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Formulation development and evaluation of omeprazole buccal tablets

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ABSTRACT

Omeprazole 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 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 99.54% 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 Omeprazole may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Omeprazole through buccal mucosa.

Keywords: Omeprazole, Sodium Alginate, HPMC K4M, SCMC 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.

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.

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another[9]. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems.

Ideal Characteristics of Buccal Drug Delivery System 10

- ✓ Should adhere to the site of attachment for a few hours.
- ✓ Should release the drug in a controlled fashion.
- ✓ Should provide drug release in a unidirectional way toward the mucosa.
- ✓ Should facilitate the rate and extent of drug absorption.
- ✓ Should not cause any irritation or inconvenience to the patient.
- ✓ Should not interfere with the normal functions such as talking and drinking.

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. [11-14]

Advantages of buccal drug delivery system

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.
6) Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
7) In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration. 8) Transmucosal delivery occurs is less-variable between patients, resulting in lower intersubject variability as compared to transdermal patches.
9) The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

Disadvantages of buccal drug delivery system

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.
These are some of the problems that are associated with buccal drug delivery.

MATERIALS

Omeprazole Procured From Lark laboratories, Bhiwadi, India. 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 Omeprazole

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.

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:

Angle of repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan\theta = h/r$$

Where, θ = angle of repose
h = height of the cone
r = radius of the cone base

Table : Formulation Chart

INGREDIENTS (MG)	FORMULATION CODES								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Omeprazole	20	20	20	20	20	20	20	20	20
Sodium Alginate	20	40	60		-	-	-	-	-
HPMC K4M	-	-	-	25	50	75	-	-	-
SCMC	-	-	-	-	-	-	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

RESULTS AND DISCUSSION

Solubility Studies:

Table 9.1: Solubility studies

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

Saturation solubility of Omeprazole in various buffers were studied and shown in the Table 9.1. The results revealed that the solubility of the Omeprazole was increased from pH 6.8 to 7.4. The solubility of the Omeprazole 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.

Standard graph in phosphate buffer pH 6.8 (λ max 304 nm)

Standard graph of Omeprazole was plotted as per the procedure in experimental method. The standard graph of Omeprazole showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

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

Concentration (µg/mL)	Absorbance
0	0
5	0.166
10	0.305
15	0.432
20	0.572
25	0.718

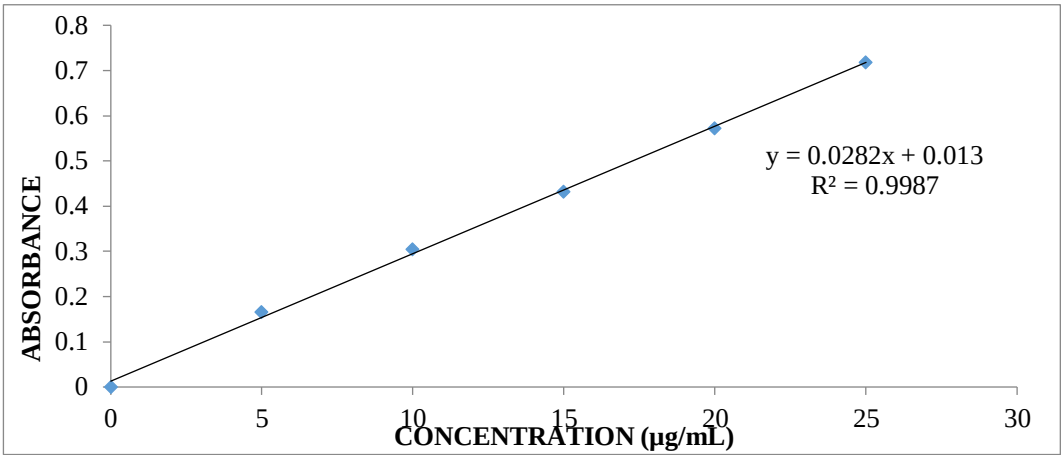

Fig: Standard graph of Omeprazole in pH 6.8 phosphate buffer

Standard graph in phosphate buffer pH 7.4 (λ max 304 nm)

Standard graph of Omeprazole 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 Omeprazole showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

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

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

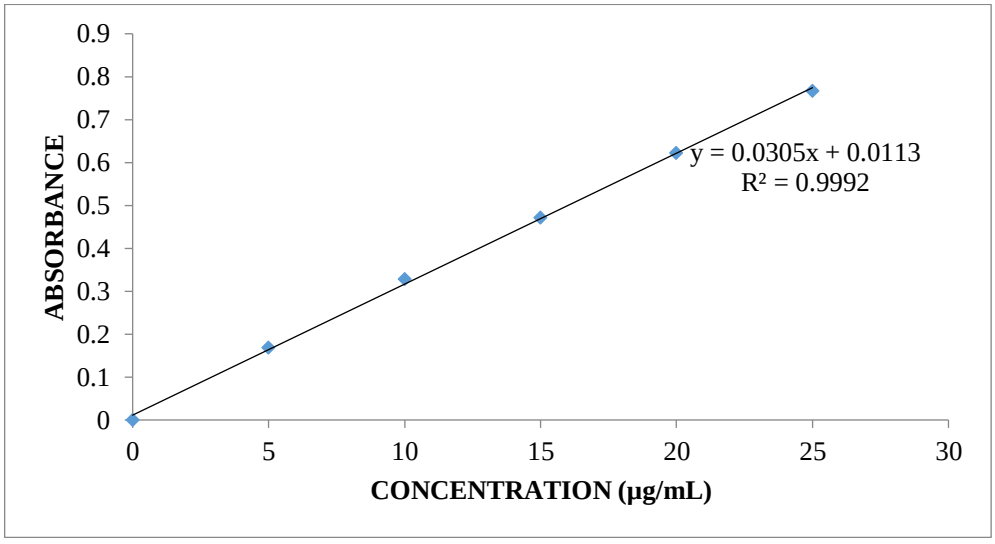

Fig : Standard graph of Omeprazole in pH 7.4 phosphate buffer

Table: 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

Evaluation:

Table : Physical evaluation of Omeprazole 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 release studies:

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

TIME	CUMULATIVE PERCENTE OF DRUG RELEASE								
(H)	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

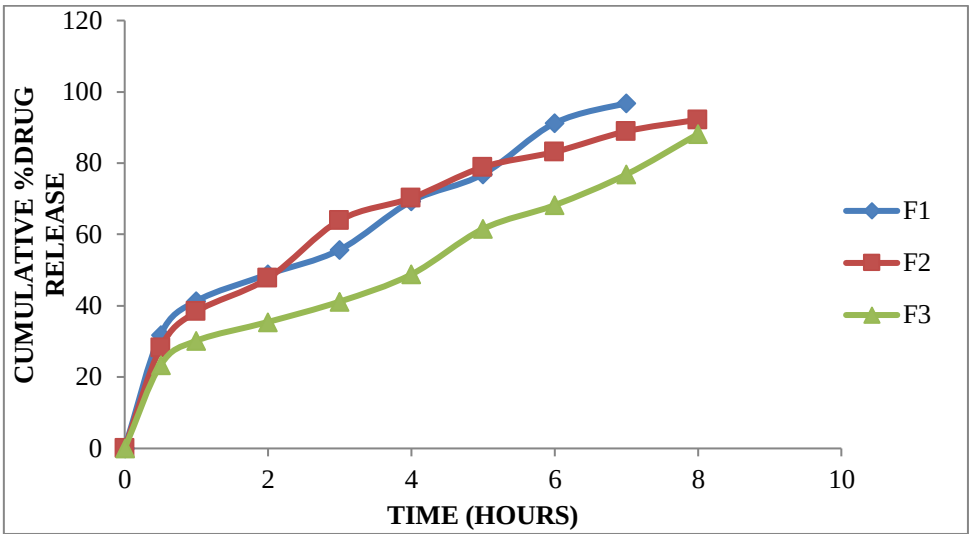

Fig: *In vitro* dissolution data for formulations F1 – F3 by using Sodium Alginate polymer

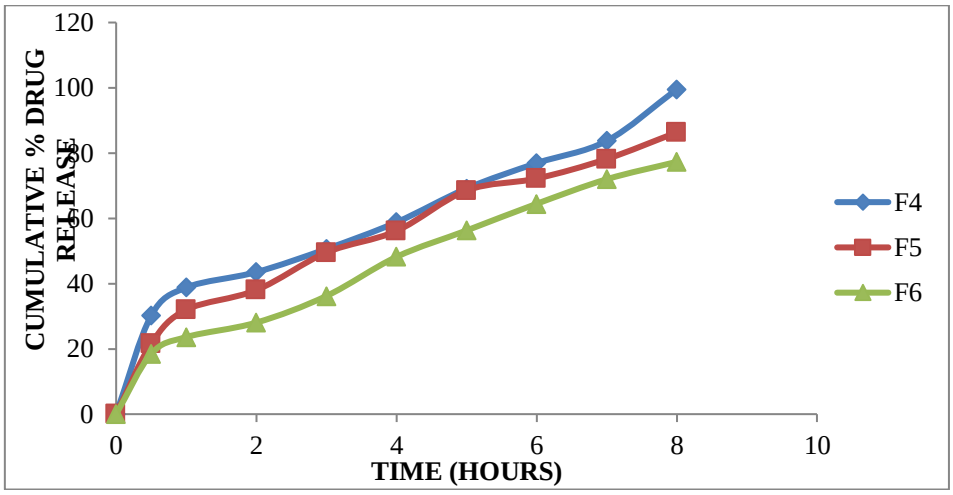

Fig: *In vitro* dissolution data for formulations F4 –F6 by using HPMC K4M polymer

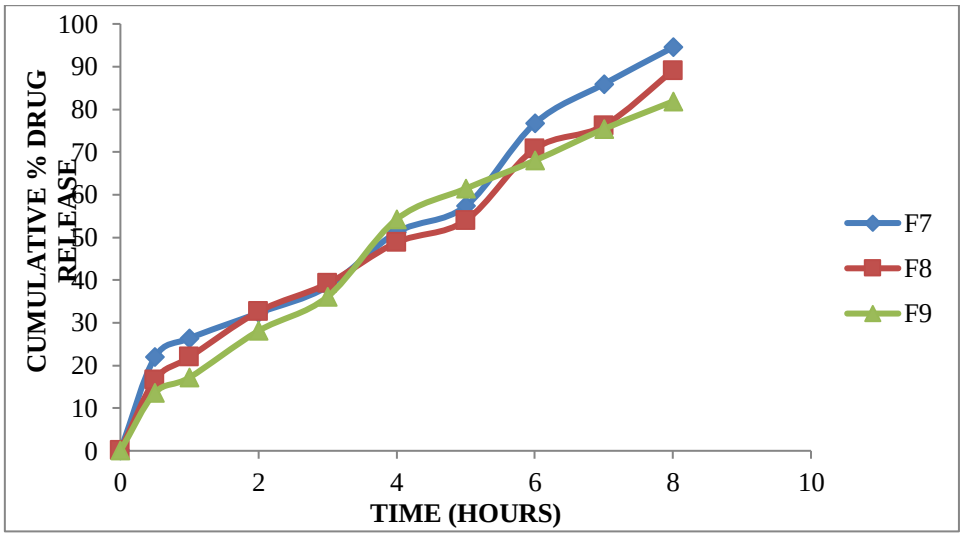

Fig : *In vitro* dissolution data for formulations F7- F9 by using SCMC polymer

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
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

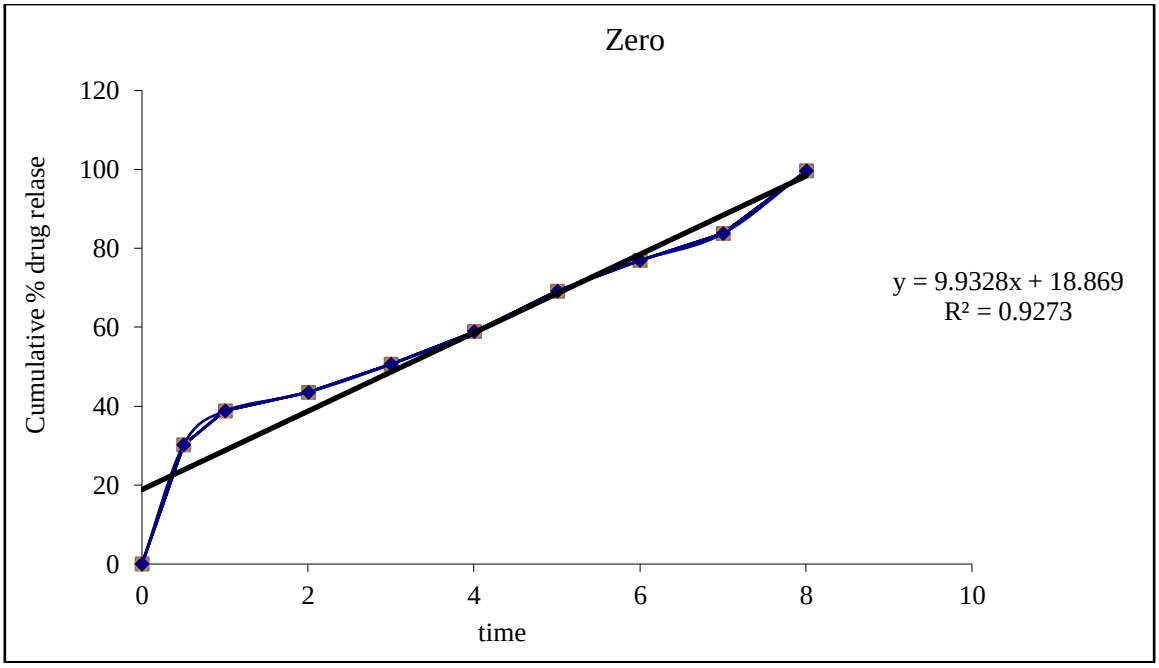

Fig : Zero order plot of optimized formulation

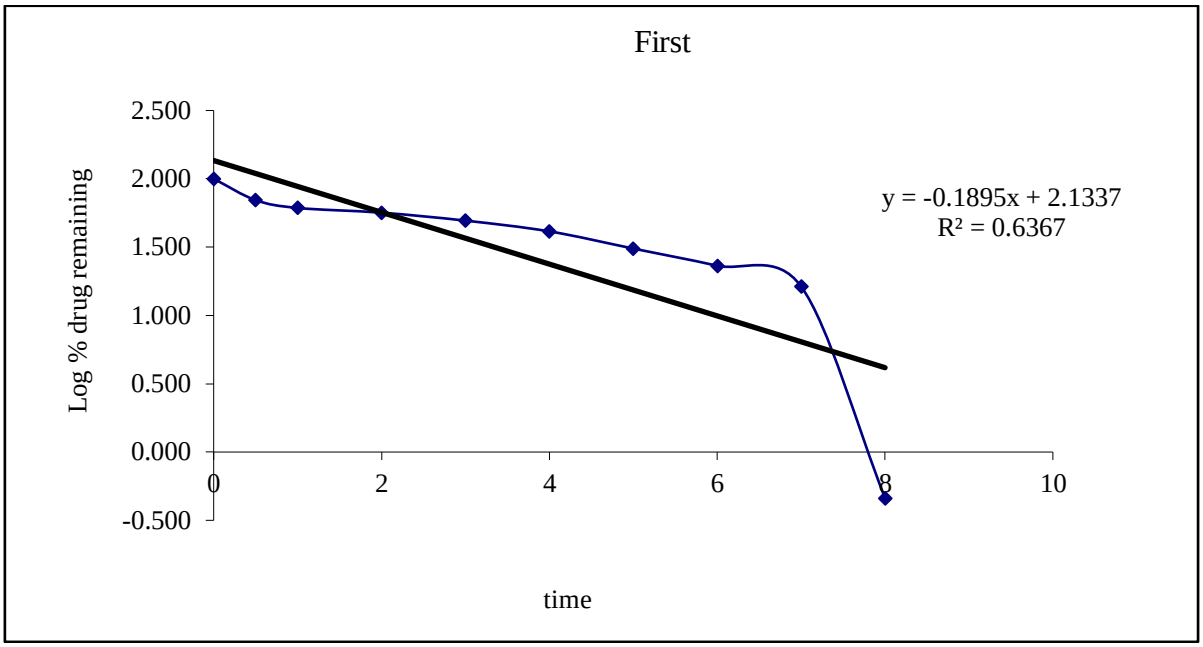

Fig: First order plot of optimized formulation

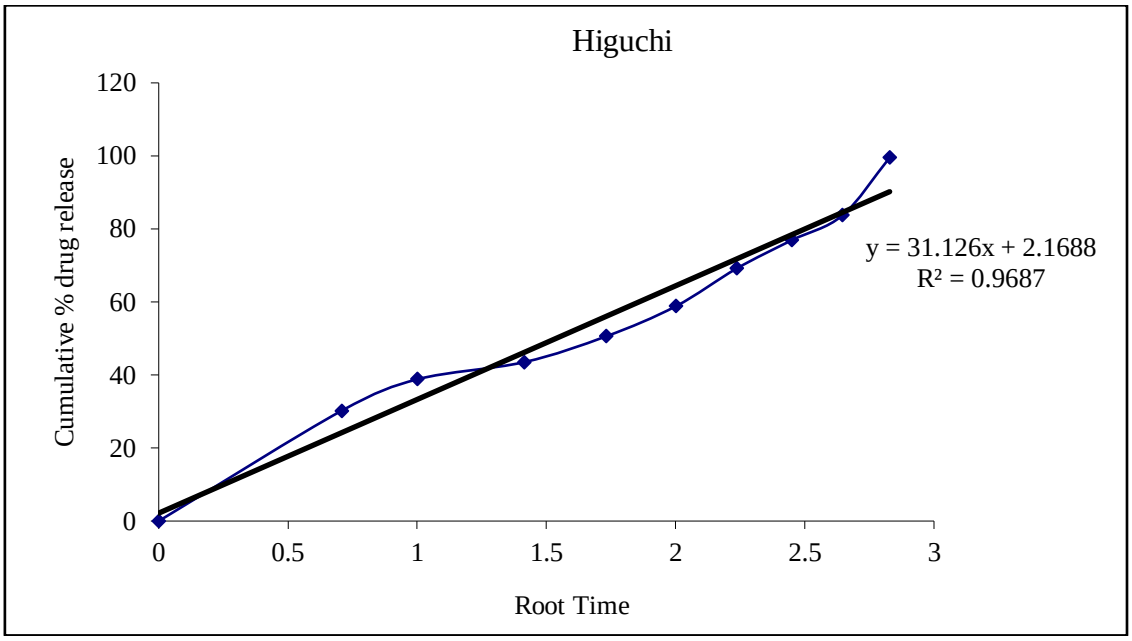

Fig : Higuchi plot of optimized formulation

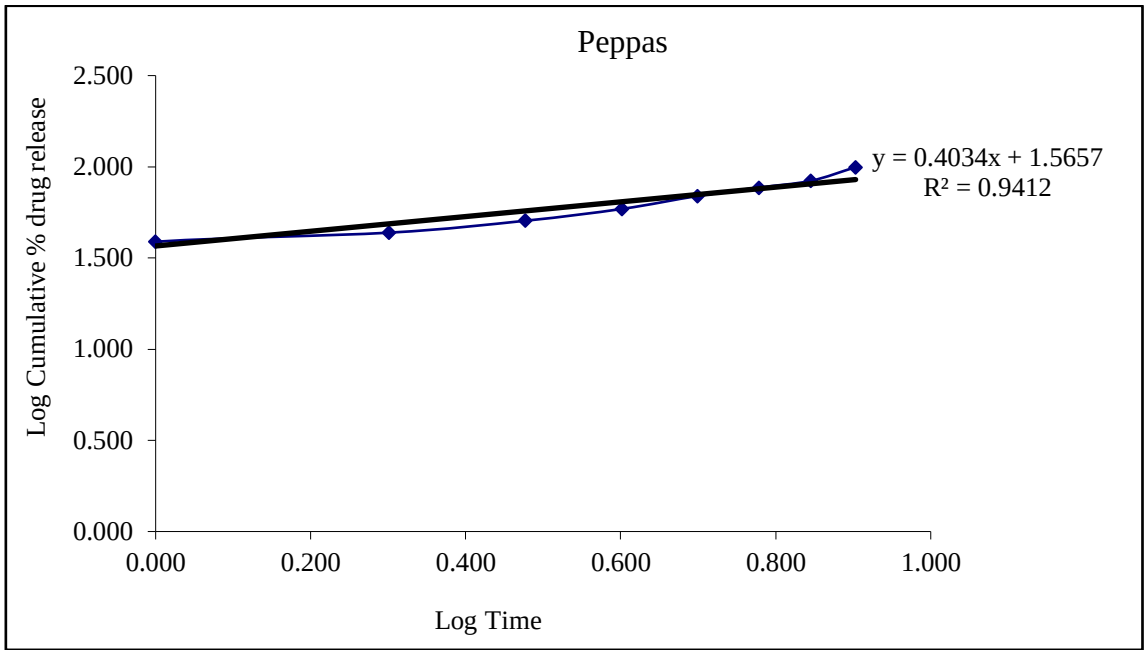

Fig: Koresmeyer-peppas plot of optimized formulation.

Drug – Excipient compatibility studies

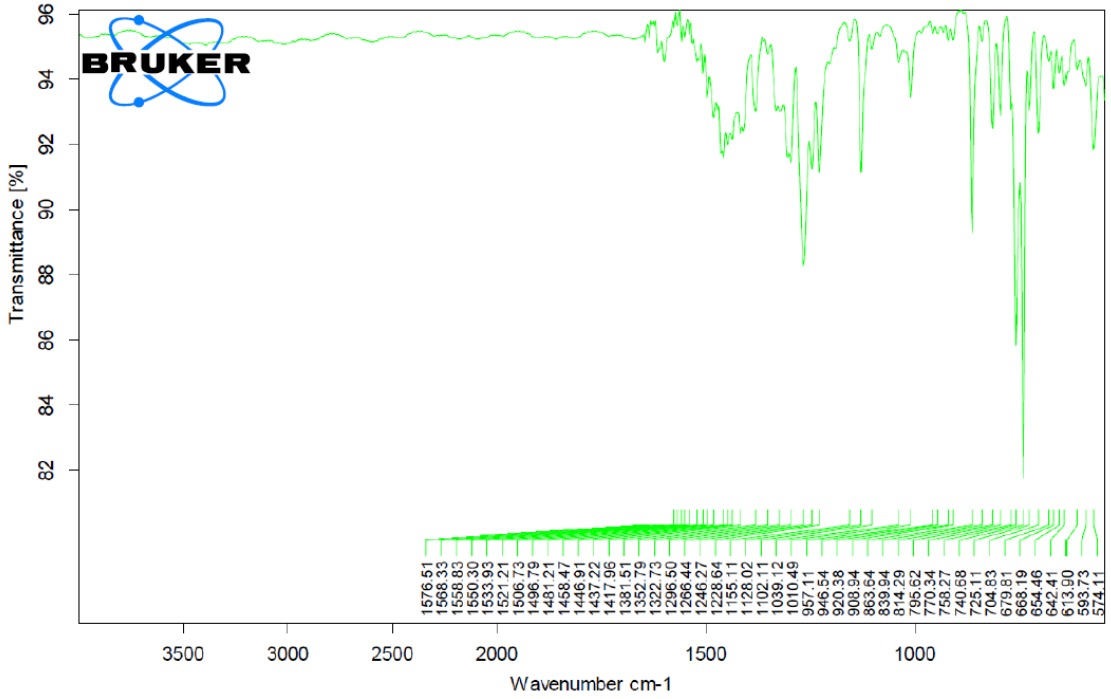

Fig : FTIR Peak of pure drug Omeprazole

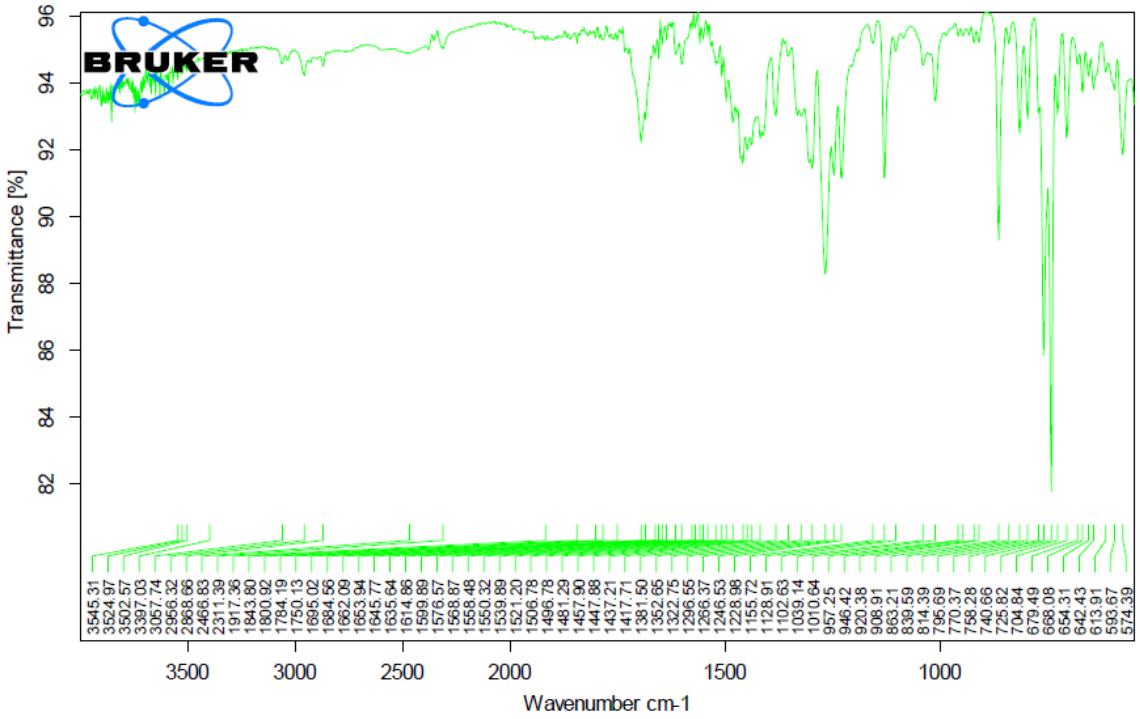

Fig : FTIR Peak of Optimised formulation

CONCLUSION

The present research was carried out to develop mucoadhesive buccal tablets of Omeprazole 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 Omeprazole 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 gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger–Ellison syndrome. Hence the mucoadhesive buccal tablets of Omeprazole 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.

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