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FORMULATION AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL TABELTS CONTAINING SOLID DISPERSION OF VALSARTAN

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ABSTRACT

The goal of present research work was to formulate and characterize mucosal adhesive buccal tablets containing solid dispersion of Valsartan. Solid dispersion was prepared with three different carriers namely, Pluronic F-68, PVP K-30 and Mannitol in ratio 1:1, 1:3, 1:5 using solvent evaporation and melting method. Solid dispersion containing Drug: Mannitol in ratio 1:1 exhibited highest drug content and solubility and was further used for tablet formulation by direct compression method using Carbopol 934, HPMC K15M and SCMC as mucosal adhesive polymers. A backing membrane of ethyl cellulose was applied to promote the unidirectional release of drug. Results obtained indicated that all the physicochemical parameters were lying in acceptable limits. Formulation F4 was found to be best as it exhibited highest drug release, swelling index and mucoadhesive strength with acceptable range of other physicochemical parameters. Hence, it was determined that valsartan mucosal adhesive buccal tablets can be formulated to enhance the solubility and bioavailability. However, the properties of tablet depend upon the polymer and its concentration.

KEYWORDS: *Mucoadhesive, Buccal, Mucosal, Solid dispersion, Valsartan, Solvent evaporation*

INTRODUCTION

Delivery of drug molecules via oral route is most desired in comparison to other administration routes but it also has some restrictions including primary hepatic metabolism, degradation of drug by enzymes within the alimentary canal, and toxicity in GI that limits oral administration of some drugs, mostly peptides, and proteins.[1 2] Most pharmaceutical dosage forms are designed for immediate release which has some drawbacks such as frequent administration is required for the medicines that have a short half-life, poor patient compliance, and higher chances of adverse effects due to fluctuation in drug levels, particularly in case of drugs with small therapeutic index. Several technological innovations were developed that brought the advancement of delivering drug in controlled way that may modernize drug therapy, offers a variety of therapeutic benefits, and overcome the shortcomings of traditional systems of drug delivery.[3]

Drug delivery via buccal mucosa is one the good substitute among the a number of routes of administration as it has several merits over the other routes for systemic delivery of medicine such as directly deliver drug to systemic, avoidance of first-pass effect, and circumvention of pre-systemic elimination within the gastrointestinal (GI) tract. These features make it a more appealing and feasible location for medicine delivery directly into the blood. Additionally, the buccal cavity is more practical for self-medication because it allows for the fast removal of the dosage form in the event of toxicity.[4] Buccal drug delivery systems can be formulated as solid unit dosage forms, ointments, gels etc.[5] In the previous few years, the mucoadhesive drug delivery system has become popular and gained substantial attention for both local and

systemic medication delivery due to exceptional approachability, avoiding first-pass metabolism, large blood supply, safety, and more patient acceptability with enhanced and better treatment.[6] In 1947 T.R. Jacoby *et al*., made attempts to formulate bio-adhesive ointment of Penicillin using gum tragacanth for topical purpose which led to an idea for the development of pharmaceutical formulations using mucoadhesive polymers.[7] Mucoadhesion is a process of interaction between the mucus layer and bioadhesive polymer covering the body tissues where wetting, absorption, and interpenetration of the involved biopolymer chains take place.[8]

Valsartan is a non-peptide, angiotensin receptor blocker used to treat hypertension. It specifically bind to angiotensin receptor type 1 and prevent angiotensin II from binding, thereby inhibiting the hypertensive effects of vasoconstriction, stimulation of aldosterone and anti-diuretic hormone production, stimulation of cardiac functions, and sodium reabsorption in the kidney.[9] [10] It is BCS class II drug having low solubility and bioavailability only 23% after oral dose. However, food interferes with its absorption.[11] [12] To enhance the solubility solid dispersion was prepared which ultimately enhance bioavailability. Delivery of drug via buccal route avoids the first pass metabolism with circumvention of food interference.

Advantages:[13,14,15]

1. It has a relatively larger surface area and a rich blood supply.
2. It bypasses hepatic first-pass metabolism so increases bioavailability.
3. The dosage form is easy to administer and prompt termination of therapy can be facilitated in an emergency.
4. An alternate to administer drug to unconscious patients.
5. Better patient compliance.
6. The prompt onset of action and extended drug release.
7. Buccal route is a better option for delivery of drugs unsuitable for delivery in acidic environment of stomach or prone to enzymatic degradation.
8. Drug absorption by passive diffusion does not require any activation.
9. Buccal mucosa is highly vascularized hence offers more penetrability than skin.

Disadvantages:[4,5,13,15]

1. This route cannot administer drugs in large doses.
2. Drugs not stable at buccal pH are challenging to deliver.
3. Limits eating and drinking.
4. Possibility of patient's swallowing the formulation.
5. This route cannot administer drugs that have a bitter taste or an unpleasant odour or causes mucosal irritation.
6. Surface area available for absorption is limited.
7. Medicines absorbed by diffusion can only be administered.
8. Continuous salivation (0.5-2 L/Day) causes the medication to dissolve.
9. When saliva is swallowed, the dissolved or suspended drug is lost and eventually the dosage form is unwillingly removed.

MATERIALS AND METHODS

Drug and excipients

Valsartan was purchased from Yarrow Chem products, Mumbai. Mannitol, Pluronic F-68, PVP K30, HPMC K15M, Carbopol 934, Sodium carboxymethyl cellulose, Magnesium Stearate, Talc, Ethyl cellulose all were taken from college drug store.

Formulation of Solid Dispersion

Melting of Fusion and Solvent method were employed to prepare solid dispersion.

Melting or Fusion Method[16]

This method was selected as Valsartan has melting point in range 116-117^{0}C, so it is a thermo stable drug. Drug and carriers (Pluronic F 68, HPMC K15M and mannitol) were taken in ratio of 1:1, 1:3, and 1:5 (FD1, FD2, FD3). Polymers were precisely weighed and melted at a temperature just over their melting point. To guarantee uniform drug dispersion, the drug is integrated into the melted carrier. Then the melt is cooled rapidly on in an ice bath. Obtained solid mass was pulverized, sieved and stored in desiccator for further use.

Solvent Method[17]

Valsartan and carriers were taken in 1:1, 1:3, and 1:5 ratios (SD1, SD2, SD3). A substantial portion of methanol was used to dissolve the polymer. To generate a homogenous solid mass, the mixture was heated at around 50°C with dynamic stirring so that solvent gets rapidly evaporate. The formulated mixture was crushed and vacuum-dried for 24 hours, then pulverized and desiccated until needed.

EVALUATION OF SOLID DISPERSIONS

The following studies were carried out for evaluation of Solid dispersion:

- Solubility studies
- Drug Content Analysis
- FT-IR

Solubility Studies[18]

The excess quantity (50 mg) of prepared solid dispersion weighed and added to 10 ml of 6.8 phosphate buffer in a conical flask. Flask is then fixed to mechanical shaker for 24 hrs. After that solution was filtered through Whatman paper, suitable dilutions were done and analyzed by UV Visible spectroscopy at 248.5 nm. The calibration curve was used to calculate solubility.

Drug Content of Prepared Solid Dispersion[18]

Solid dispersions of valsartan were tested for drug content uniformity. Solid dispersions equivalent to 10 mg of Valsartan was dissolved in 10 ml of 6.8 pH phosphate buffer. Then solution was kept for 24 hours for the complete extraction of the drug. After that solution was filtered and diluted with phosphate buffer to make a concentration 10 µg/ml and analyzed by UV-visible and percentage of drug was calculated.

Compatibility study using FT-IR

A Thermo Nicolet FTIR was used to perform infrared spectroscopy at Subharti College of pharmacy, Meerut. A small amount of pure drug and mixture of drug with different carriers was taken and placed at the surface and the spectrum was obtained in the range of 4000 to 400 cm-1. IR Spectral studies were used to observe the interaction between drugs and excipients by looking for any shift in drug peaks in the spectrum of a physical mixture of drug.

Formulation of Valsartan Mucoadhesive Tablets[19]

Valsartan oral mucosal adhesive tablets were formulated by direct compression using a concave faced single punch tableting machine. Three mucoadhesive polymers were selected: Carbopol 934 P, HPMC K15M, SCMC. All the powders were precisely weighed then Valsartan was mixed with Carbopol. In a different mortar, the rest polymers were blended with talc. Both mixtures and remaining excipient were mixed together for 5 minutes. Finally, the mixture passed through sieve and compressed at low pressure. After that a backing membrane was applied by putting the tablet in die and place 40 mg of ethyl cellulose over it and finally compressed. Total six batches were prepared keeping amount of solid dispersion constant and variable amount of polymers as shown in Table 1.

POST-COMPRESSION EVALUATION PARAMETERS

Tablets were assessed for a variety of physicochemical factors, including in-vitro release of drug, mucoadhesive strength, weight variation, tablet hardness and diameter, friability, and thickness.

Weight Variation[20]

Twenty tablets were weighed separately and then together. Average weight was then calculated and % weight variation was determined by the formula given below:

Table 1: Composition of Various Batches

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
SD eq. to	40	40	40	40	40	40
Carbopol 934	40	30	20	40	30	20
HPMC K15M	40	50	60	-	-	-
SCMC	-	-	-	40	50	60
Mannitol	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Microcrystalline Cellulose	10	10	10	10	10	10
Ethyl Cellulose	40	40	40	40	40	40

% Weight variation = Weight of each tablet – Average weight of tablets/Average weight of tablets × 100

Tablet Thickness and Diameter[21]

These are the key parameter for determining the uniform size of tablets. From each batch, ten tablets were randomly selected, and they were sized with a Vernier Caliper.

Tablet hardness[22]

Force prerequisite for breakdown of a tablet in diametric position is defined as hardness. Six tablets from each batch were chosen randomly and placed diametrically between the two probes of hardness tester out of which one probe is fixed and one is movable. The movable probe was subjected to a force and the breaking force was recorded in terms of kg/cm^2.

Friability[21]

A friabilator is used to perform this test. 10 tablets from each batch were chosen at random and initial weight was noted. Tablets are then placed in plastic chamber of friabilator for the combine consequence of abrasion and shock, revolve the friabilator at a speed of 25 rpm for 4 min. Then, remove the tablets, dusted off the fines and record the weight. Following formula was used to calculate percentage friability:

% Friability = Initial weight of tablets – Final weight of tablets/Initial weight of tablets×100

Drug Content Uniformity[23]

10 tablets from each batch were taken, weighed individually and average weight was also calculated. All tablets then crushed, and a powder corresponding to 40 mg of medication was dissolved in pH 6.8 phosphate buffer, and the amount was increased to 100 ml. A 10 mL volumetric flask was filled with 1 mL of the stock solution, and the volume was made up using pH 6.8 phosphate buffers. After it solution was filtered, the absorbance was measured spectrophotometrically at 248.5 nm using a pH 6.8 phosphate buffer as a blank.

Surface pH[24]

This is done to determine any side effect due to alteration in pH as an acidic or basic pH may result in mucosal irritation. The tablets were set aside in contact of distilled water for 2 hours, and then electrode was bring to the tablet surface and allows equilibrating for 1 min and noting down the pH.

Swelling Index[25]

To determine the swelling index three tablets from each batch were randomly chosen and weighed (W1). 5 ml of phosphate buffer was added in a petri dish and then tablet was placed into it. At time intervals of 1, 2, 4 and 6 hours tablets were taken out, cleaned excess water with filter paper and reweighed. Following equation was used to calculate swelling index:

Swelling index = [(W2-W1)/W1X100]

In-vitro Dissolution Studies[26]

The USP-II (Paddle type) dissolving apparatus was employed for the in-vitro dissolution investigations, which were run at 50 rpm for 6 hours. The dissolution medium was made up to 900 mL with 6.8 phosphate buffer, and the temperature was kept at 37 ± 0.5^0C. At regular intervals, 5ml of medium was taken and replaced with the 5 ml of fresh buffer. Samples were diluted with buffer, filtered, and measured at 248.5 nm on a UV spectrophotometer. The cumulative drug release percentage was determined.

In-vitro Mucoadhesive strength[25]

Mucoadhesion test was done according to the previously established by Li Karen Lu [25] and porcine mucosal surface was employed as model surface. Porcine buccal mucosa was slaughtered, immediately placed in tyrode solution and carried to the laboratory. A pan balance was modified to determine the mucoadhesive forces of the tablets. Porcine buccal mucosa was sliced into appropriate-sized pieces and rinsed in tyrode solution. A piece of buccal mucosa with a diameter of around 1 cm was mounted on a glass slide with bilayered adhesive tape and hung from the balance's left side. Afterwards, a glass slide with porcine oral mucosa was placed at the top of a 50 ml inverted beaker, which was then filled using 6.8 phosphate buffer and put inside a 500 ml beaker. The glass slide containing buccal mucosa was lowered to make contact with the mucosa and held there for 5 minutes. The weights were then placed on the right side of the scale, and the total weight was recorded. The formula for calculating mucoadhesive strength was:

Force of adhesion (N) = Bioadhesive strength (gm)/1000 × 9.81

RESULTS AND DISCUSSION

Pre-formulation Studies

The λ_{max} was found to be 248.5 nm in methanol. Solubility of pure Valsartan was found to be 0.18 mg/ml in water and and 1.85 mg/ml phosphate buffer pH 6.8.

Calibration curve of Valsartan in Methanol, Phosphate buffer pH 6.8 and water.

Table 2: Absorbance of Pure Valsartan in Different Solvent

S.No.	Concentration (µg/ml)	Absorbance at 248.5 nm		
		Methanol	Phosphate Buffer pH 6.8	Water
1.	0	0	0	0
2.	2	0.086	0.07	0.040
3.	4	0.170	0.149	0.078
4.	6	0.254	0.226	0.121
5.	8	0.318	0.299	0.165
0	10	0.402	0.354	0.211

Figure 1: Calibration Curve in Methanol

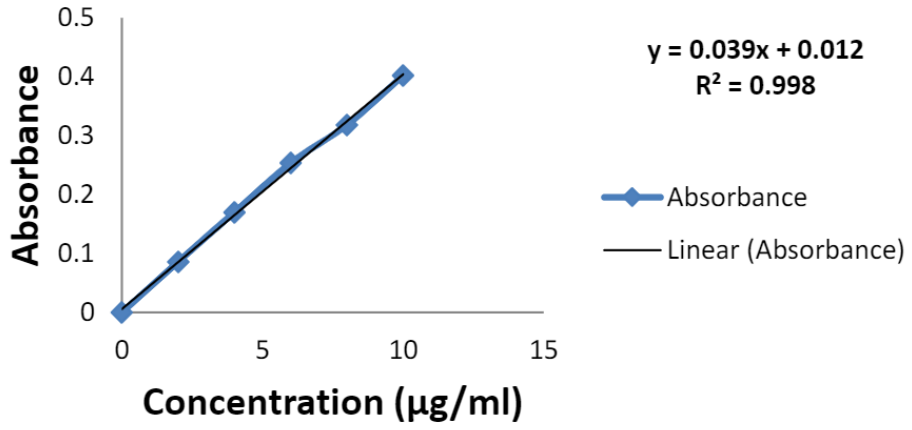


Figure 2: Calibration Curve in Phosphate Buffer pH 6.8

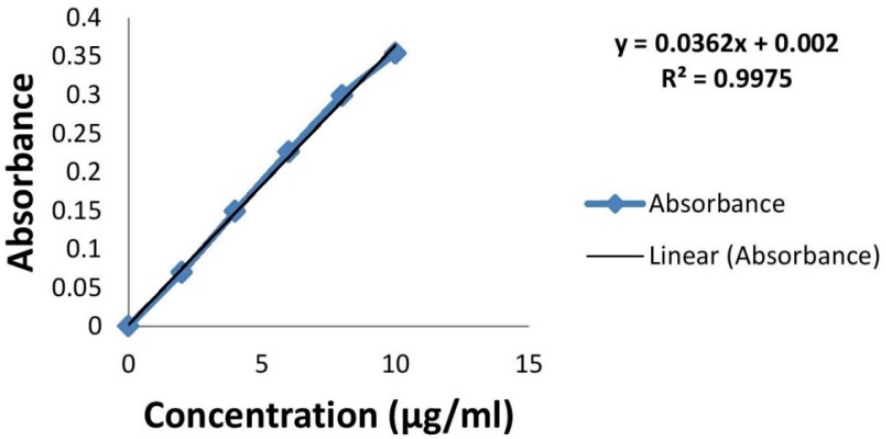
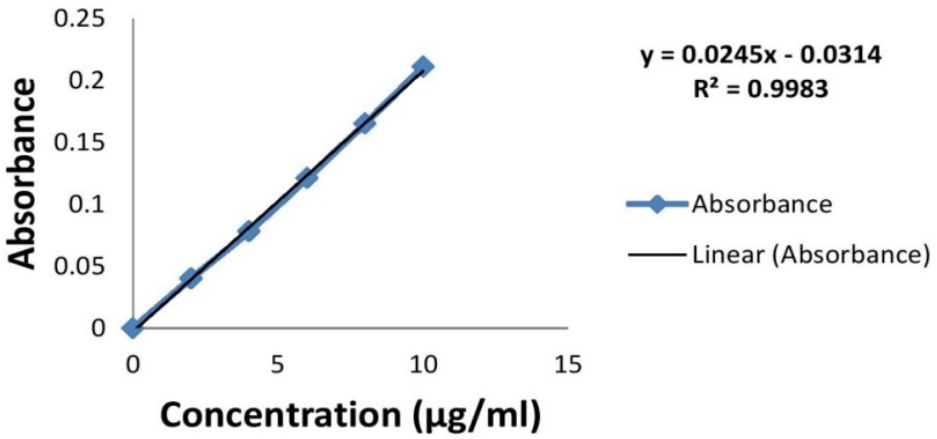


Figure 3: Calibration Curve in Water



COMPATIBILITY STUDIES USING FT-IR

FT-IR spectrum was determined for drug, polymers separately and then for mixture of drug and polymers. The obtained spectrum of drug and polymer contained all of Valsartan's distinctive peaks, showing that the drug and polymers are compatible. The result showed that Valsartan and polymers are chemically compatible since the functional groups do not interfere and the drug's major peaks do not change in drug-polymer combinations. It was also determined that the chemical integrity of the drug had not changed much.

EVALUATION OF SOLID DISPERSIONS

Solid dispersion containing drug and mannitol in ratio 1:1 showed highest solubility (4.09 mg/ml) and drug content (99.45%) while solid dispersion in ratio 1:3 and 1:5 showed 3.41 and 2.37 mg/ml respectively. The increase in solubility of solid dispersion in comparison to pure drug given below:

1. Physical Evaluation of Tablets

Tablets in each batch were found to be white in color from one side and light yellow from another side having backing membrane of ethyl cellulose, odorless, concave and round in shape.

2. Post Compression Evaluation

Weight variation, hardness, thickness & diameter, friability and surface pH of each batch

All of the parameters were found to be within the acceptable ranges and their numerical values are listed in the Table 5. Weight of all the tablets varied between 225.4 ± 3.17 to 227.2 ± 3.22 mg , which was within the limit according to Indian Pharmacopoeia (7.5 % deviation). Diameter was found to be same for all tablets i.e.8 mm. Thickness of the tablet for each batch found to be uniform and lies in range of 4.14 ± 0.09 to 4.21 ± 0.05.

Table 3: Interpretation of IR-spectrum

Ingredients	Functional Groups with wave number (cm^{-1})				
	N-H Stretching	C-H Stretching (Aromatic)	COOH Stretching	N-CO Stretching	C-H Bending (Aromatic)
Valsartan	3400	3202	3302	2250	1600
Valsartan + Carbopol 934	3401	3221	3344	2241	1609
Valsartan + HPMC K15M	3407	3209	3313	2233	1615
Valsartan + SCMC	3419	3215	3317	2247	1605

Figure 4: FT-IR spectra of pure Valsartan

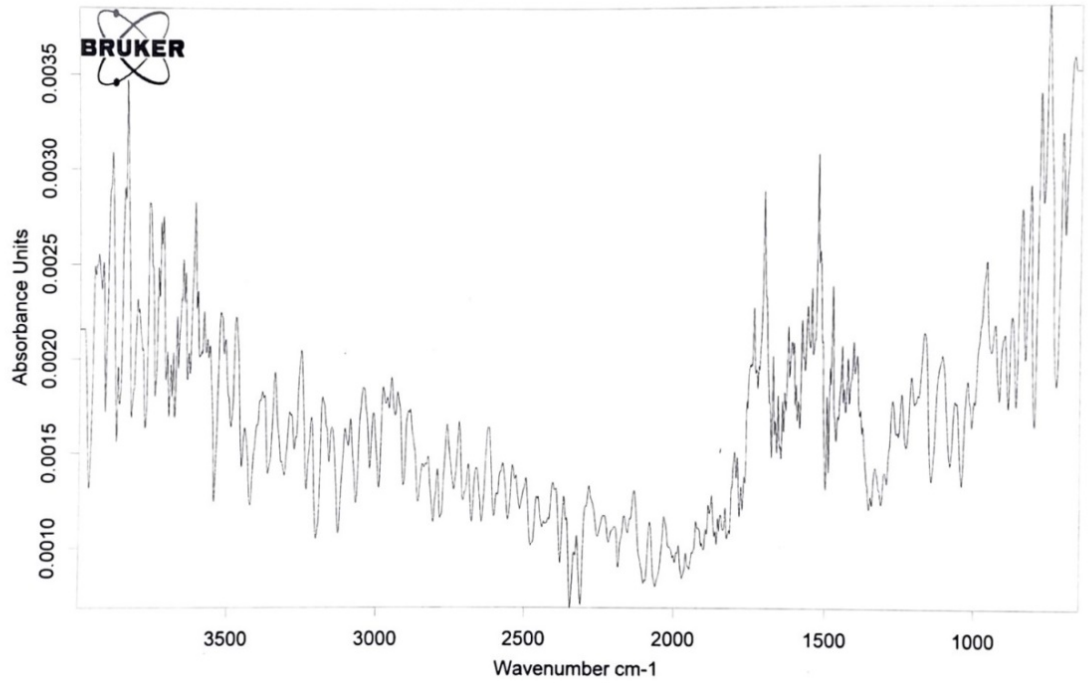


Figure 5: FT-IR spectra of Drug + Carbopol 934P

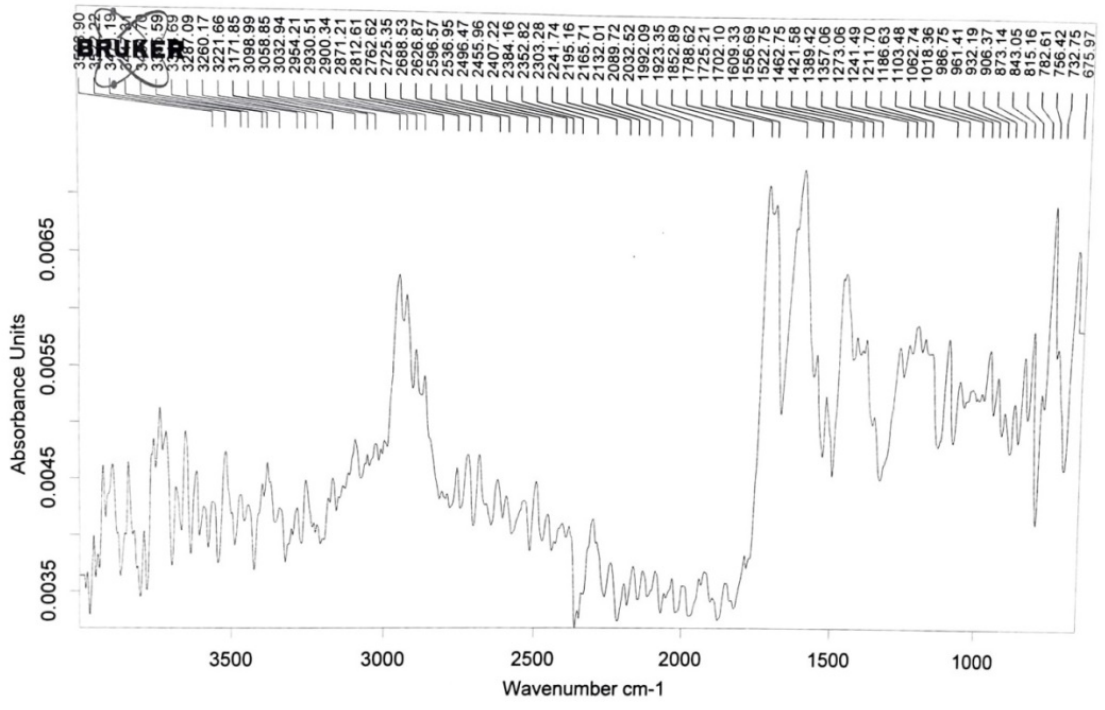


Figure 6: FT-IR spectra of Valsartan + HPMC K15 M

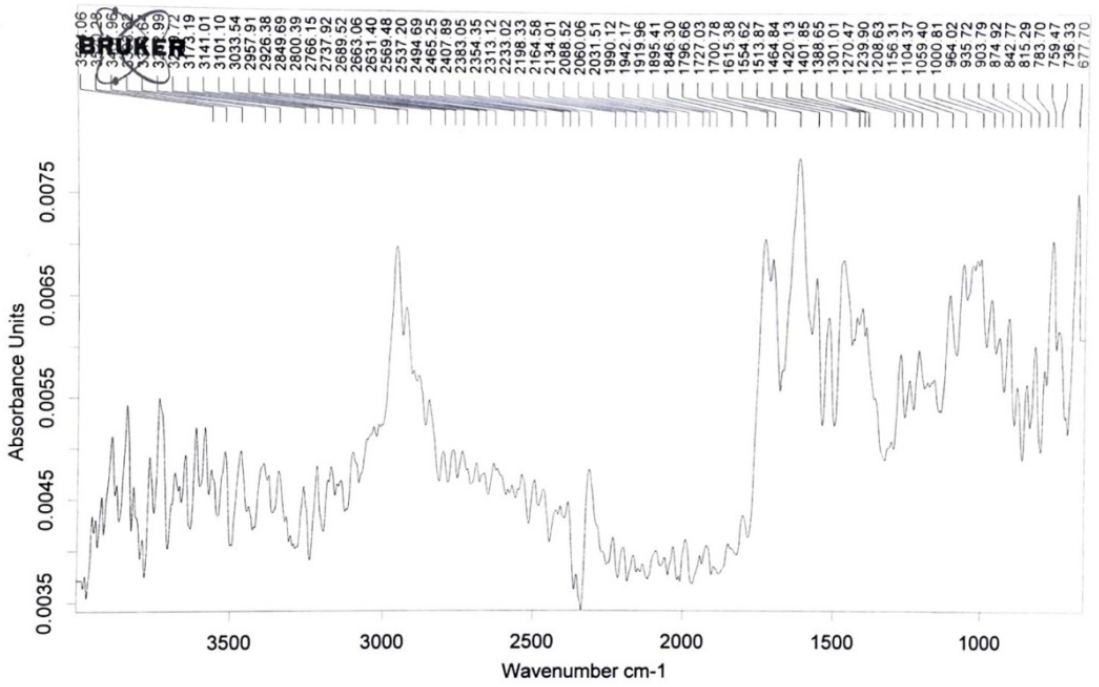


Figure 7: FT-IR spectra of Valsartan + SCMC

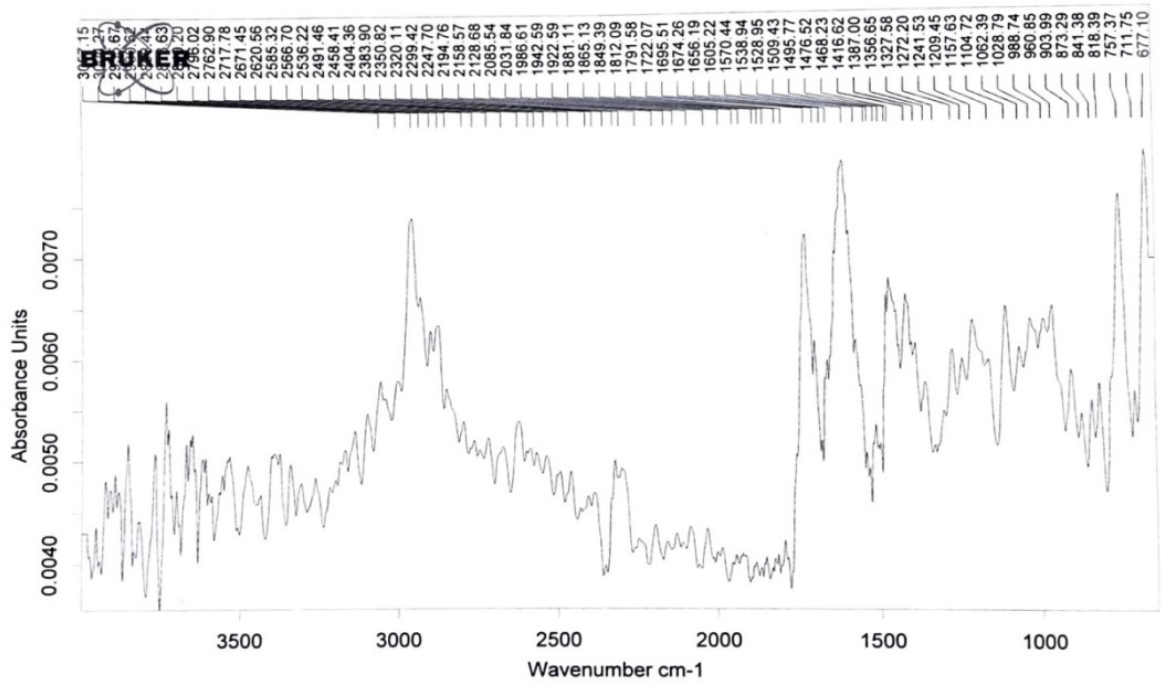


Table 4: Solubility and Drug Content of Prepared Solid Dispersions

Batch Code	Drug: Carrier Ratio	Solubility (mg/ml)	Drug Content (%)
Pure Drug	–	1.85	
SD1	1:1	4.09	99.45
SD2	1:3	3.41	98.91
SD3	1:5	2.37	97.29

Similarly, hardness of different batches was in between 7.83 ± 0.51 to 8.75 ± 0.68 kg. Friability of tablets was ranged from 0.31% ± 0.47%, which is an acceptable range according to Indian Pharmacopoeia i.e. less than 1%, showing that tablets are having good compactness to resist mechanical shock and abrasion. Tablets of all the batches had surface pH in between 6.82 ± 0.06 to 6.94 ± 0.11 that is close to the neutral pH and within the tolerable limit of buccal pH 6.5 to 7.5.

Table 5: Results of Post Compression Study

Batch	Weight Variation (mg ± SD)	Diameter (mm)	Thickness (mm ± SD)	Hardness (kg ± SD)	Friability (%)	Surface pH ± SD	Drug Content
F1	227.2 ± 3.22	8	4.14 ± 0.09	8.16 ± 0.81	0.36	6.82 ± 0.11	98.91 ± 1.31
F2	226.1 ± 3.89	8	4.2 ± 0.04	8.16 ± 0.93	0.47	6.94 ± 0.11	97.97 ± 0.37
F3	225.8 ± 2.41	8	4.19 ± 0.05	7.83 ± 0.51	0.45	6.82 ± 0.06	97.16 ± 1.73
F4	225.4 ± 3.17	8	4.19 ± 0.07	8.50 ± 0.77	0.31	6.84 ± 0.41	99.18 ± 0.44
F5	226.4 ± 3.13	8	4.16 ± 0.09	8.75 ± 0.68	0.42	6.86 ± 0.25	99.59 ± 0.25
F6	226.1 ± 2.48	8	4.21 ± 0.05	8.16 ± 0.93	0.35	6.85 ± 0.09	98.57 ± 0.21

Table 6: In vitro Drug Release Profile of all Six Batches

Time (hrs)	Percentage Cumulative drug release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
30	1.90	1.62	1.62	2.18	2.12	1.95
60	5.70	4.81	4.81	7.5	7.44	6.66
90	12.36	9.73	9.96	15.27	16.34	13.88
120	20.87	16.95	17.23	26.41	27.87	23.45
180	32.12	28.04	27.09	40.18	43.48	36.66
240	47.07	41.92	39.403	57.48	61.79	53.004
300	66.26	60.50	56.082	77.96	82.72	72.817
360	87.92	83.95	76.62	100.97	105.84	99.179

3. Drug Content Uniformity

The drug content of different batches varied between 97.16 to 99.59 % as shown in table 5 that showed good drug content uniformity among all batches.

4. In vitro Dissolution Studies

The polymer impact and drug release pattern of the manufactured batches of mucoadhesive tablets were investigated in vitro, and the results are displayed in the table 6. Formulation F3 had the lowest drug release (76.62%) while Formulation F5 had the highest drug release (105.84%). In case of batches with Carbopol 934 and HPMC K15M the drug release found to be low as compared to batches with Carbopol 934 and SCMC.

4. In-vitro Mucoadhesive Strength

Results obtained are shown in figure 8. Formulation F4 showed highest mucoadhesive strength (48.5 gm), while the F3 showed least. It was observed that mucoadhesive strength was increased with increasing concentration of Carbopol.

Figure 8: Comparative Release Profile of Formulation F1 to F6

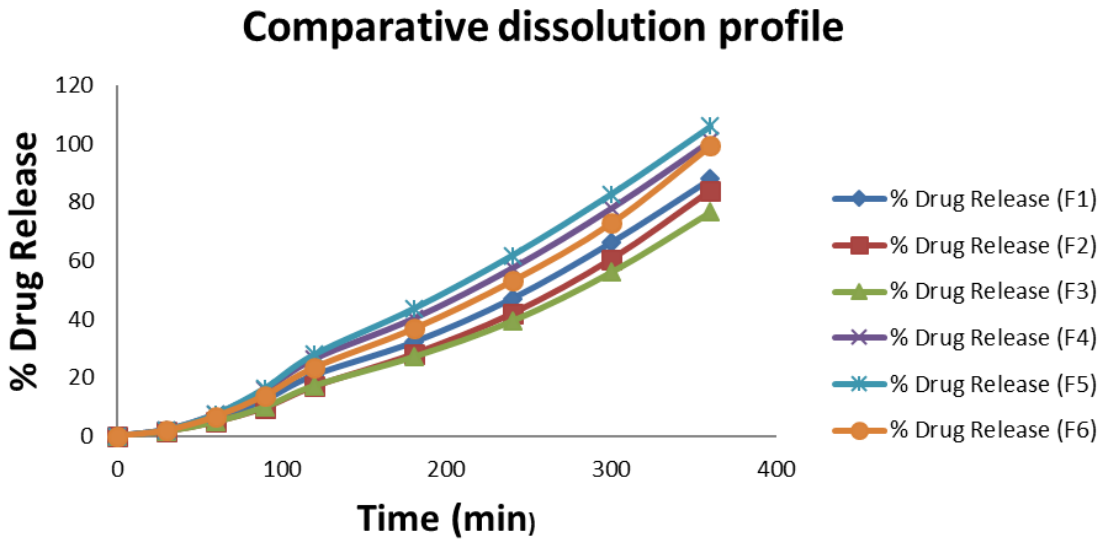
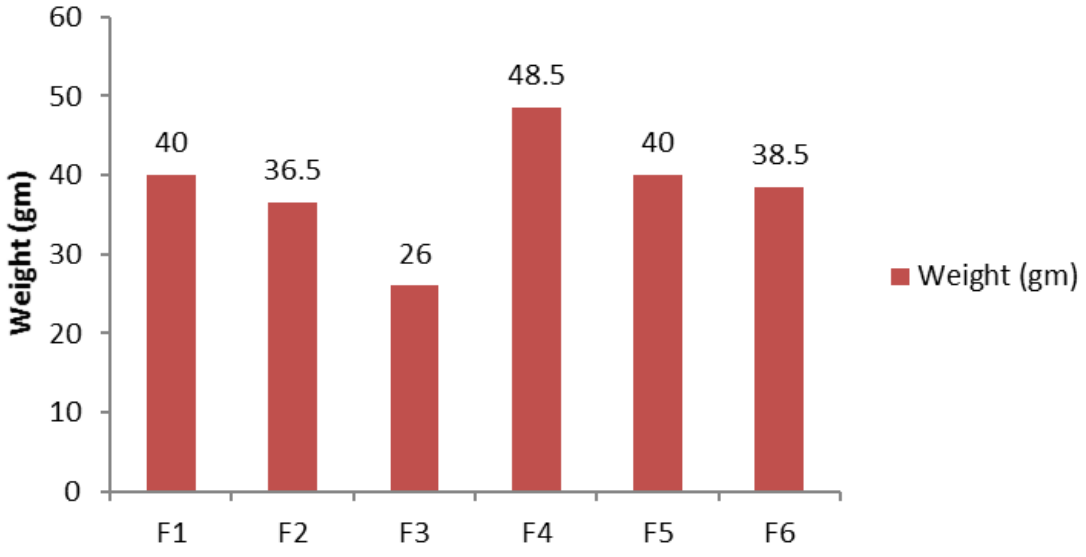


Figure 9: Result of Mucoadhesive Strength



CONCLUSION

The present work was performed to prepare oral mucosal adhesive tablets of Valsartan by incorporating solid dispersion to enhance solubility, bioavailability and avoid food interference in its absorption. Among the 6 batches, F4 found to be best as it showed highest release, swelling index as well as mucoadhesive strength. Its physical and chemical properties also compiled with pharmacopoeia standards. The results showed that CP plays a significant impact in raising swelling index and mucoadhesive strength. Additionally, the tablet may be a useful substitute method for avoiding the first-pass impact and enhancing Valsartan's mucosal membrane absorption.

BIBLIOGRAPHY

1. Begum, S. A., Sura, R. S., Phanindra, B., *et al*. Formulation and Evaluation of Mucoadhesive Buccal Tablets of Captopril. *Res J Pharm Dos Forms Technol*. 2019; 11(3): 164. doi:10.5958/0975-4377.2019.00028.4
2. Pawar, S. P. *Journal of Drug Delivery and Therapeutics Innovation and optimization of Rizatriptan Benzoate Oromucosal Tablets by Using Design of Experiment (DoE)*. 2022; 12(2): 103-120.
3. Kumar, S., Kumar, A., Gupta, V., Malodia, K. and Rakha, P. Oral Extended Release Drug Delivery System/: A Promising Approach/: *Asian J Pharma Tech*. 2012; 2(2): 38-43.
4. Montenegro-Nicolini, M. and Morales, J. O. Overview and Future Potential of Buccal Mucoadhesive Films as Drug Delivery Systems for Biologics. *AAPS PharmSciTech*. 2017; 18(1): 3-14. doi:10.1208/s12249-016-0525-z
5. Rothner, J. T., Cobe, H. M., Rosenthal, S. L. and Bailin, J. An adhesive penicillin ointment for topical application. *J Dent Res*. 1949; 28(6): 544-548. doi:10.1177/00220345490280060301
6. Ahmed, T. A., Bawazir, A. O., Alharbi, W. S. and Safo, M. K. Enhancement of simvastatin ex vivo permeation from mucoadhesive buccal films loaded with dual drug release carriers. *Int J Nanomedicine*. 2020; 15: 4001-4020. doi:10.2147/IJN.S256925
7. Kaul, M. An Overview of Buccal Drug Delivery System. *Int J Pharm Res*. 2021; 13(01): 1303-1321. doi:10.31838/ijpr/2021.13.01.556
8. Gandhi, P. A. A Review Article on Mucoadhesive Buccal Delivery System. *Int J Pharm Res Dev*. 2011; 3(0974): 159-173.
9. Vaddeswrapu Madhavi* Baa, Parthiban P. Formulation and invitro evaluation of valsartan sustained release tablets. 2018; (September).
10. Xu, W., Sun, Y., Du, L., Chistyachenko, Y. S., Dushkin, A. V. and Su, W. *Journal of Drug Delivery Science and Technology Investigations on Solid Dispersions of Valsartan with Alkalizing Agents/: Preparation, Characterization and Physicochemical Properties*. *J Drug Deliv Sci Technol*. 2018; 44(October 2017): 399-405. doi:10.1016/j.jddst.2018.01.012
11. P, D. B. and Ng, R. R. A. O. Formulation and Evaluation of Valsartan Fast Disintegrating Tablets By Vacuum Drying Technique. 2016; 9(2).
12. Kulkarni*, R. S. and Behera, D. A. L. Formulation and evaluation of immediate release tablet of valsartan. 2015; 6(2): 808-815. doi:10.13040/IJPSR.0975-8232.6(2).808-15
13. Ramesh, B., Saravanakumar, K., Nagaveni, P., Mohan, Kumar A., Jaya Preethi, P. and Vivek Kumar, P. A Review on Buccal Drug Delivery System. *Int J Res Pharm Sci*. 2014; 5(3): 200-204. doi:10.5958/0975-4377.2017.00019.2
14. Singh, P. K., Singh, D. and Bijauliya, R. K. A Comprehensive Review on Buccal DrugDelivery System. *Int J Res Dev Pharm Life Sci*. 2017; 6(3): 2606-2618. doi:10.21276/ijrdpl.2278-0238.2017.6(3).2606-2618
15. Shital, G., Shinkar, D. and Ravindra, S. Mucoadhesive Buccal Drug Delivery/: An Overview. *J Adv Pharm Edu Res*. 2013; 3(4): 319-332.
16. Akhter, S., Uddin, A. K. M. S., Nath, A. K., Kadir, M. F. and Islam, S. Dissolution Studies of Ketoprofen Solid Dispersion with PEG 6000 and HPMC 6 cps. 2020; 23(1): 44-53.
17. Sharma, A. and Jain, C. P. Preparation and Characterization of Solid Dispersions of Carvedilol with PVP K30. 2010; 5(April): 49-56.
18. Sb, S., Sa, S., Ra, D. and Vn, S. Solid Dispersion of Valsartan for Solubility Improvement using β-cyclodextrin. 2018; 5(6): 313-319. doi:10.15406/mojbb.2018.05.00122
19. Koirala, S., Nepal, P., Ghimire, G., *et al*. Formulation and Evaluation Of Mucoadhesive Buccal Tablets Of Aceclofenac. *Heliyon*. 2021; 7(3): e06439. doi:10.1016/j.heliyon.2021.e06439
20. Srinivas, D., Debnath, S., Manjunath, S. Y. and Division, P. Formulation and Evaluation of Valsartan Film Coated Tablets. 2010; 2(5): 534-540.

21. Bindhumadhavi, K., Chandralekha, K. P. and Rao, A. S. Formulation and Evaluation of Valsartan Floating Tablets. 2019; 9: 520-526.

22. Sharma, D., Singh, M., Kumar, D., Singh, G. and Rathore, M. S. Formulation Development And Evaluation of Fast Disintegrating Tablets of Ambroxol Hydrochloride For Pediatrics- A Novel Approach For Drug Delivery. *Indian J Pharm Educ Res*. 2014; 48(4): 40-48. doi:10.5530/ijper.48.4s.6

23. Singh, S. K., Shrivastava, G. and Singh, P. K. Formulation and Evaluation of Mucoadhesive Buccal Tablets of Zolmitriptan. 2016; 5(7): 1402-1419. doi:10.20959/wjpps20167-7216

24. Karki, R. Formulation and Evaluation of Mucoadhesive Buccal Tablets of Valsartan. 2016; (December).

25. Li, K. L. and Castillo, A. L. Formulation and Evaluation of A Mucoadhesive Buccal Tablet of Mefenamic Acid. *Brazilian J Pharm Sci*. 2020;56:1-19. doi:10.1590/S2175-97902019000418575

26. Milind, G. M. and Yadav, G. Y. A. Formulation and Evaluation of Mucoadhesive Buccal Tablets of Propranolol. 2018; 9(7): 2905-2913. doi:10.13040/IJPSR.0975-8232.9(7).2905-13