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Research

Formulation And Evaluation Of Mucoadhesive Buccal Tablets Of Valsartan

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Abstract

Buccoadhesive tablets of Valsartan 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 Valsartan may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in bioavailability of Valsartan through buccal mucosa.

Keywords: Valsartan, 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.

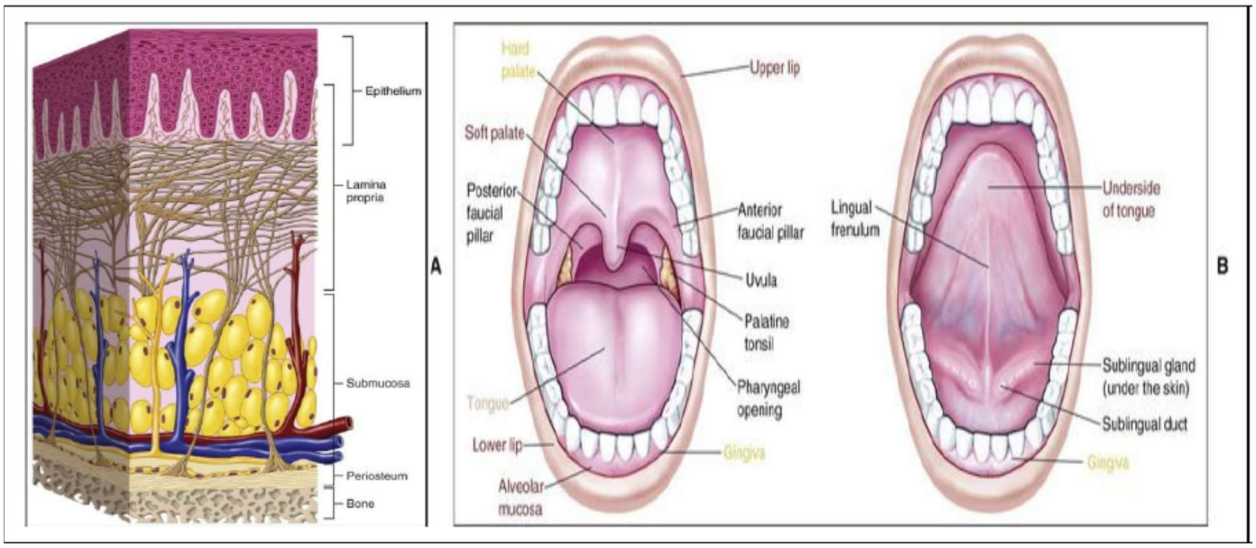

Fig 1: Anatomy of Oral Mucosa

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.

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

Valsartan-Procured From Dr. Reddy's, Provided by SURA LABS, Dilsukhnagar, Hyderabad.,Carbopol 934 Zydus Cadila, Ahmedabad, HPMC K4M-Acurate Pharma, Sodium CMC-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

Determination of Valsartan Melting point

The melting point of Valsartan was determined by capillary tube method according to the USP. A sufficient quantity of Valsartan powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Valsartan in the tube passed into liquid phase.

Preformulation studies

Analytical method used in the determination of Valsartan

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.

Preparation of standard graph in phosphate buffer pH 6.8: 100 mg of Pure drug was dissolved in small amount of Methanol (5-10 ml), allowed to shake for few minutes and then the volume was made up to 100ml with phosphate buffer pH 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 6.8. From this secondary stock 0.2, 0.4, 0.6, 0.8, 1, ml was taken separately and made up to 10 ml with phosphate buffer pH 6.8 to produce 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 226 nm using a UV spectrophotometer. Standard calibration curve values were shown in Table (9.1). The standard calibration curve of Valsartan in phosphate buffer pH 6.8 was shown in fig 9.1.

Preparation of standard graph in phosphate buffer pH 7.4: 100 mg of drug was dissolved in small amount of phosphate buffer and make the volume up to 100ml with phosphate buffer pH 7.4, from this primary stock(1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 7.4. From this secondary stock 0.2, 0.4, 0.6, 0.8, 1 ml were taken separately and made up to 10 ml with phosphate buffer pH 7.4, to produce 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 226 nm using a UV spectrophotometer. Standard calibration curve values were shown in Table (9.2). The standard calibration curve of Valsartan in phosphate buffer pH 7.4 was shown in fig 9.2.

Preformulation parameters

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 characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

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

Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION CODES								
	V1	V2	V3	V4	V5	V6	V7	V8	V9
Valsartan	40	40	40	40	40	40	40	40	40
Carbopol 934	20	40	60	-	-	-	-	-	-
HPMC K4M	-	-	-	20	40	60	-	-	-
Sodium CMC	-	-	-	-	-	-	20	40	60
MCC	116	96	76	116	96	76	116	96	76
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

Organoleptic properties

Table 1: Organoleptic properties

S NO.	Properties	Reported results	Observed results
1	State	Solid	Solid
2	Colour	White	White
3	Odour	Odourless	Odourless
4	Melting point	116-117	116°C

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 Valsartan in various buffers were studied and shown in the Table 9.1. The results revealed that the solubility of the Valsartan was increased from pH 6.8 to 7.4. The solubility of the Valsartan 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. Based on the Solubility study more solubility is showed in pH 6.8, So pH 6.8 is selected for Dissolution medium.

Standard graph in phosphate buffer pH 6.8 (λ_{max} 226 nm)

Standard graph of Valsartan 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 Valsartan showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Table 3: Standard graph values of Valsartan 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

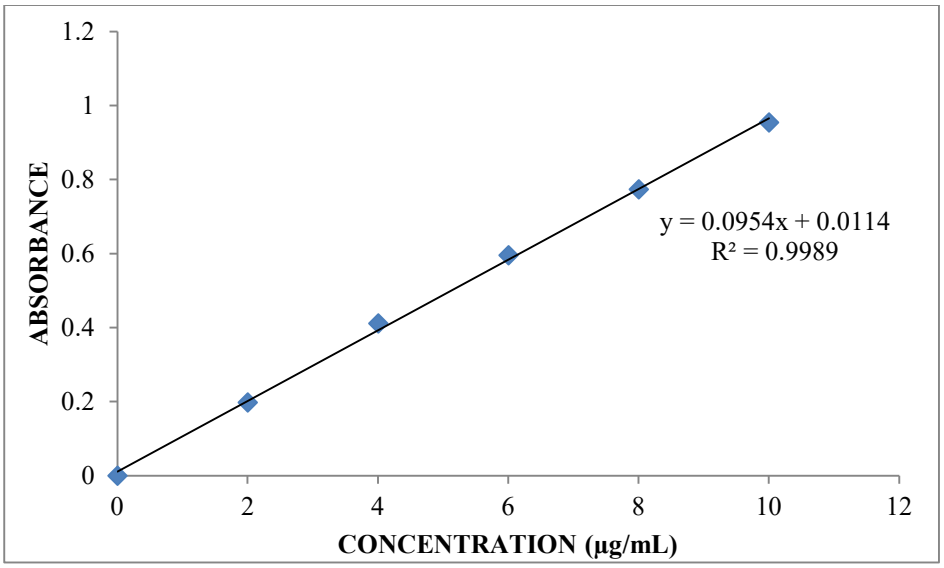

Fig 1: Standard graph of Valsartan in pH 6.8 phosphate buffer

Table 4: Standard graph values of Valsartan 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

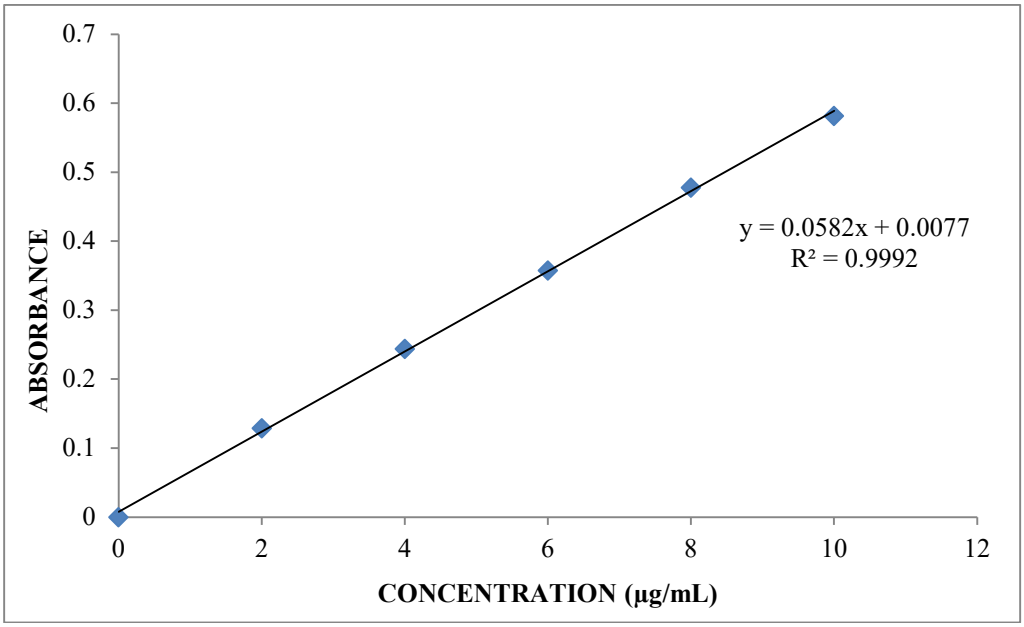

Fig 2: Standard graph of Valsartan in pH 7.4 phosphate buffer

Preformulation parameters of powder blend

Table 5: Pre-formulation parameters of Core blend
Physical properties of pre-compression blend

Formulation Code	Angle of repose (Θ)	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

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

Table 6: *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

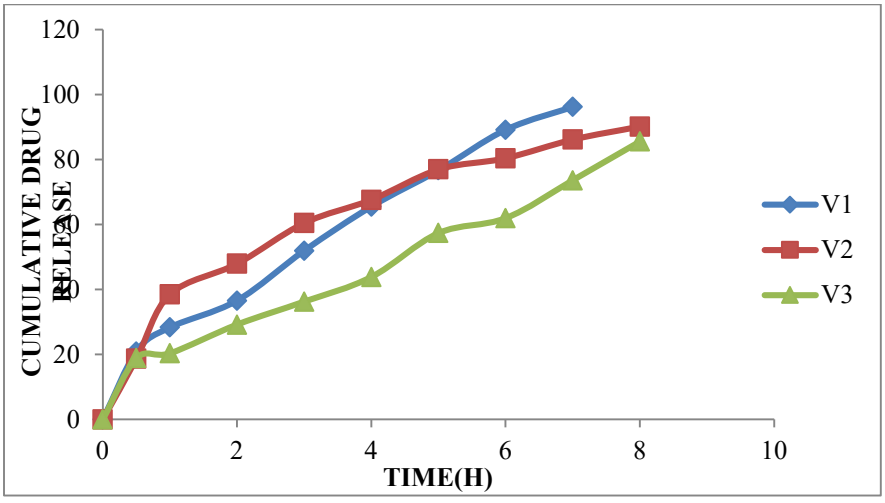

Fig 3: *In vitro* dissolution data for formulations V1 – V3 by using Carbopol 934 polymer

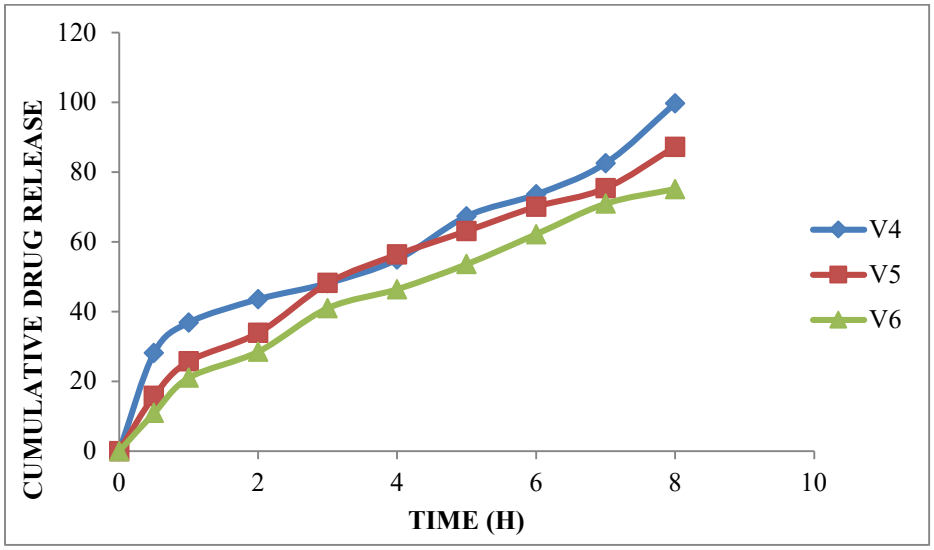

Fig 4: *In vitro* dissolution data for formulations V4 –V6 by using HPMC K4M polymer

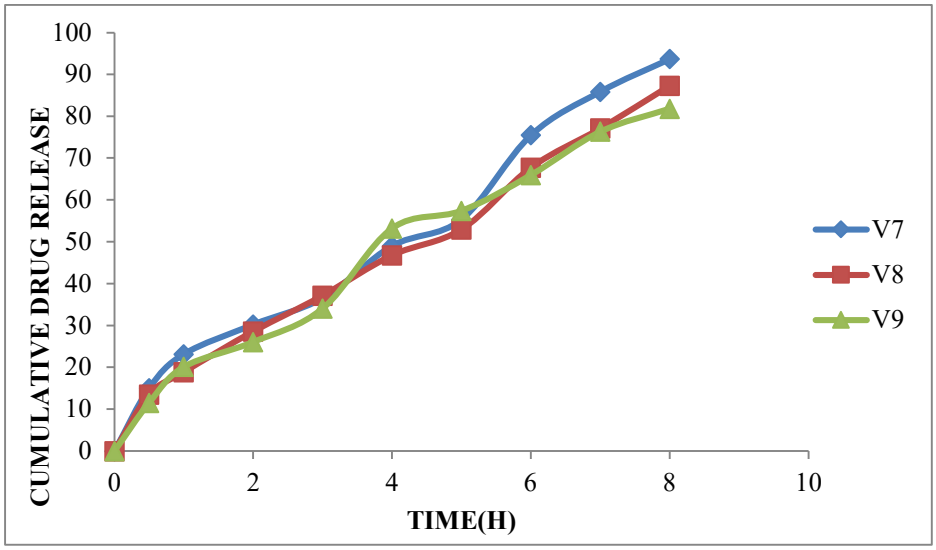

Fig 5: *In vitro* dissolution data for formulations V7- V9 by using Sodium CMC polymer

From the above graphs it was evident that Carbopol 934 in the concentration of 40mg of polymer of the total tablet weight (V2) drug with other Two Formulations V1, V3. Where as in V2 formulation the quantity of polymer was less hence it showed more drug retardation with more drug release that is 90.13 % in 8 hrs. From the above graphs it was evident that HPMC K4M in the Polymer concentration of 20mg (V4) is showing better result 99.72% drug release when compared with other two formulations V5, V6, as the concentration of polymer increases the retarding of drug release decreased. From the above graphs it was evident that Sodium CMC in the Polymer concentration 20mg formulation (V7), is showing better result 93.73% drug release when compared with other two formulations. Where as in V8, V9 formulations the concentration become high and the drug release was less. From the above results it was evident that the formulation V4 is best formulation with desired drug release pattern extended up to 8 hours. Based on the Dissolution data V2, V4 and V7 was observed more drug release compared to other formulation, So V2, V4 and V7 formulation was selected pH study.

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 Valsartan 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 7: 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

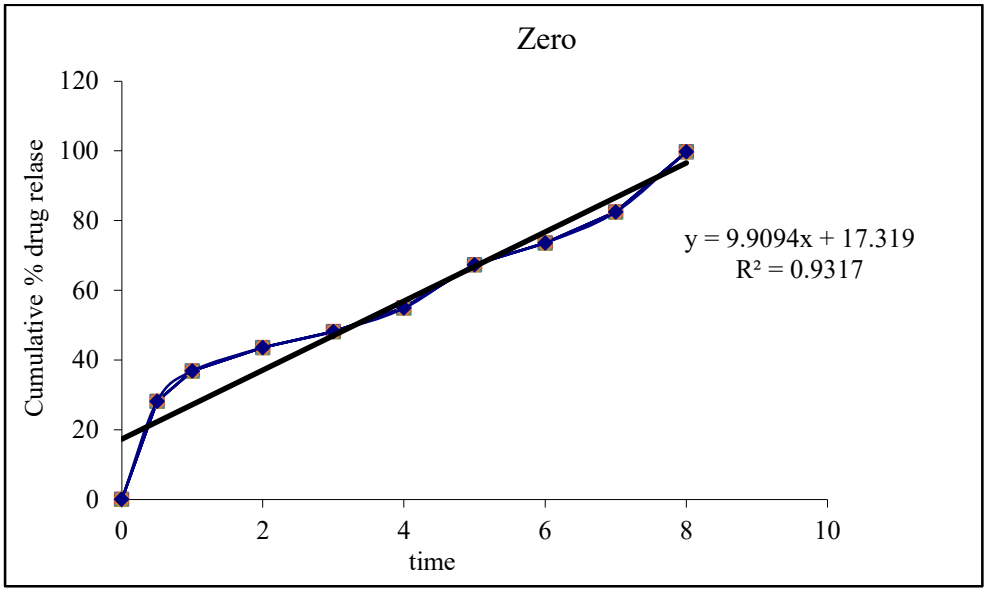

Fig 6: Zero order plot of optimized formulation

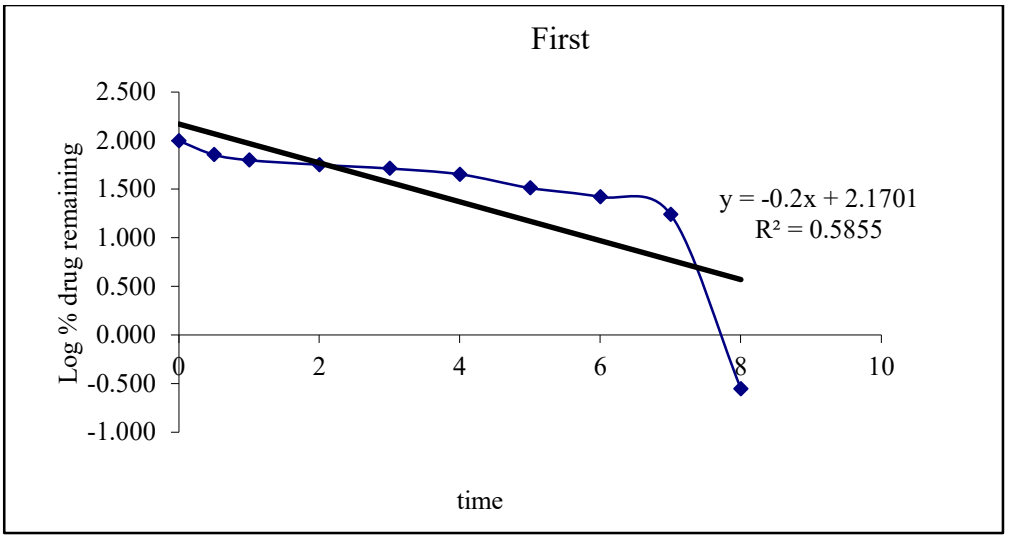

Fig 7: First order plot of optimized formulation

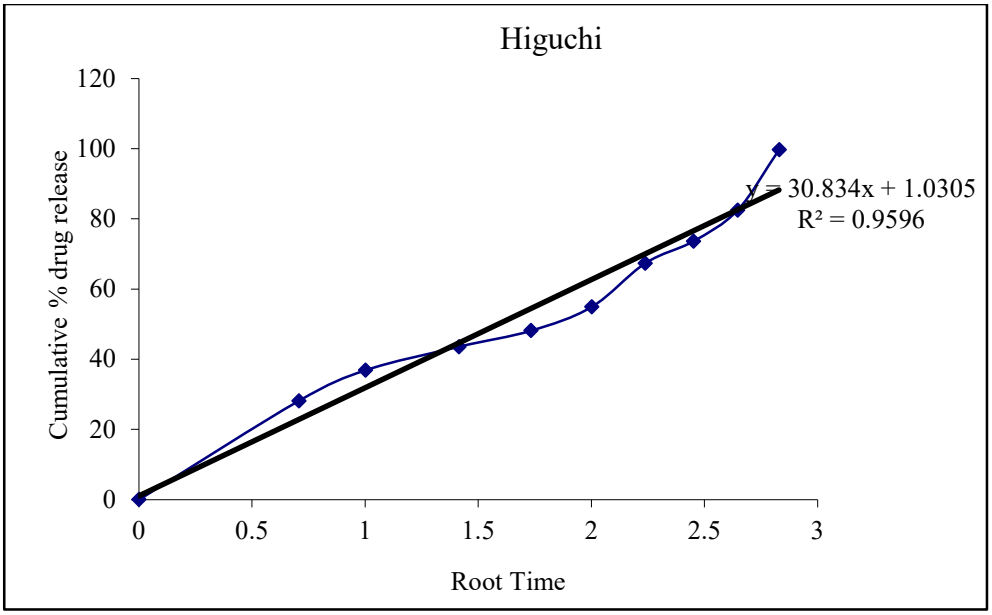

Fig 8: Higuchi plot of optimized formulation

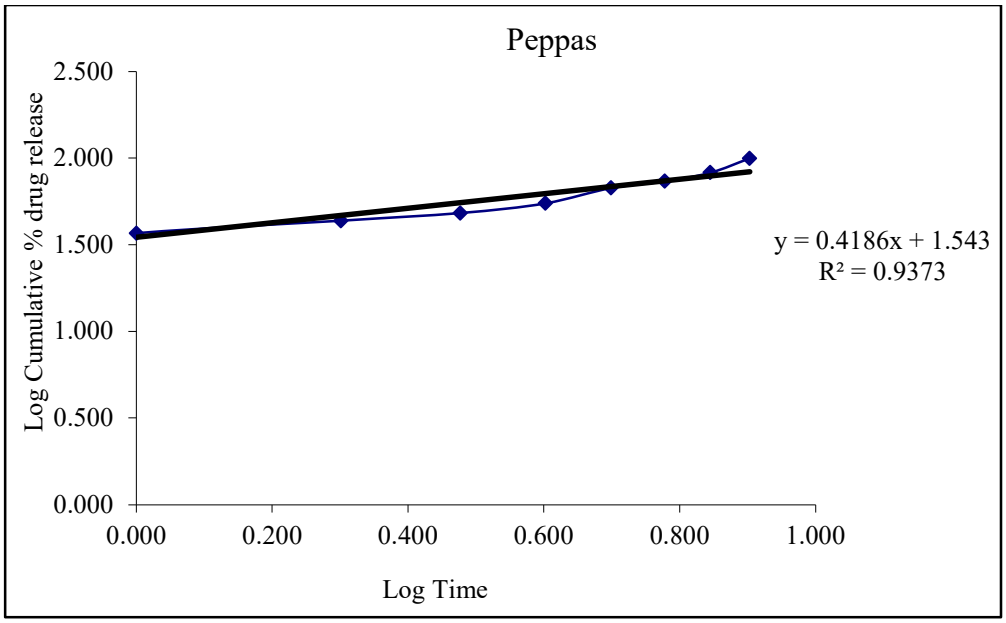

Fig 9: Koresmeyer-peppas plot of optimized formulation.

This formulation was following Higuchi release mechanism with regression value of 0.959. From the above graphs it was evident that the formulation V4 was followed Higuchi release mechanism.

Drug and excipient compatibility studies

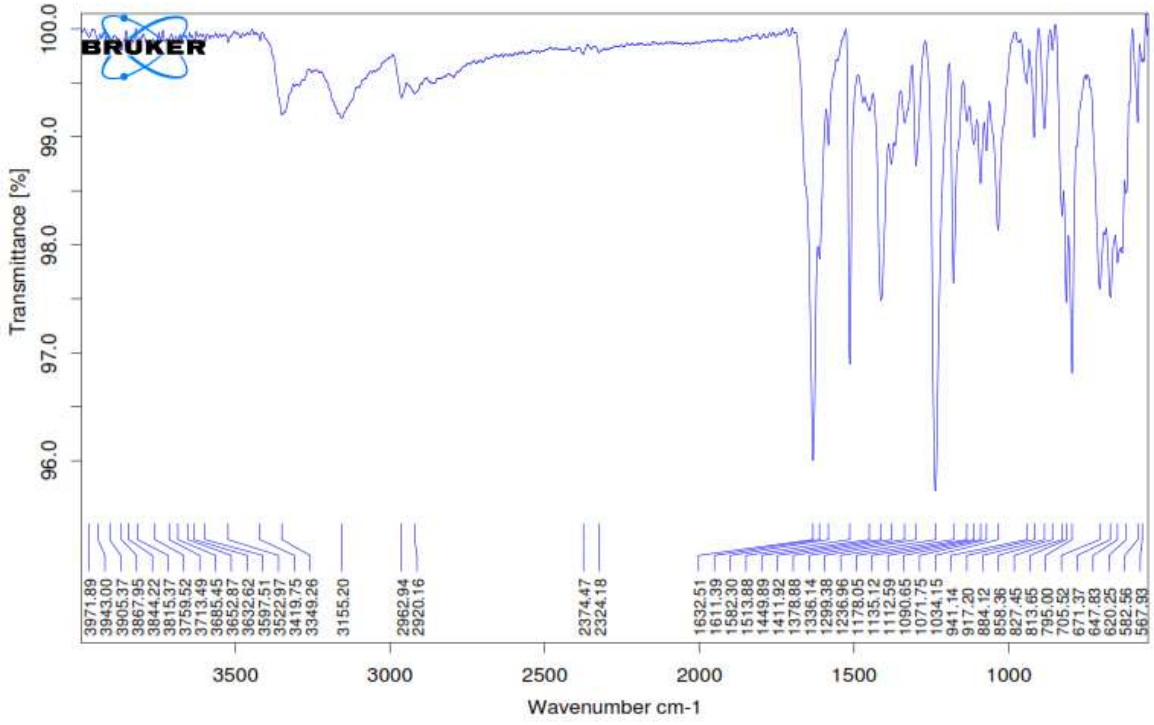

Fig 10: FTIR Peak of pure drug Valsartan

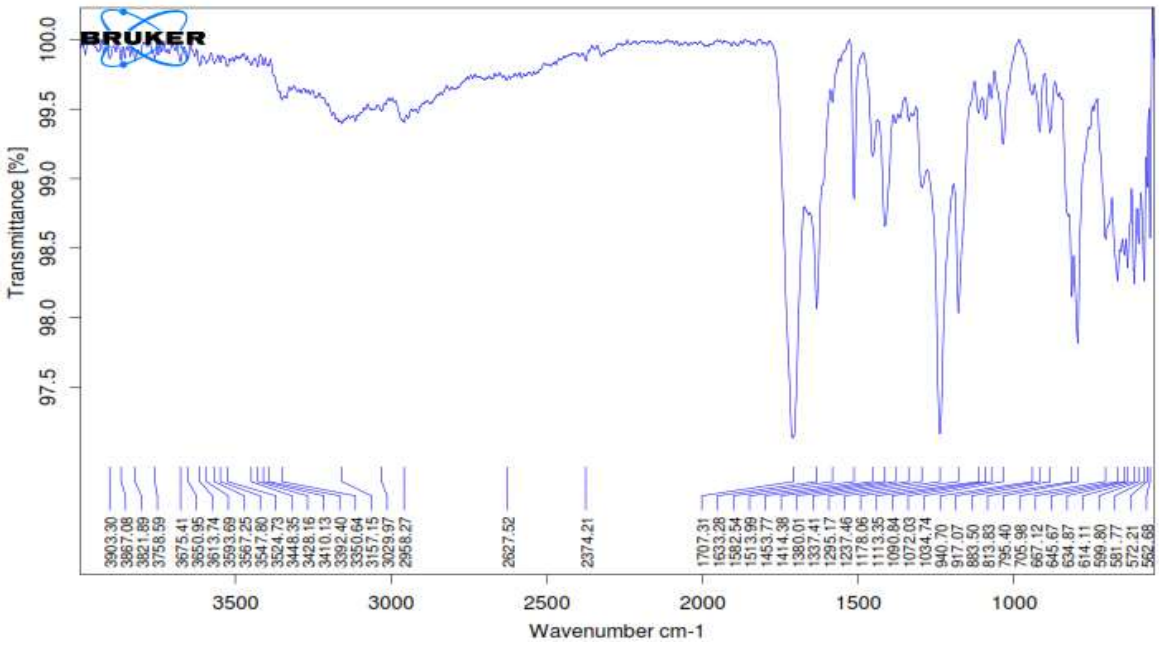

Fig 11: FTIR Peak of Optimised formulation

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra.

CONCLUSION

The present research was carried out to develop mucoadhesive buccal tablets of Valsartan 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 Valsartan 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 Valsartan 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 Valsartan can certainly be administered through the oral mucosa and HPMC K4M is suitable for development of Buccoadhesive system.

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