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Research Article

Valsartan Buccal Patches- A Promising Approach to Enhance Drug Delivery.

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ABSTRACT

Majority of the drugs are administered to the body with the basic aim to achieve a stable blood or tissue concentration which is therapeutically effective and nontoxic for an extended period of time. This can be achieved if proper dosage regimens are designed and attempt is made to attain a maximum rate and extent of drug absorption. By the use of new drug delivery systems, one can enhance the bioavailability and therapeutic index of medical agents as well as reduce side effects and can improve acceptance and compliance by the patients. The present work was aimed to formulate and evaluate buccoadhesive patches of Valsartan. Valsartan is an anti-hypertensive drug. Though seems an easier way, but proved very efficient to use buccal patches as drug delivery system. Suitable polymers HPMCK15, PVPK30, and PEG400 were selected as release retardants. Prepared formulations were appropriately evaluated and results analyzed. Among the various concentration of polymeric combinations, the combination ratio 2:1(HPMCK15:PVPK30) was found to be most suitable. The formulation R6 combination of polymers HPMCK15, PVPK30 fulfills the requirement of good buccal patches. It showed highest drug release up to 95.29% for 12hr. Preformulation and formulation results revealed that the buccal patches incorporated with valsartan proved to be a highly efficient drug delivery system showing improved release characteristics. The release analysis revealed diffusion mediated drug release following Higuchian model. Concluded the formulation as one desired and acceptable.

KEYWORD

Valsartan, HPMC, PVP, PEG, buccal patches.

1. INTRODUCTION

The oral route of drug administration is popular, convenient & widely accepted method of administration of the drug. For the past two decades, there has been enhanced demand because of certain limitations of conventional oral route. Oral route of drug administration have wide acceptance up to 60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance but poor patient compliance. [1] Majority of the drugs are administered to the body with the basic aim to achieve a stable blood or tissue concentration which is therapeutically effective & nontoxic for an extended period of time. This can be achieved if proper dosage regimens are designed & attempt is made to attain a maximum rate & extent of drug absorption. By the use of new drug delivery system one can enhance the bioavailability & therapeutic index of medical agents as well as reduce side effects & can improve acceptance & compliance by the patients. [2]

1.1. Mucoadhesive Drug Delivery System

Mucoadhesive drug delivery system is defined as drug delivery system, which utilizes property of bioadhesion of certain water-soluble polymers, which become adhesive on hydration and hence can be used to a particular region of the body for extended period of time. The mucosal layer lines a number of regions of the body including the gastro intestinal tract, the airway, the nose, the ear, the eye. These represent potential sites for attachments of any bioadhesive system and hence, the Mucoadhesive delivery system includes buccal drug delivery system, oral drug delivery system, rectal drug delivery system, vaginal drug delivery system, ocular drug delivery system, nasal drug delivery system.[3] Drug Delivery via the Buccal Lining have certain advantages [4] such as bypass of the gastro intestinal tract and hepatic portal system, increasing the bioavailability of orally administered drug that otherwise undergo hepatic first- pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle GI tract. Improved patient compliance, sustained drug delivery can be possible, increased ease of administration, a faster initiation and decline of delivery, lower inter subject variability.

1.2. Buccal Patch

Bioadhesive formulations have a wide scope of application, for both systemic and local effects of drug. The mucosa is relatively permeable with a rich blood supply. Buccal route of drug delivery provides direct access to the systemic circulation through the jugular vein and thus bypass liver and a high bioavailability is obtained. Retentive buccal mucoadhesive formulation may be a viable alternative to the conventional oral medication as they can be readily attached for a longer period of time and removed at any time. In recent years, delivery of therapeutic agent through various trans-mucosal routes gained significant attention owing to their pre-systemic metabolism or instability in the acidic environment associated with oral administration. The ease of administration and ability to terminate drug delivery when required make it a potential and attractive route of drug delivery.

Buccal patches are highly flexible and thus much more readily tolerated by patients than tablets. Patches also ensure more accurate dosing of the drug compared to gel and ointment. Bioadhesion

is the phenomenon between two materials which are held together for extended period of time by interfacial force. It is generally referred as bioadhesion when interaction occurs between polymer and epithelial surface.

Absorption of drug via the mucous membrane of oral cavity was noted in 1847 by SOBREEO that was discovery of nitroglycerine given by buccal route. Buccal delivery is the administration of the drug via buccal mucosa (lining of cheek) to the systemic circulation. Drug delivery through the buccal mucosa offers a novel route of drug administration. Various synthetic polymers are under investigation as carrier for buccal drug delivery like chitosan, polyvinyl Pyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxyl propyl methyl cellulose (HPMC) Carbopol. Mostly those polymers are seen potential and comparatively economical and also non-toxic, biodegradable polymer, are mostly use because it give wide opportunities for development of better drug delivery systems. An ideal buccal patch should be flexible, elastic, and adequate strong to withstand breakage due to stress from mouth activities. [5] Mechanism of action of patches is as presented in below fig. 1.

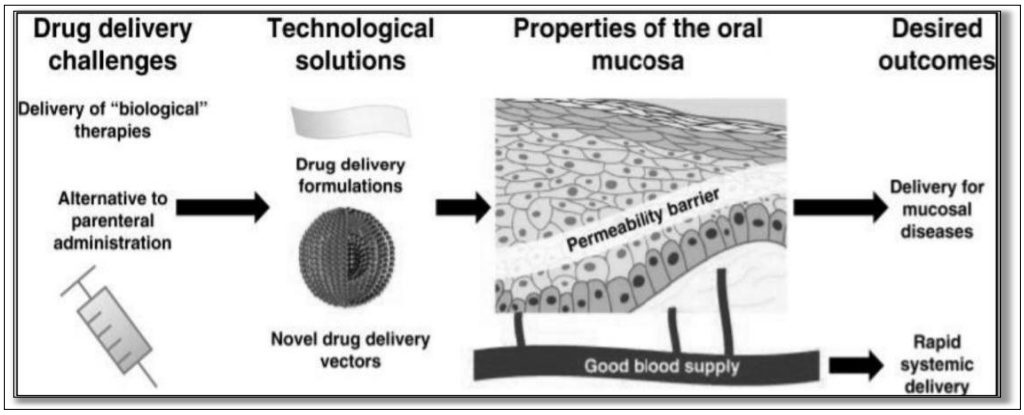

Fig. 1. Drug delivery through buccal mucosa. [6]

Most research has described bio-adhesive bond formation as a three step includes wetting and swelling of polymer, interpenetration between the polymer chains and the mucosal membrane formulation of chemical bond between the entangled chains. [7] Factors affecting bioadhesion [8] include physicochemical characteristics of drug and physicochemical behavior of membrane and polymer related factors. Basic components of buccal patches are active ingredient, polymer, plasticizer, and permeation enhancer, solvent. The role of backing membrane is to give attachment of bioadhesive device to the mucus membrane. These membranes prevent drug loss and offers better patient compliance. The material used as backing membrane should be inert and impermeable the drug. The commonly used materials in backing membrane include Carbopol, HPMC, CMC and HPC. [9] The present work was aimed to formulate and evaluate buccoadhesive patches of Valsartan. Valsartan is an anti-hypertensive drug. Hypertension is a chronic elevation of blood pressure. The renin: angiotensin: aldosterone system [10] is important in the maintenance of cardiovascular homeostasis & the control of electrolyte balance. It also has

a modulatory effect on sympathetic nerve activity. A high renin & angiotensin concentration is a common finding in malignant hypertension. Valsartan is one of the most effective drugs for management of hypertension. It has half-life (up to 6 hrs.) and small dose. The overall bioavailability is very low i.e. about 25% which make it a suitable candidate for formulating its buccal patch. Patches dosage forms have more advantages over other dosage forms.

2. MATERIALS AND METHODS

Valsartan obtained as a gift sample from Lupin Laboratories Ltd., HPMCK15, PVPK30, and PEG400 was purchased from Loba Chemie. Pvt., Ltd. Mumbai. Solvents Methanol, Dichloromethane used are of analytical grade and purchased from Qualigens, Mumbai.

2.1. Preformulation Studies

Preformulation testing is the first step in rational development of dosage forms of a drug substance. Preformulation studies were performed for the obtained sample of drug valsartan for identification and compatibility studies. [11] Identification tests as organoleptic properties including colour, taste, odour, melting point, solubility and partition coefficient [12] were performed.

2.1.1. Compatibility study of drug & polymers: FT-IR Spectroscopy

Ft-IR spectroscopy was carried out to check the compatibility between drug and polymers. The FT-IR spectra of drug valsartan with polymers were compared with the standard FT-IR spectrum of the pure drug. The infrared data is helpful to confirm the identity of drug and to detect interaction of the drug and polymer. [13]

2.1.2. In-Vitro Permeation study of pure drug

The *in-vitro* drug permeation studies were carried out by using diffusion cell. The buccal mucosa of gout, clamped between the receptor and donor compartments. The receptor compartment was filled with 5 ml of diffusion medium (Phosphate buffer pH 6.8). The contents were stirred at 500 rpm. The temperature of the system was maintained at 37 ± 0.2^0C. Accurately weighed 5mg of valsartan was dissolved in phosphate buffer pH 6.8 and placed in donor compartment. At suitable time intervals, aliquots 1 ml was collected and diluting up to 10 ml with phosphate buffer and absorbance was measuring at 248nm using a double beam UV spectrophotometer. The diffusion medium of the same volume 1 ml, replaced into the receptor compartment. Duration of the experiment was 12 hours. The amount of drug permeated through buccal mucosa was calculated from absorbance of aliquots. [14]

2.2. Formulation Development

2.2.1. Preparation of Buccal Patches

Solvent casting method was used wherein the calculated quantity of accurately weighed HPMCK15 dispersed in Dichloromethane: Methanol and swelled up to 1hr. Then added with PVPK30 as mucoadhesive agent & PEG400 as plasticizer in above solution. Accurately weighed quantities of Valsartan added in above polymeric solution. The solution mixed occasionally to get semisolid consistency. Then this was casted on a petri-plate having $9cm^2$ area containing mercury, which covered with funnel to control the sudden evaporation of solvent and allowed to

dry at room temperature to overnight. The dried patch separated and cut into 1×1cm diameter, the aluminum foil used as backing membrane. Stored in desiccator for further study. [15]

Table 1. Formulation batches of Valsartan buccal patches.

For Formulation code	Valsartan (mg)	HPMCK15 (mg)	PVPK30 (mg)	PEG400 (ml)	Methanol: Dichloromethane (ml)
R1	Placebo	200mg	-	0.2ml	**10ml**
R2	Placebo	100mg	100mg	0.2ml	**10ml**
R3	90mg	200mg	-	0.2ml	**10ml**
R4	90mg	100mg	100mg	0.2ml	**10ml**
R5	90mg	150mg	100mg	0.25ml	**10ml**
R6	90mg	200mg	100mg	0.3ml	**10ml**
R7	90mg	100mg	150mg	0.25ml	**10ml**
R8	**90mg**	**100mg**	**200mg**	**0.3ml**	**10ml**

2.3. Evaluation of prepared buccal patches

2.3.1. Physical appearance

Physical appearance evaluation includes visual inspection and evaluation of texture by feel or touch. [16]

2.3.2. Weight uniformity

Five patches of $1cm^2$ are weighed individually and average of those patches measured. [16]

2.3.3. Folding endurance

The flexibility of patches can be measured quantitatively in terms is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patches (approximately 1×1cm) at the same place till it broke. The number of times patches could be folded at the same place, without breaking gives the value of folding endurance. [16]

2.3.4. Moisture content

The patch was weighed and kept in desiccator containing calcium chloride at room temperature and dried it for at least 24 hr. Then the patch was weighed. The % moisture content was calculated using appropriate formula. [16]

2.3.5. Surface pH

Patch was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. [17]

2.3.6. Percent Drug Content

A film cut into 1×1cm and takes three peaches of 1×1cm patches, takes in separate 100ml of phosphate buffer pH6.8 and continuously stirred for 24hr. 1ml sample withdraw and diluted with phosphate buffer pH6.8 up to 10ml. Measure absorbance at 248nm using UV-Spectrophotometer, average drug content calculated using formula. [16]

2.3.7. In vitro release studies

The drug release studies performed by using paddle type dissolution apparatus, the dissolution apparatus thermostated at the temperature of 37±0.2^0 C and stirred at 50 rpm. Each patch fixed on glass slide. The slide his immersed in the vessel containing 900ml of phosphate buffer pH6.8 solution. 1ml sample withdrawn at 1hr. interval and diluted up to 10ml with phosphate buffer pH 6.8. Measured absorbance at 248 nm using UV-Spectrophotometer against blank phosphate buffer pH 6.8, % drug release calculated. [16]

2.3.8. *In vitro* permeation study (Diffusion Study)

The *in vitro* buccal permeation study of Valsartan buccal patches through the goat buccal mucosa performed using diffusion cell thermostated at the temperature 37ºC ± 0.2ºC and stirred at rate of 500 rpm. Goat buccal mucosa was fitted between the donor and receptor compartments (phosphate buffer pH6.8). The patch was placed on the mucosa and the compartments were clamped together. The donor compartment was phosphate buffer (pH 6.8). 1ml samples were withdrawn & made suitable dilution, maintained sink condition. Then samples were analyzed spectrophotometrically at 248 nm. The drug permeation was correlated with cumulative drug released. [18]

2.3.9. Drug Release Kinetics

Data of the *in-vitro* release were fit into different equations and kinetic models to explain the release kinetics of Valsartan from these buccal patches. The kinetic models used were a zero-order equation, first order equation, Higuchi release, and Korsemeyer and Peppas models. The interpretation of data was based on the value of the resulting regression coefficients. [19]

3. RESULTS AND DISCUSSION

3.1. Preformulation Study

3.1.1. Organoleptic evaluation

The results of organoleptic evaluation of valsartan are as tabulated in below table 2. All the values comply with specified limits.

Table 2. Organoleptic Evaluation

Sr. No.	Test	Standard	Result
1	State	Solid	**Complies**
2	Color	White powder	**Complies**
3	Odor	Odorless	**Complies**
4	Taste	Tasteless	**Complies**
5	Solubility	Freely soluble in methanol & Slightly soluble in water	**Complies**
6	Melting point	105-110^{0}C	**108^{0}C**
7	**Log p**	**-1to 4mg/ml**	**1.499mg/ml**

3.1.2. Compatibility study

The FT-IR spectra of valsartan and that of the drug-polymer blend interpreted appropriately and revealed no significant interactions and changes in drug and polymers, proving them compatible with one another. The FT-IR spectrum is given in below fig. 2 and fig. 3.

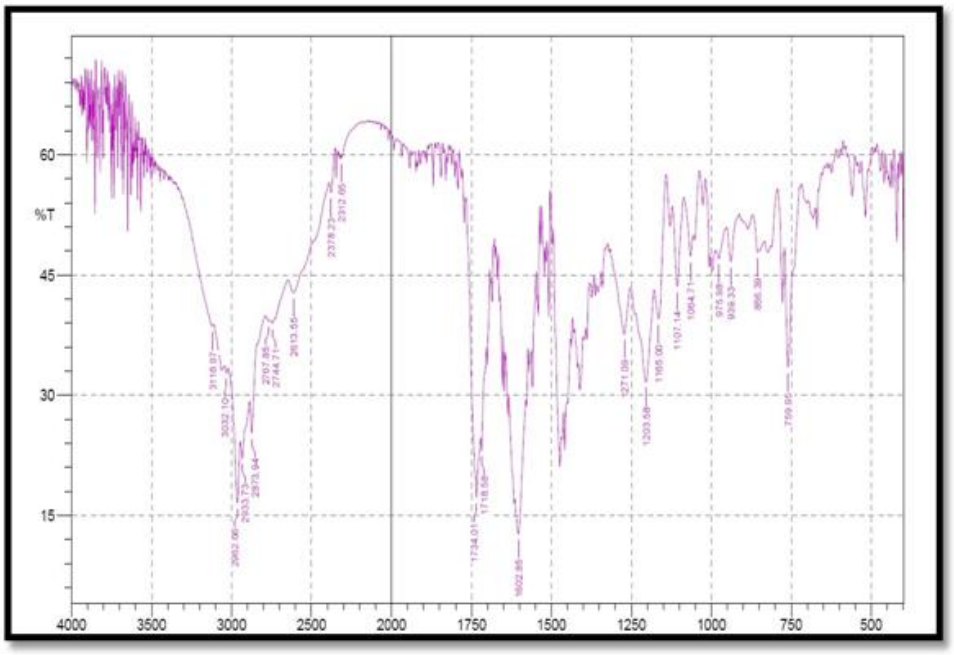

Fig. 2. FT-IR spectrum of Valsartan.

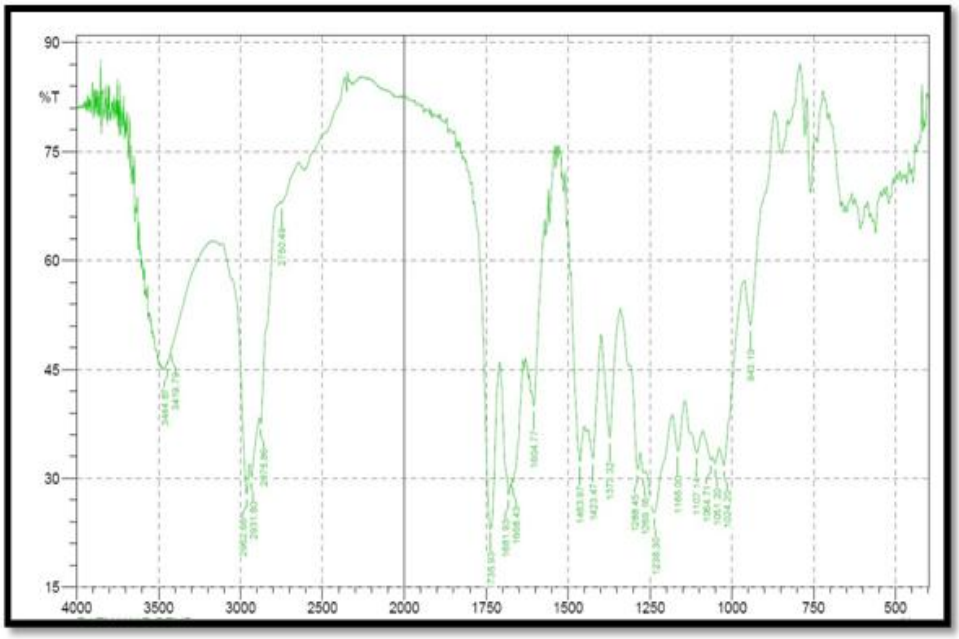

Fig. 3. FT-IR Spectrum of Valsartan, HPMCK15 & PVPK30.

3.1.3. *In vitro* permeation of pure drug

The *In vitro* permeation of pure drug was done and it was found that at the end of 6 hours, about 96% drug permeated effectively. This finding had a positive meaning; hence study could be further continued.

3.2. Evaluation of Buccal Patches

3.2.1. General Properties of Patches

The prepared Valsartan buccal patches were evaluated for physical appearance, weight uniformity, folding endurance, moisture content, surface pH, drug content and the results obtained are summarized in below table 3.

Table 3. Evaluation of Valsartan Buccal Patches.

Sr. No.	Formulation code	Physical appearance of Patches	Weight uniformity ±SD	Folding endurance	% Moisture Content	pH±SD	% Drug Content±SD
1	**R3**	Smooth, transparent, uniform, thin & flexible.	24.4±1.67mg	>100	20.83%	6.7±0.1	97.64%
2	**R4**	Smooth, transparent, uniform, thin & flexible.	24.8±2.28mg	>100	12.5%	6.8±0.1	97.35%
3	**R5**	Smooth, transparent, uniform, thin & flexible.	25.4±2.70mg	>100	16%	6.5±0.1	97.94%
4	**R6**	Smooth, transparent, uniform & flexible.	30.4±2.54mg	>100	20%	6.8±0.1	98.23%
5	**R7**	Smooth, transparent, uniform & flexible.	25.8±1.30mg	>100	12%	6.6±0.1	97.05%
6	**R8**	Smooth, transparent, uniform & flexible.	30.8±2.38mg	>100	10%	6.5±0.1	97.64%

The folding endurance was measured manually, by folding the patches repeatedly at a point till they broke. The number of times of patches could be folded at the same place without breaking gave the value of the folding endurance. Hence the breaking time was taken at the end point. The folding endurance was found to be more than 100. It was found that the folding endurance was increased with the addition of PVP with HPMC. The % moisture content was found in the order of to R3<R4<R5<R7<R8<R6 i.e. 20.83%, 20%, 16%, 12.5%,12% & 10% due to the high degree of hydration of mucoadhesive polymer like HPMC. So the formulation having only HPMC shows high % moisture content than the formulation having HPMC and PVP. All the prepared formulations of Valsartan buccal patch showing the pH range within the range of mucus pH i.e. 6.5 to 6.8. The observed surface pH of the formulation R3, R4, R5, R6, R7 & R8 is 6.7, 6.8, 6.5, 6.8, 6.6 & 6.5 respectively. The results are found that there is no significant difference of surface pH in all the formulation. The observed results of content uniformity indicated that the drug was uniformly dispersed. The observed content uniformity of formulation R3, R4, R5 R6, R7 & R8 is 97.64%, 97.35%, 97.94%, 98.23%, 97.05% & 97.64%.

3.2.2 In vitro Dissolution Study

The results of *in vitro* studies are shown in the Table 4. Distinguishable difference was observed in the release of Valsartan containing HPMC and PVP. The graph was plotted by taking Cumulative percentage release vs. Time and the graphs were shown in the Figure 4. The cumulative percentage drug release observed in the formulation R3 after 7 hr. was found to be 92.94%. The cumulative percentage drug release observed in formulation R4 and R8 after 12 h was found to be 84.70%, 90.00%, 95.29%, 82.05% & 76.76% respectively. The observed results were indicating the highest percentage of HPMC showing good release characteristics in the formulation R3 due to hydration and excessive swelling percentage of polymer. But in the presence of PVP may retard the release of drug more than 11 to 12 h may be due to increase in bioadhesion property of polymer. So out of all the formulation R6 retards the release rate and used to achieve the sustained release characteristics up to 12 h than the other formulations.

Table 4. *In vitro* Dissolution Study of different formulations.

Sr. No.	**Time(hr)**	**% Drug Release**					
-	-	R3	R4	R5	R6	R7	R8
1	1	15.88	5.29	10.58	13.23	5.29	2.64
2	2	29.11	10.58	13.23	15.88	7.94	5.29
3	3	45.00	15.88	18.52	21.17	13.23	10.58
4	4	60.88	21.47	23.82	26.47	18.52	15.88
5	5	76.76	26.47	31.76	34.41	23.82	21.97
6	6	87.35	37.05	39.70	42.35	29.11	26.47
7	7	92.64	47.64	50.23	52.94	34.41	31.76
8	8	-	52.94	58.23	60.88	42.35	37.05
9	9	-	63.52	68.86	71.47	55.58	50.23
10	10	-	71.47	76.76	82.05	60.58	63.52
11	11	-	76.76	82.05	90.00	74.11	68.86
12	**12**	-	84.70	90.00	95.29	82.02	76.76

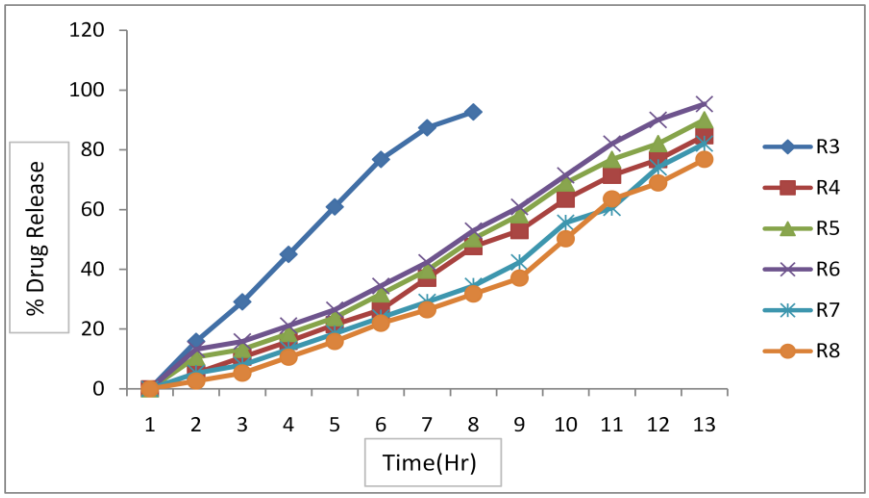

Fig. 4. *In vitro* Dissolution profile of formulations R3-R8.

3.2.3. In vitro Diffusion Study

The results of *in vitro* drug permeation studies are shown in the Table 5. Distinguishable difference was observed in the diffusion of Valsartan containing HPMC and PVP. The graph was plotted by taking Cumulative percentage diffusion vs. Time and the graphs were shown in the Figure 5. The cumulative percentage drug permeation observed in the formulation R3 after 7 hr. was found to be 93.22%. The cumulative percentage drug release observed in formulation R4 and R8 after 12 h was found to be 85.10%, 90.21%, 95.29%, 82.18% & 77.08% respectively. The observed results were indicating the highest percentage of HPMC showing good diffusion characteristics in the formulation R3 due to hydration and excessive swelling percentage of polymer. But in the presence of PVP may retard the permeation of drug more than 11 to 12 h may be due to increase in bioadhesion property of polymer. So out of all the formulation R6 retards the permeation rate and used to achieve the sustained release characteristics up to 12 h than the other formulations.

Table 5. *In* vitro Diffusion Study of different formulations.

Sr. No.	Time (hr.)	% Drug Diffusion					
-	-	R3	R4	R5	R6	R7	R8
1	1	15.62	5.54	10.36	14.01	5.40	3.35
2	2	32.11	11.24	14.89	15.76	8.17	5.25
3	3	47.59	15.91	18.83	21.75	14.45	10.51
4	4	60.72	21.49	24.52	26.56	18.54	15.91
5	5	75.03	25.98	32.99	33.72	23.64	22.23
6	6	89.34	37.38	38.54	41.45	29.63	27.15
7	7	93.22	48.61	50.51	53.86	34.89	31.24
8	8	-	52.94	58.10	60.72	42.48	37.66

9	9	-	64.52	68.90	71.67	56.78	50.65
10	10	-	71.38	76.78	82.00	61.67	63.64
11	11	-	75.76	83.64	90.00	73.86	69.05
12	12	-	85.10	90.21	95.29	82.18	77.08

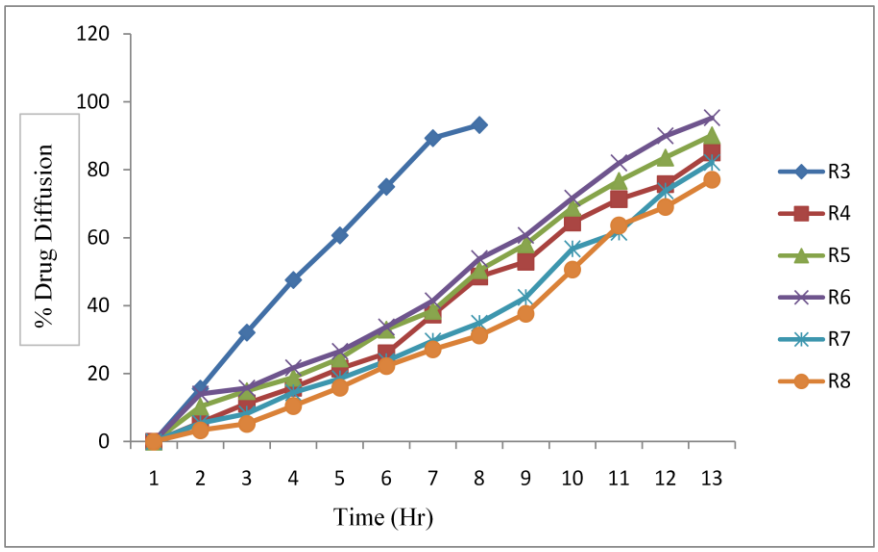

Fig. 5. *In vitro* Diffusion profile of formulations R3-R8.

3.2.4. Drug Release Kinetics

The release kinetics of Valsartan patch followed Higuchi model. To understand the mechanism of release of Valsartan from the patches the drug release data was fit into Higuchi model and it showed the highest regression coefficient values for higuchi model, indicating diffusion to be the predominant mechanism of drug release. The graph as in figure 6 was plotted between cumulative percent release and square root of time. The regression value for drug release profile of formulation R6 was found to be 0.9863, other formulations values as in table 6. These indicate that, diffusion is the mechanism of drug release from the system.

Table 6. Drug release kinetics parameters.

Kinetics Model	**Regression value(R^2)**
Zero order	0.973
First order	0.748
Hixon order	0.958
Korsemeyer Pappas	0.260
Higuchi plot	0.983
Best model	**Higuchi model**

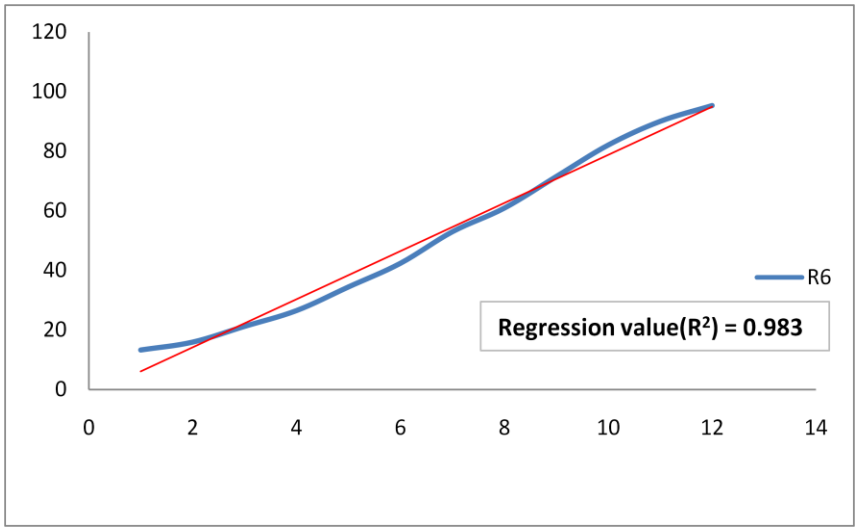

Fig.6. Higuchi plot.

4. CONCLUSION

Among the various concentration of polymeric combinations, the combination ratio 2:1(HPMCK15:PVPK30) was found to be most suitable. The formulation R6 combination of polymers HPMCK15, PVPK30 fulfills the requirement of good buccal patches. It showed highest drug release up to 95.29% for 12hr. Thus from the present study it can be concluded that, buccoadhesive patches of Valsartan with HPMCK15 & PVPK30 meet the ideal requirement for buccal patches which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability. So, buccoadhesive patches are thought to be more promising drug delivery system for improving bioavailability of drug as well as the patient's compliance, because mucosa is relatively permeable with a rich blood supply and that results in delivery of drug providing direct access to the systemic circulation through the jugular vein and thus bypass liver and a high bioavailability is obtained. The ease of administration and ability to terminate drug delivery when required makes it a potential and attractive route of drug delivery.

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