0.64 ± 0.32	13.4	1.23 ± 0.43
F7	20.89 ±0.0049	0.51 ± 0.97	0.67 ± 0.21	14.6	1.24 ± 0.48
F8	20.76 ±0.0058	0.52 ± 0.64	0.62 ± 0.91	14.7	1.21 ± 0.57
F9	22.61 ±0.0041	0.56 ± 0.53	0.61 ± 0.87	12.3	1.22 ± 0.56

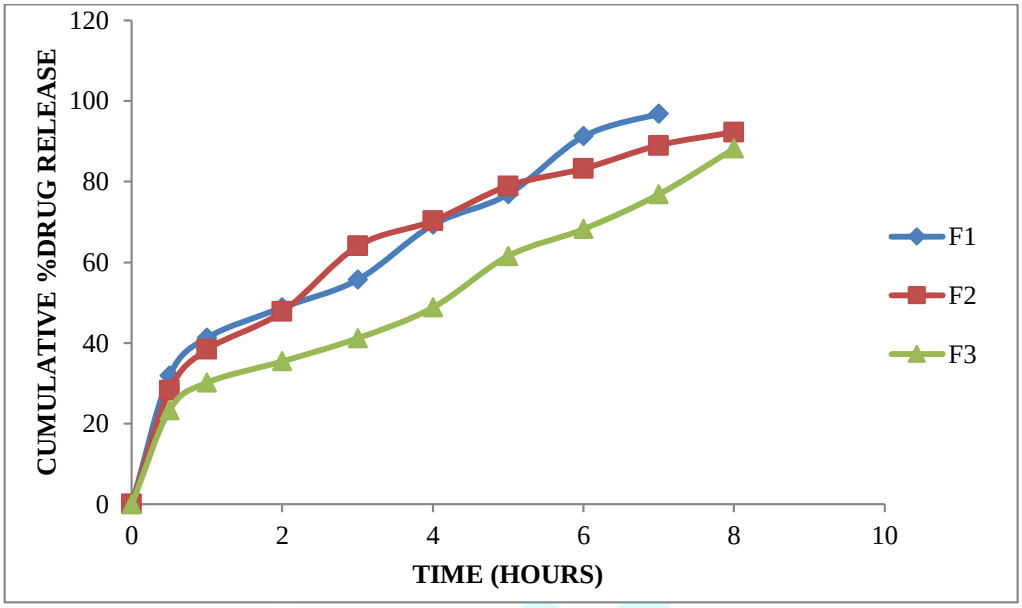
Physical evaluation of Esomeprazole buccal tablets

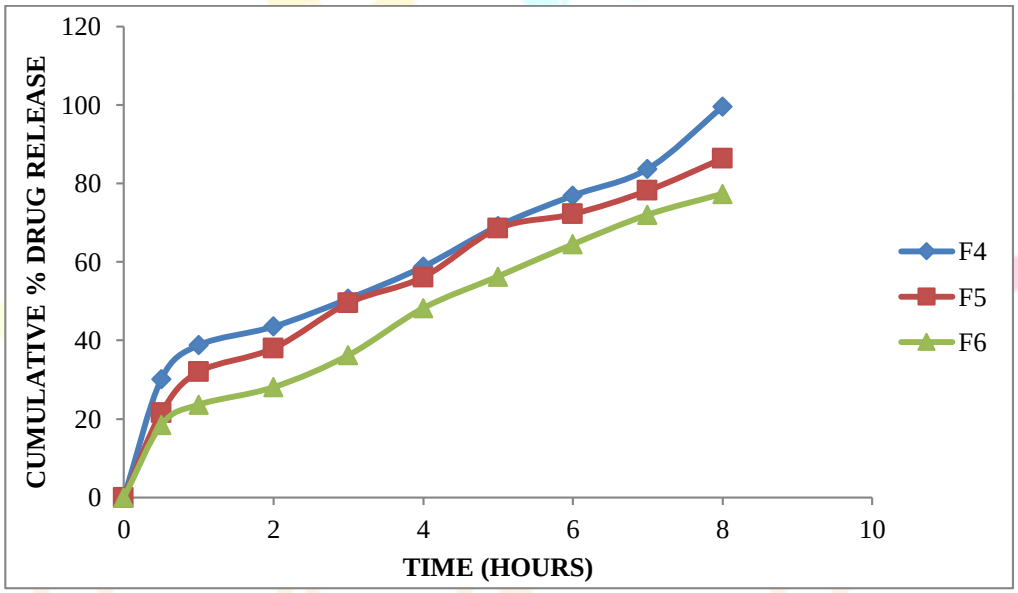
Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	199.68	3.99	4.9	0.63	96.56
F2	200.15	3.16	4.3	0.52	98.42
F3	197.36	4.24	5.1	0.34	97.59
F4	200.25	3.58	4.9	0.49	99.61
F5	199.77	3.82	4.6	0.54	99.78
F6	197.68	4.01	3.9	0.68	99.61
F7	198.38	3.98	4.6	0.42	100.1
F8	200.31	3.23	5.2	0.57	98.15
F9	199.53	4.14	4.8	0.42	98.45

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

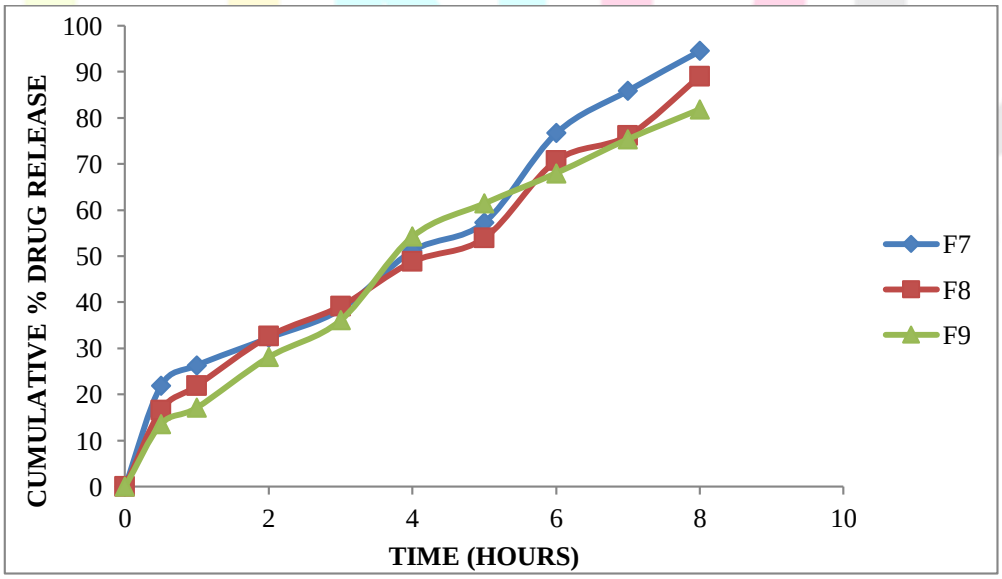
TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	31.89	28.19	23.35	30.19	21.58	18.47	21.91	16.59	13.58
1	41.34	38.37	30.20	38.81	31.99	23.62	26.34	21.93	17.16
2	48.82	47.72	35.46	43.52	38.01	28.05	32.28	32.62	28.09
3	55.71	63.97	41.18	50.61	49.53	36.20	38.46	39.17	36.10
4	69.32	70.24	48.79	58.79	56.14	48.19	51.17	48.81	54.23
5	76.91	78.89	61.56	69.15	68.53	56.27	57.34	53.96	61.42
6	91.24	83.15	68.22	76.91	72.20	64.45	76.68	70.72	67.99
7	96.79	88.93	76.83	83.72	78.19	71.98	85.91	76.15	75.37
8		92.19	88.16	99.54	86.34	77.31	94.49	89.05	81.83

***In vitro* dissolution data for formulations F1 – F3 by using Chitosan polymer**





***In vitro* dissolution data for formulations F4 –F6 by using HPMC K100 polymer**



***In vitro* dissolution data for formulations F7- F9 by using Carbopol p934 polymer**

Moisture absorption, surface pH of selected formulations

Formulation Code	Moisture absorption	Surface pH
F2	90	5.10
F4	98	6.05
F7	95	6.12

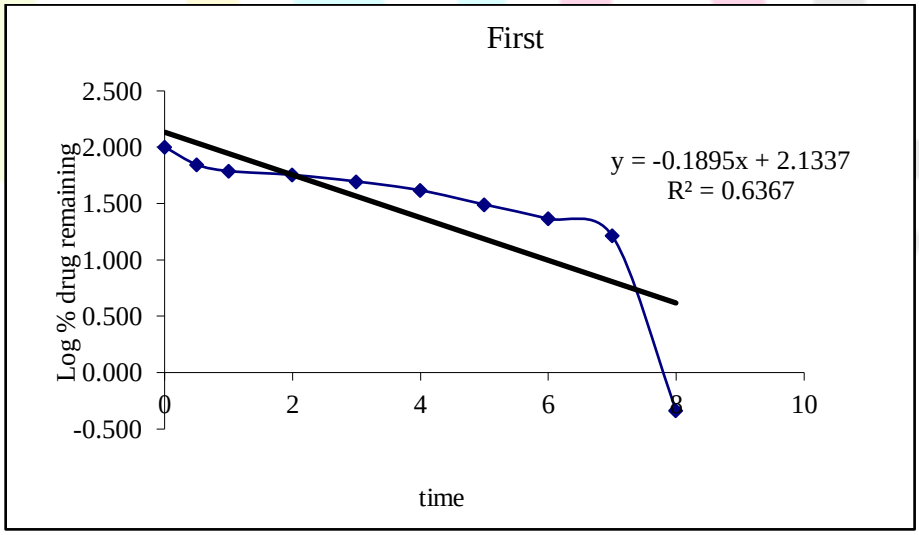
RELEASE KINETICS

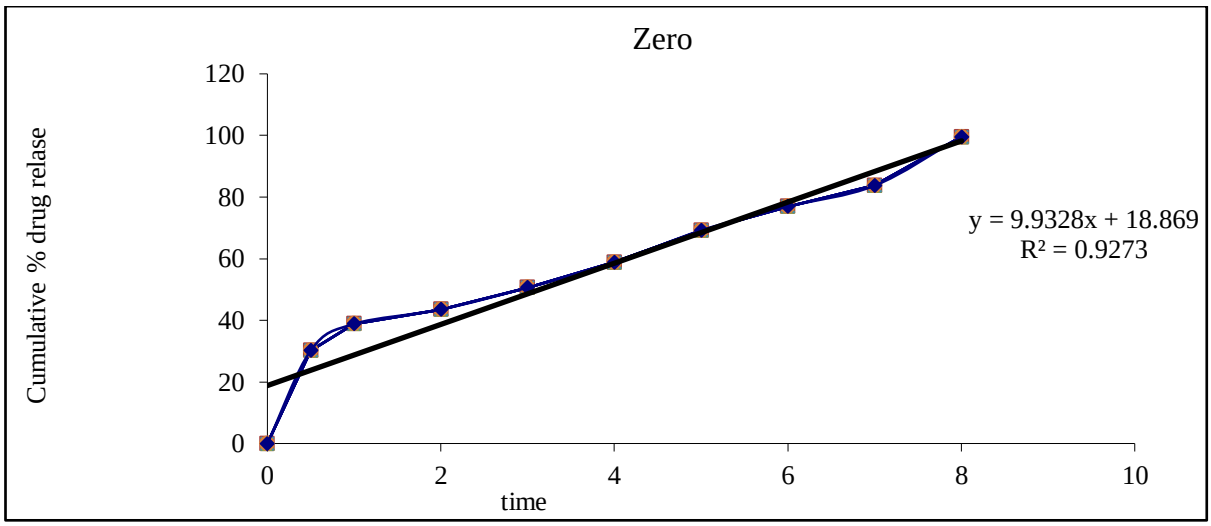
Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Esomeprazole release from buccal tablets.

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
30.19	0.5	0.707	1.480	-0.301	1.844	60.380	0.0331	-0.520	69.81	4.642	4.118	0.524
38.81	1	1.000	1.589	0.000	1.787	38.810	0.0258	-0.411	61.19	4.642	3.941	0.701
43.52	2	1.414	1.639	0.301	1.752	21.760	0.0230	-0.361	56.48	4.642	3.837	0.805
50.61	3	1.732	1.704	0.477	1.694	16.870	0.0198	-0.296	49.39	4.642	3.669	0.973
58.79	4	2.000	1.769	0.602	1.615	14.698	0.0170	-0.231	41.21	4.642	3.454	1.187
69.15	5	2.236	1.840	0.699	1.489	13.830	0.0145	-0.160	30.85	4.642	3.136	1.505
76.91	6	2.449	1.886	0.778	1.363	12.818	0.0130	-0.114	23.09	4.642	2.848	1.794
83.72	7	2.646	1.923	0.845	1.212	11.960	0.0119	-0.077	16.28	4.642	2.534	2.107
99.54	8	2.828	1.998	0.903	-0.337	12.443	0.0100	-0.002	0.46	4.642	0.772	3.870

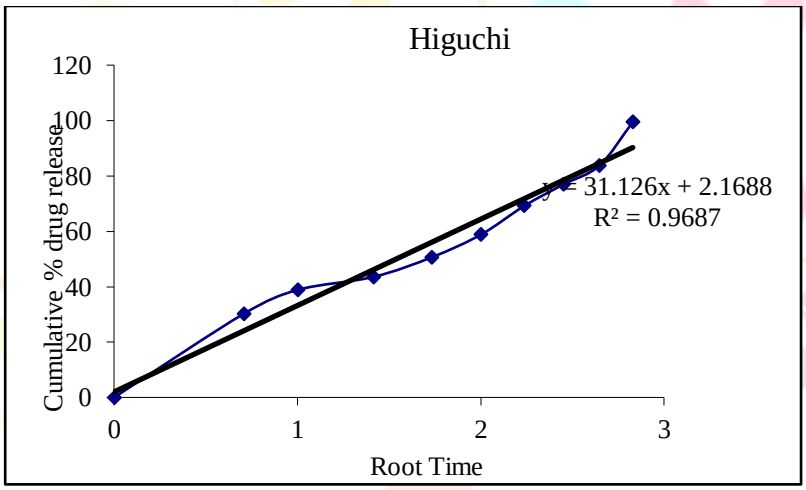
Zero order plot of optimized formulation



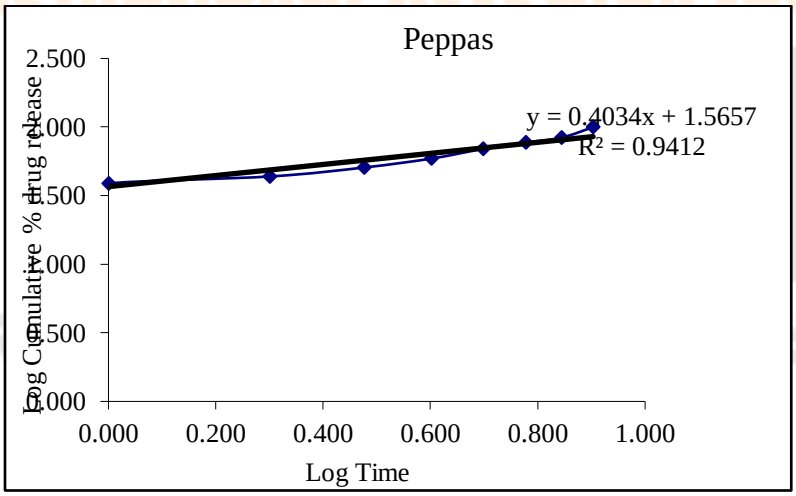


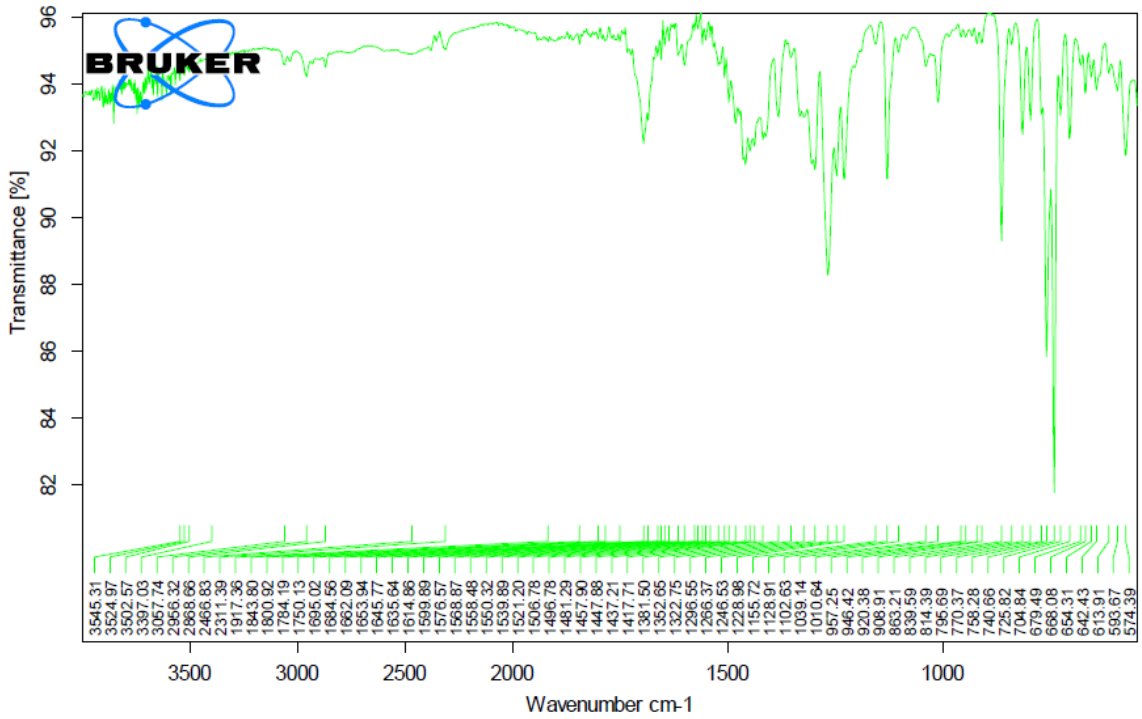
First order plot of optimized formulation

Higuchi plot of optimized formulation

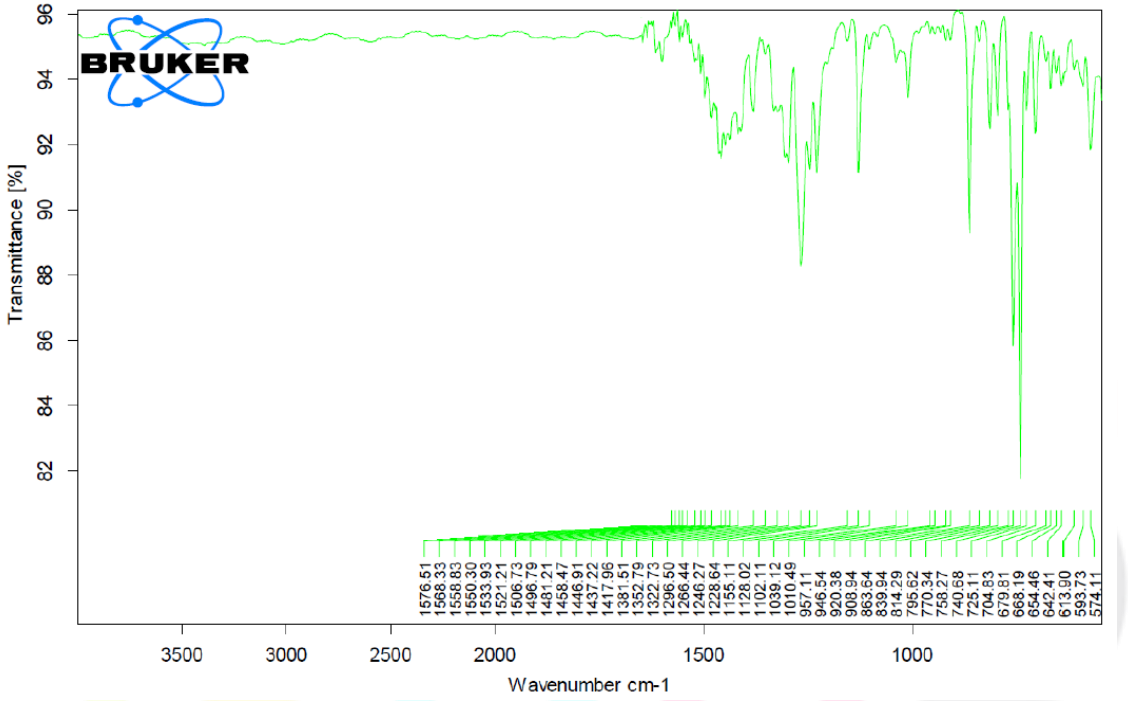


Koresmeyer-peppas plot of optimized formulation.





FTIR Peak of pure drug Esomeprazole



FTIR Peak of Optimised formulation

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra of pure Esomeprazole drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Esomeprazole 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.

CONCLUSION

The present research was carried out to develop mucoadhesive buccal tablets of Esomeprazole using different types of polymers Chitosan, HPMC K100 and Carbopol p934. 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 Esomeprazole could be prepared using Chitosan, HPMC K100 and Carbopol p934 polymers by using direct compression method. The prepared mucoadhesive buccal tablets subjected to infrared spectrum study suggested that there was no drug -polymer interaction.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 gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger–Ellison syndrome. Hence the mucoadhesive buccal tablets of Esomeprazole may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability through buccal mucosa.

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