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Formulation and evaluation of venlafaxine hydrochloride mucoadhesive buccal tablets

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ABSTRACT

Buccoadhesive tablets of Venlafaxine HCL were prepared by using Carbopol 934, HPMC K4M and Sodium CMC as mucoadhesive polymers. Nine formulations were developed with varying concentrations of polymers. V1 to V9 formulations were composed of Carbopol 934, HPMC K4M and Sodium CMC in ratios of 1:1, 1:2 and 1:3. The formulated mucoadhesive buccal tablets were assessed for quality attributes like weight variation, hardness, thickness, friability, drug content, moisture absorption, surface pH and *in vitro* drug release studies. Optimized formulation V4 showed maximum release of the drug (99.72%). The FTIR results showed no evidence of interaction between the drug and polymers. All the evaluation parameters given the positive result and comply with the standards. The results indicated that the mucoadhesive buccal tablets of Venlafaxine HCL may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in bioavailability of Venlafaxine HCL through buccal mucosa.

Keywords: Venlafaxine HCL, Carbopol 934, HPMC K4M, Sodium CMC 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.

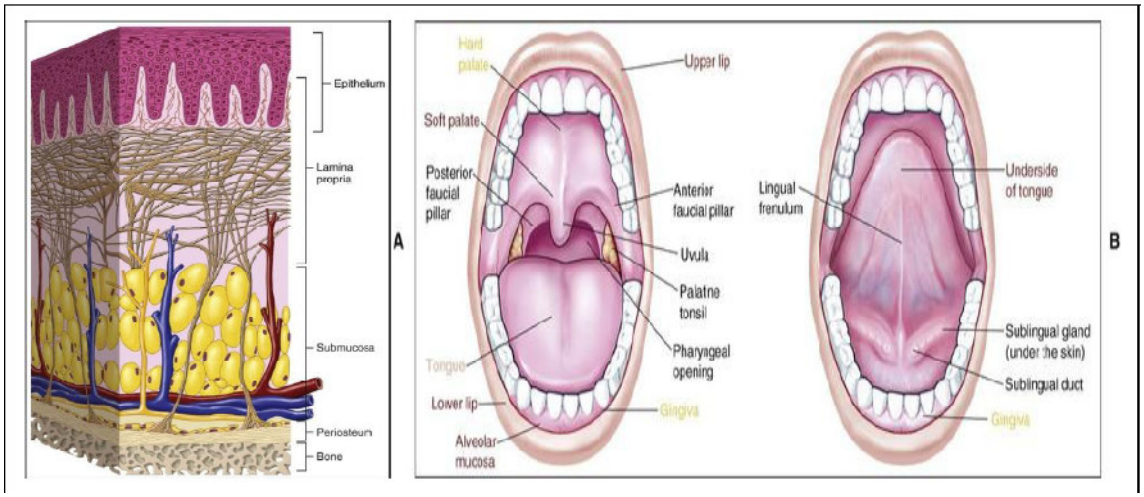

Figure 1: Anatomy of Oral Mucosa

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.

Aim and objective

Aim

The aim of present work is to formulate and evaluate bioadhesive buccal tablets of Venlafaxine HCL drug to release the drug unidirectionally in the buccal cavity.

Objective

The main objective of the present study is to avoid first pass metabolism, prolonging duration of action of drug and to enhance the bioavailability of drug by using bioadhesive polymers like Carbopol 934, HPMC K4M, Sodium CMC and Microcrystalline cellulose as a diluent, Magnesium stearate as a lubricant to perform all possible evaluation parameters.

Methodology

MATERIALS AND METHOD MATERIALS

Venlafaxine HCL by SURA LABS, Dilsukhnagar, Hyderabad.HPMC Carbopol 934 was gift sample from Zydus Cadila, Ahmedabad, HPMC K4M was gift sample from Acurate Pharma , MCC and Magnesium stearate was gift sample from Chemdie Corporation. Chemdie Corporation, Sodium CMC, Talc and Saccharin sodium was gift sample from Sd fine Chem.Ltd. Mumbai

Table 1: Formulation Chart

INGREDIENTS (MG)	FORMULATION CODES								
	V1	V2	V3	V4	V5	V6	V7	V8	V9
Venlafaxine HCL	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Carbopol 934	20	40	60	-	-	-	-	-	-
HPMC K4M	-	-	-	20	40	60	-	-	-
Sodium CMC	-	-	-	-	-	-	20	40	60
MCC	118.5	98.5	78.5	118.5	98.5	78.5	118.5	98.5	78.5
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 2: Solubility studies

S.No	Medium	Amount present (µg/mL)
1	Phosphate pH 6.8 buffer	99.76
2	Phosphate pH 7.4 buffer	97.24

Saturation solubility of Venlafaxine HCL in various buffers were studied and shown in the Table 2. The results revealed that the solubility of the Venlafaxine HCL was increased from pH 6.8 to 7.4. The solubility of the Venlafaxine HCL in phosphate buffer pH 6.8 is 99.76µg/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} 226 nm)

Standard graph of Venlafaxine HCL was plotted as per the procedure in experimental method and its linearity is shown in Table 9.2 and Fig 9.1**.** The standard graph of Venlafaxine HCL showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Table 3: Standard graph values of Venlafaxine HCL in pH 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
2	0.198
4	0.411
6	0.595
8	0.773
10	0.954

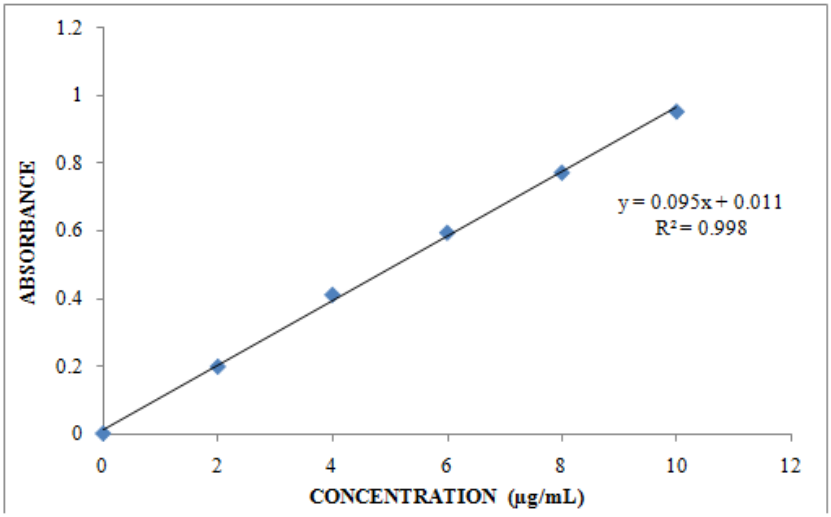

Fig 2: Standard graph of Venlafaxine HCL in pH 6.8 phosphate buffer

Standard graph in phosphate buffer pH 7.4 (λ_{max} 228 nm)

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

Table 4: Standard graph values of Venlafaxine HCL in pH 7.4 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
2	0.129
4	0.244
6	0.358
8	0.478
10	0.582

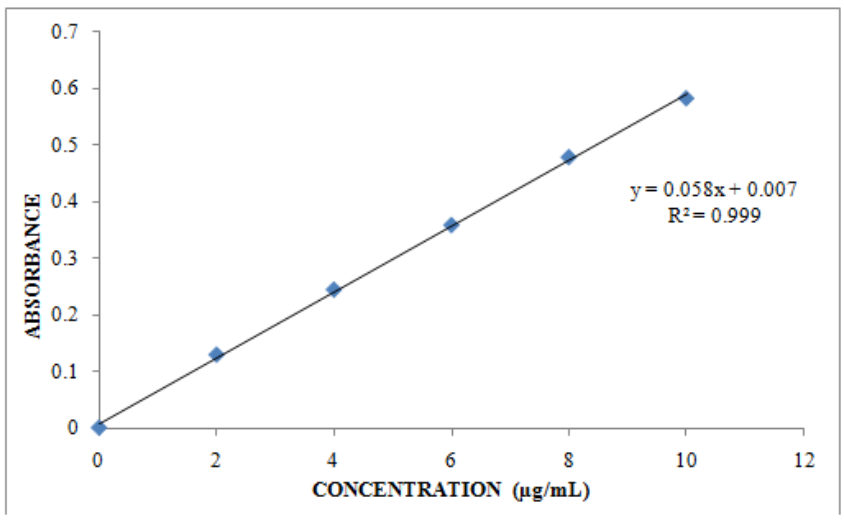

Fig 3 : Standard graph of Venlafaxine HCL in pH 7.4 phosphate buffer

Table 5: Physical properties of pre-compression blend

Formulation Code	Angle of repose (□)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
V1	28.75	0.481	0.572	15.90	1.18
V2	27.33	0.475	0.566	16.07	1.19

V3	25.38	0.524	0.599	12.52	1.14
V4	26.43	0.412	0.483	14.69	1.17
V5	24.77	0.488	0.537	9.12	1.10
V6	26.42	0.439	0.521	15.73	1.18
V7	28.19	0.559	0.649	13.94	1.16
V8	29.58	0.331	0.393	15.77	1.18
V9	28.73	0.362	0.428	15.42	1.18

Evaluation of buccal tablets

Table 6: Physical evaluation of Venlafaxine HCL buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
V1	198.47	4.01	4.9	0.56	96.10
V2	196.92	4.92	4.0	0.36	98.65
V3	199.30	4.35	5.3	0.24	99.10
V4	197.12	4.87	4.1	0.68	97.34
V5	198.82	4.28	5.2	0.59	98.58
V6	199.27	4.13	5.6	0.32	96.14
V7	200.04	4.79	4.1	0.77	99.82
V8	198.75	4.35	5.0	0.62	95.38
V9	197.80	4.60	4.8	0.43	98.76

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 Venlafaxine HCL from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs 9.3 to 9.5.

Table 7: *In vitro* dissolution data for formulations V1 – V9

TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE								
	V1	V2	V3	V4	V5	V6	V7	V8	V9
0	0	0	0	0	0	0	0	0	0
0.5	20.89	18.72	18.90	28.16	15.82	10.92	15.05	13.53	11.58
1	28.32	38.50	20.35	36.86	25.73	21.03	23.19	18.92	20.16
2	36.58	47.93	29.17	43.57	33.90	28.51	30.27	28.60	26.09
3	51.91	60.46	36.26	48.16	48.17	40.99	36.59	37.18	34.10
4	65.54	67.59	43.83	54.92	56.34	46.42	49.01	46.82	53.23
5	76.73	76.98	57.41	67.34	63.10	53.60	55.39	52.99	57.42
6	89.15	80.42	61.96	73.62	70.09	62.17	75.53	67.76	65.99
7	96.21	86.18	73.63	82.53	75.37	70.96	85.89	77.14	76.37
8		90.13	85.57	99.72	87.24	75.12	93.73	87.34	81.83

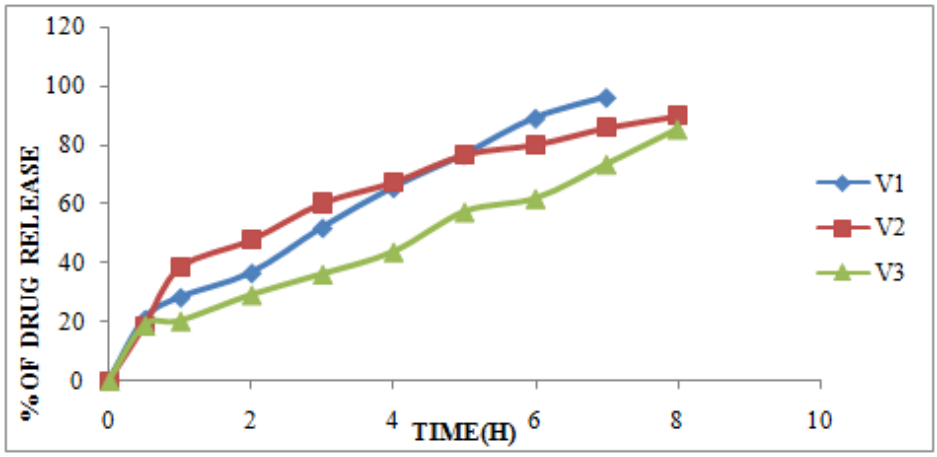

Fig 3 : *In vitro* dissolution data for formulations V1 – V3 by using Carbopol 934 polymer

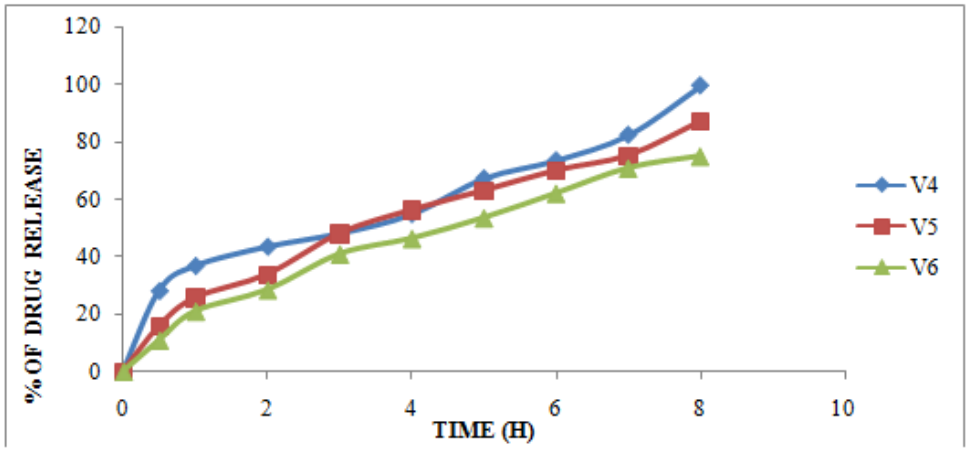

Fig 4: *In vitro* dissolution data for formulations V4 –V6 by using HPMC K4M polymer

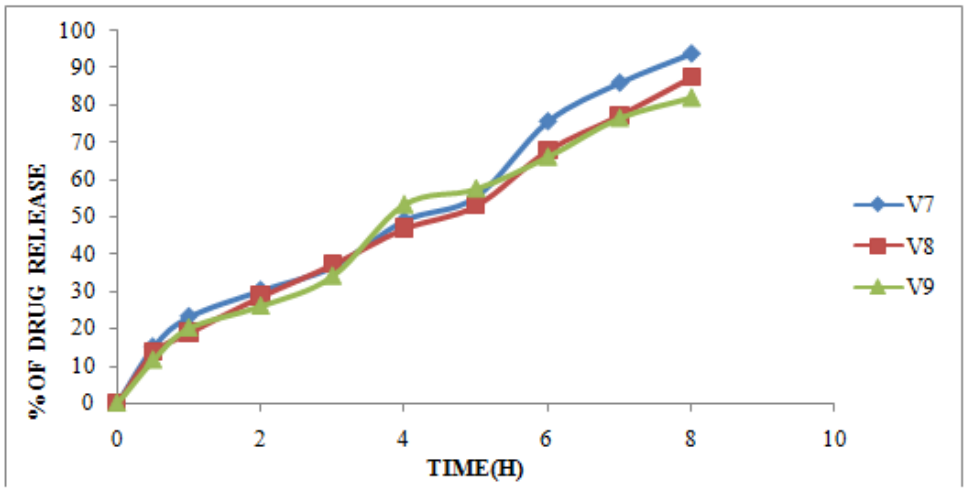

Fig 5: *In vitro* dissolution data for formulations V7- V9 by using Sodium CMC polymer

Table 8 : Moisture absorption, surface pH of selected formulations

Formulation Code	Moisture absorption	Surface pH
V4	97	6.13
V7	95	6.09

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 V4 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 5.51 to 6.13 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 Venlafaxine HCL 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 9: 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
28.16	0.5	0.707	1.450	-0.301	1.856	56.320	0.0355	-0.550	71.84	4.642	4.157	0.485
36.86	1	1.000	1.567	0.000	1.800	36.860	0.0271	-0.433	63.14	4.642	3.982	0.660
43.57	2	1.414	1.639	0.301	1.752	21.785	0.0230	-0.361	56.43	4.642	3.836	0.806
48.16	3	1.732	1.683	0.477	1.715	16.053	0.0208	-0.317	51.84	4.642	3.729	0.913
54.92	4	2.000	1.740	0.602	1.654	13.730	0.0182	-0.260	45.08	4.642	3.559	1.083
67.34	5	2.236	1.828	0.699	1.514	13.468	0.0149	-0.172	32.66	4.642	3.196	1.445
73.62	6	2.449	1.867	0.778	1.421	12.270	0.0136	-0.133	26.38	4.642	2.977	1.665
82.53	7	2.646	1.917	0.845	1.242	11.790	0.0121	-0.083	17.47	4.642	2.595	2.047
99.72	8	2.828	1.999	0.903	-0.553	12.465	0.0100	-0.001	0.28	4.642	0.654	3.987

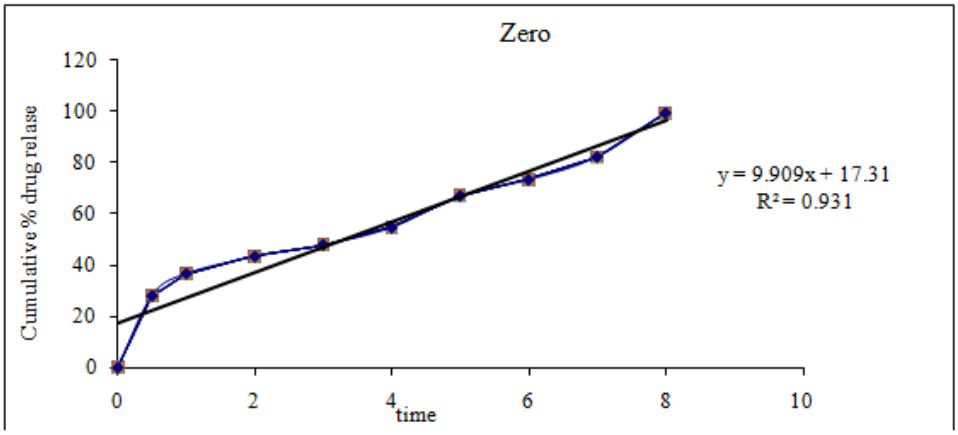

Fig 6: Zero order plot of optimized formulation

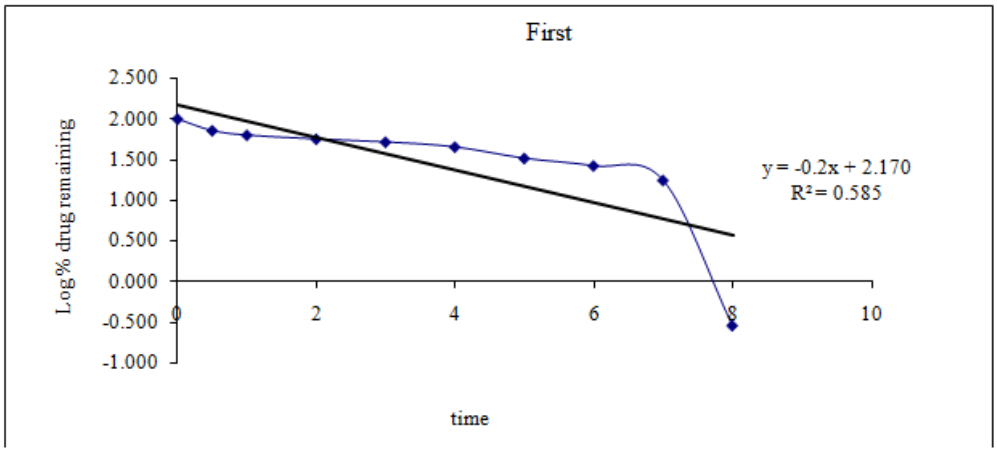

Fig 7 : First order plot of optimized formulation

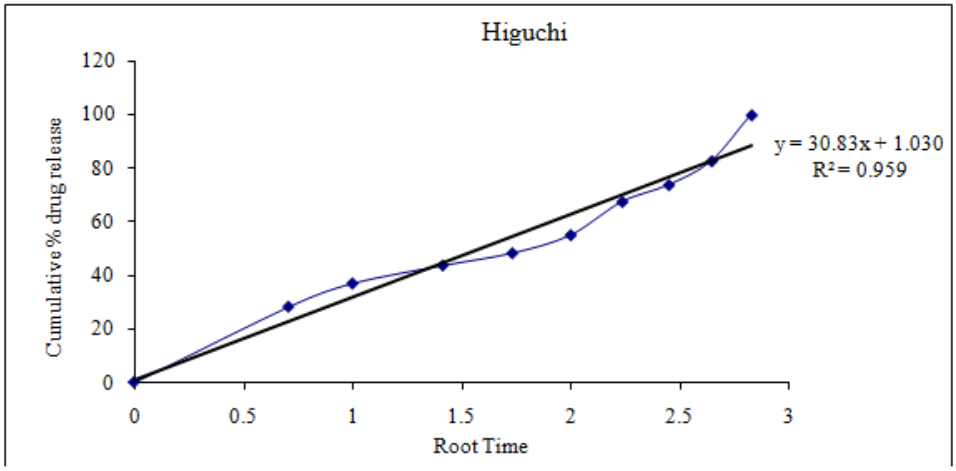

Fig 8: Higuchi plot of optimized formulation

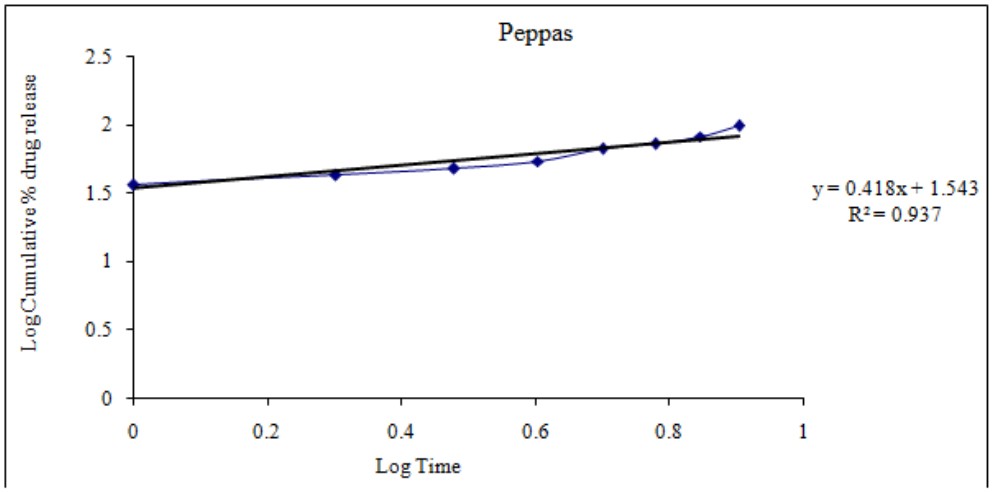

Fig 9: Koresmeyer-peppas plot of optimized formulation.

This formulation was following Higuchi release mechanism with regression value of 0.959.

Drug – excipient compatibility studies by physical observation

Venlafaxine HCL 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 Venlafaxine HCL drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Venlafaxine HCL 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.

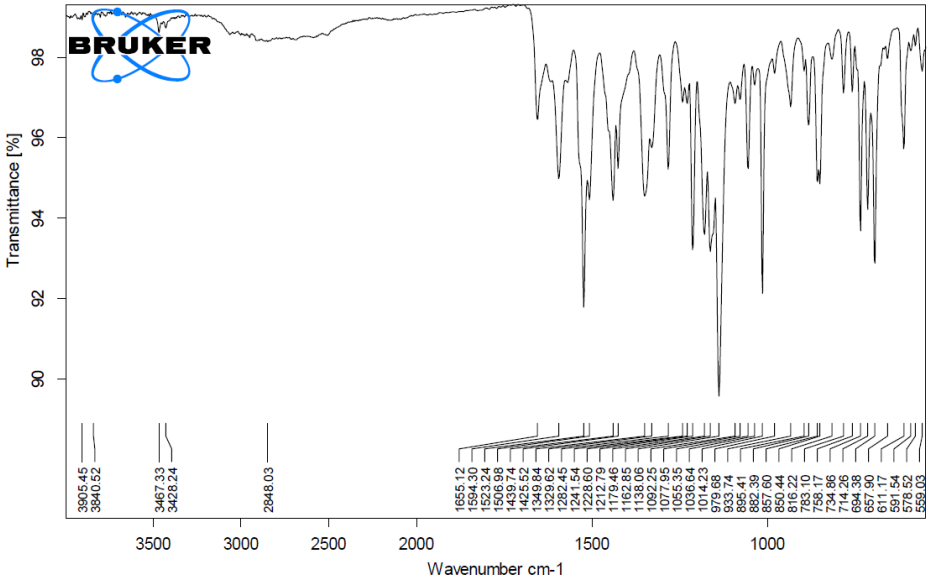

Fig 10 : FTIR Peak of pure drug Venlafaxine HCL

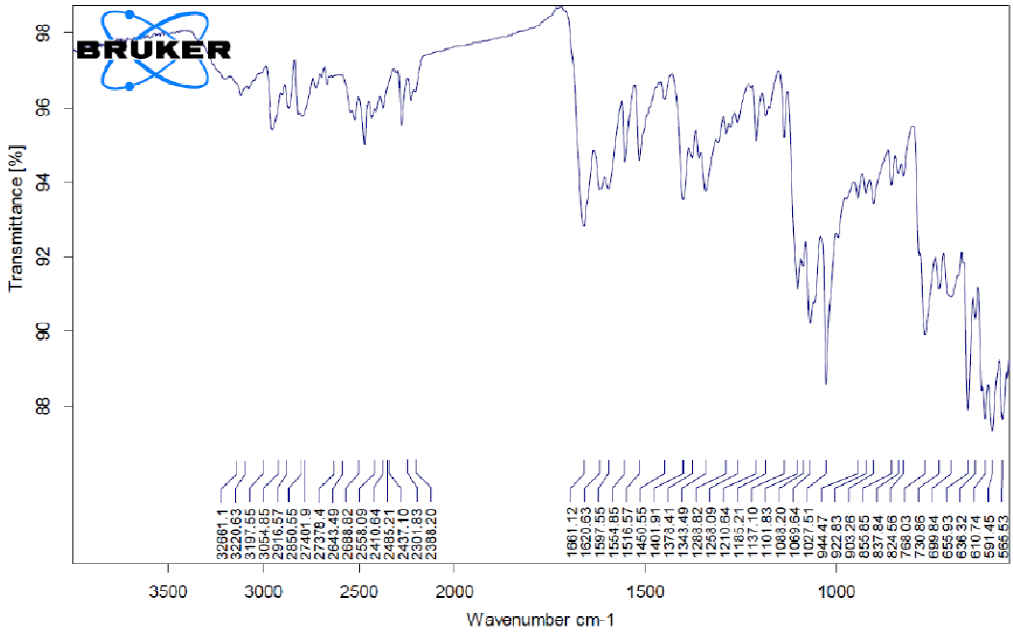

Fig 11: FTIR Peak of Optimised formulation

CONCLUSION

The present research was carried out to develop mucoadhesive buccal tablets of Venlafaxine HCL using various polymers. 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 Venlafaxine HCL could be prepared using Carbopol 934, HPMC K4M and Sodium CMC 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 pharmacopeial 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. The *in-vitro* release of Venlafaxine HCL was extended for 8 h. Formulations V4 batch shows good *in vitro* drug release 99.72%. From the results of present investigation it can be concluded that Venlafaxine HCL can certainly be administered through the oral mucosa and HPMC K4M is suitable for development of buccoadhesive system.

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