International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685, Impact Factor: RJIF 5.28
Received: 05-01-2021, Accepted: 07-02-2021, Published: 26-03-2021
www.pharmacyjournal.net
Volume 6, Issue 1, 2021, Page No. 30-33

Formulation and evaluation of valsartan buccal patches

Dhanashri Patil[1], Firoj Tamboli[1*], Harinath More[1], Shivani Khairmode[1], Prajakta Tambare[1], Pramila Patil[2], Shalaka Patil[3]

[1] Department of Pharmacognosy, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India
[2] Appasaheb Birnale College of Pharmacy, Sangli, Maharashtra, India.
[3] Rajarambapu College of Pharmacy, Kasegaon, Sangli, Maharashtra, India

Abstract
The aim of the present investigation was to formulation and evaluation of buccal patch of valsartan for the treatment of antihypertensive. Valsartan drug is BCS class 1 drug used to treat hypertension (high blood pressure). Thiazide diuretics, calcium channel blocker, ACE inhibitor, angiotensin 2 receptor antagonist (ARBs), and beta blockers these are the most widely use antihypertensive drug. Study interactions between the amount HPMC and Eudragit L – 100 were selected as variables are Folding endurance, drug release and swelling index. Buccal patches prepared by using solvent casting method. Preformulation studies were conducted and formulated patches were subjected for evaluation of various physicochemical parameters like thickness, weight uniformity, content uniformity, folding endurance.

Keywords: valsartan, hydroxypropyl methylcellulose, *in vitro* drug release, buccal patch

Introduction

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for the drug absorption [1]. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion. The use of mucoadhesive polymers in buccal drug delivery has a greater application [2]. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offers greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability [3]. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action [4].

Valsartan is an orally active nonpeptide triazole-derived antagonist of angiotensin (AT) II with antihypertensive properties. Valsartan selectively and competitively blocks the binding of angiotensin II to the AT1 subtype receptor in vascular smooth muscle and the adrenal gland, preventing AT II-mediated vasoconstriction, aldosterone synthesis and secretion, and renal reabsorption of sodium, and resulting in vasodilation, increased excretion of sodium and water, a reduction in plasma volume, and a reduction in blood pressure [5].

Materials and methods

Materials

Valsartan and Hydroxypropyl methylcellulose (HPMC) were obtained as a gift sample from Pharmaceutical Company. Eudragit L-100, Propylene glycol, Aspartame, DMSO, ethanol were obtained from store department of the institute.

Preparation of Valsartan buccal films

The buccal films were prepared by solvent casting method (Mahajan *et al*., 2011) in which the polymers were dissolved in water to form a clear solution. The drug was dissolved in ethanol before mixing with the polymer solution. Propylene glycol was added to the mixture. The solution was casted into a Petri dish and dried. The dry film was cut into square shaped sections (4 cm^2) [6, 8].

Evaluation tests for buccal patches

Surface pH

Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch [8].

Folding endurance [9]

Thickness measurements

The thickness of each film is measured at five different Locations (center and four corners) using an electronic digital micrometer [10]

Swelling study

Swelling studies of prepared patches were performed using 6.8 pH phosphate buffers for 3 hr and the results are shown in Swelling behavior of a buccal drug delivery system is an important property for uniform and prolonged release of the drug and effective mucoadhesion. The effect of various compositions of patches on the swelling index of the patches was studied by plotting the graph between percent swelling and time [11, 12].

$$\text{Swelling index} = \frac{W2-W1}{W1} \times 100$$

W2- Final weight
W1- Initial weight

***In vitro* Drug Release**

The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through Whatman filter paper and analyzed for drug content after appropriate dilution.

The *in- vitro* buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien/Franz type glass diffusion cell at 37°C±0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with buffer [13, 15].

Results and discussion

The main goal of the present work was to develop and evaluate new buccal patches comprising a drug-containing polymer like, HPMC, Propylene glycol and Aspartame in various combinations and proportions.

Determination of drug content

Table 1: Determination of drug content

Sr. No	Conc. (µg/ml)	Absorbance (249 nm)
1	1	0.155
2	2	0.365
3	3	0.632
4	4	0.984
5	5	1.261

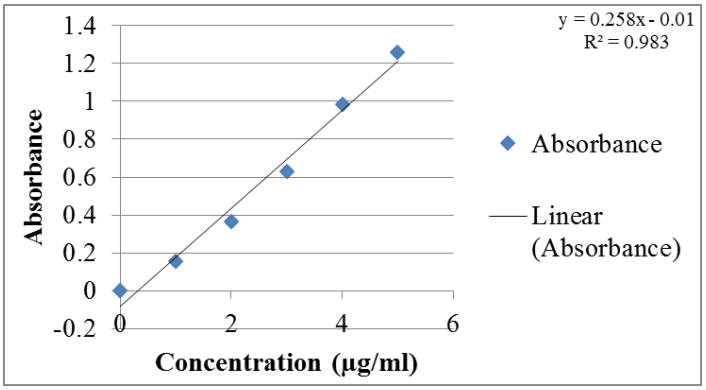

Fig 1: Graph of Valsartan in phosphate buffer pH 6.8

Table 2: Formulation Table

Batch	Valsartan (mg)	HPMC (mg)	Eudragit L-100 (mg)	DMSO (ml)	Propylene glycol (ml)	Aspartame (mg)	Ethanol (ml)
1	25	100	70	0.6	2	0.2	25
2	25	90	85	0.6	2	0.2	25
3	25	80	100	0.6	2	0.2	25
4	25	60	75	0.6	2	0.2	25
5	25	100	100	0.6	2	0.2	25

Folding Endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 75 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on five patches.

Swelling index

Swelling studies of prepared patches were performed using 6.8 pH phosphate buffers for 3 hr and the results as swelling behavior. Swelling behavior of a buccal drug delivery system is an important property for uniform and prolonged release of the drug and effective mucoadhesion. The effect of various compositions of patches on the swelling index of the patches was studied by plotting the graph between percent swelling and time as shown in fig.2 Maximum swelling was observed in batch F3 (59.24%) while batch F5 showed minimum swelling (54.70%). Maximum swelling percentage was observed for F3 batch because of more.

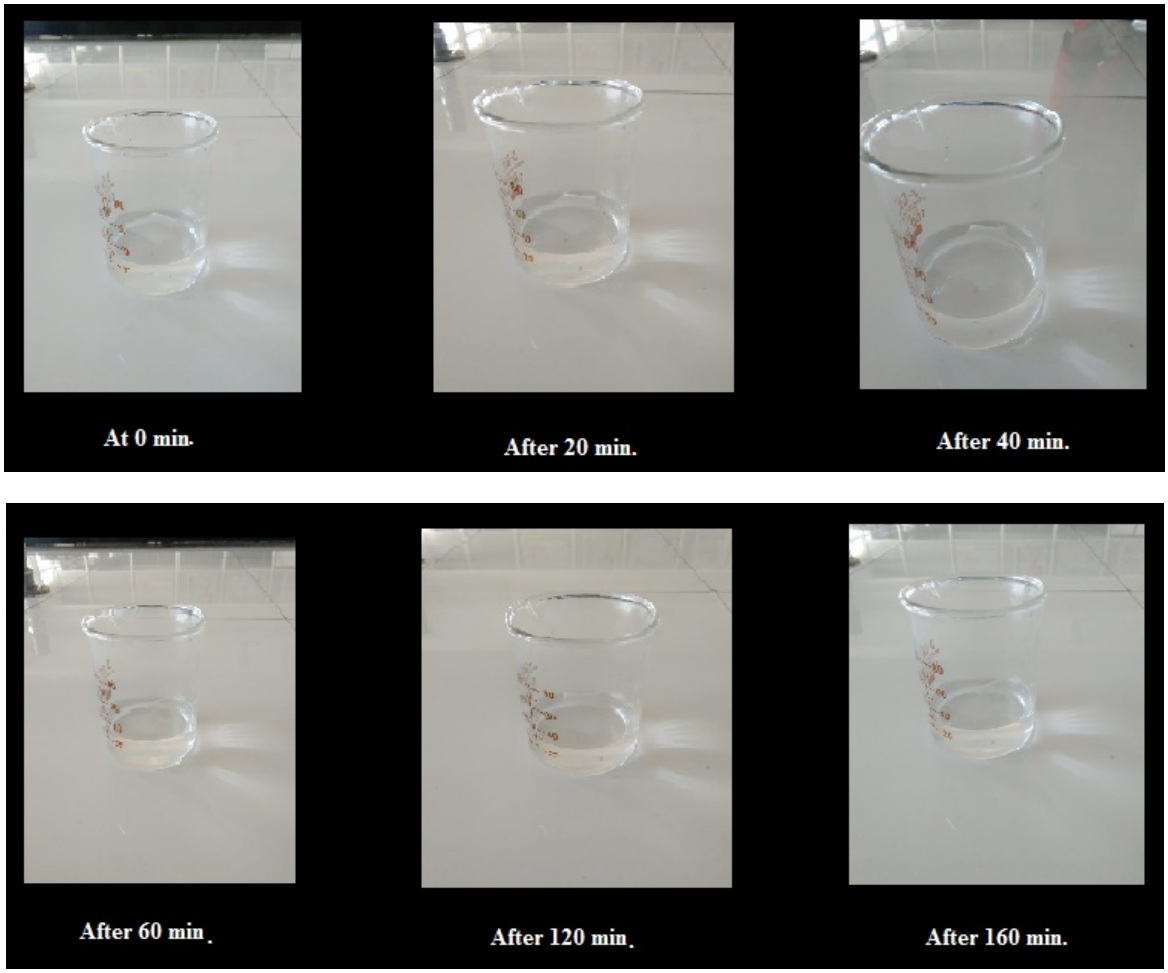

Fig 2: Swelling Index

Table 3: Swelling Index

Sr. No.	Batch	Swelling Index
1	F1	59.16%
2	F2	55.51%
3	F3	59.24%
4	F4	56.91%
5	F5	54.70%

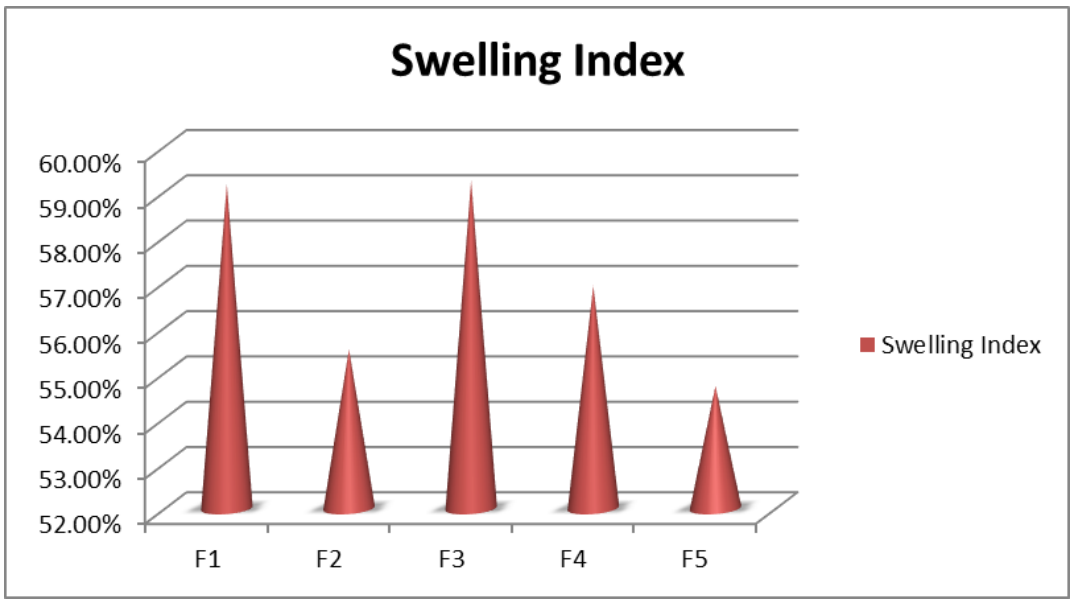

Fig 3: Comparative Swelling Index of all Formulations

Table 4: Evaluation of thickness, weight, pH, folding endurance & drug release

Formulation	Thickness (mm)	Weight (mg)	Surface pH study	Folding Endurance (mg)	Drug release (%)
F1	0.75±2.32	174.66±2.50	6.78±0.22	79±2.12	79.9±1.05
F2	0.67±1.26	178.66±2.83	6.72±0.48	76±1.47	79.3±2.15
F3	0.75±2.18	171.33±0.16	6.64±0.40	84±2.66	76.6±1.75
F4	0.69±1.20	173.66±2.14	6.76±0.34	81±1.82	82.5±1.01
F5	0.74±2.68	163.66±1.64	6.50±0.32	78±2.24	80±1.08

Drug release study

In vitro drug release through cellophane membrane

The release profile of drug from buccal films was performed by using Franz diffusion cell. The formulation was placed on cellophane membrane mounted between the donor and receptor compartment of the diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 6.8. solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (0.1 ml) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer at 249 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The amount of drug released across the cellophane membrane was determined as a function of time. Maximum *in vitro* release was found to be 82.5% over a period of 160 min in batch F4 while minimum *in vitro* release was found to be 76.6% in batch F3 these results were further supported by swelling studies results, where highest swelling was shown by batch F3 and hence resulting in faster drug release.

Table 5: Total *in vitro* drug release profile

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
20	14	13	9.3	13.8	14.2
40	21.9	21.3	23.9	22.2	22.52
80	40.21	42.1	41.2	42.7	40.5
120	68.4	68.93	69.4	69.3	68.6
160	79.9	79.3	76.6	82.5	80

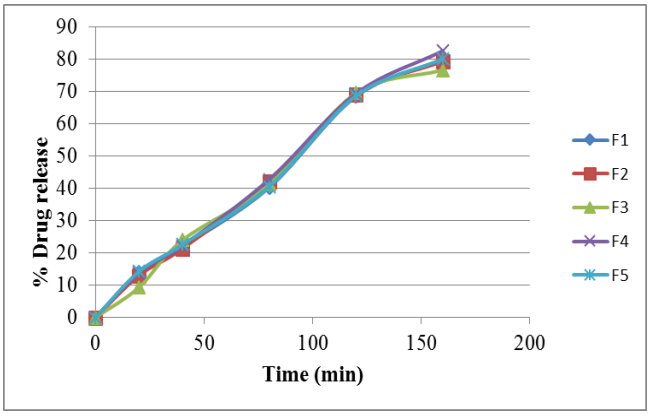

Fig 4: Total cumulative drug release profile

Conclusion

The buccal patches of valsartan by using polymer like HPMC, Eudragit L-100 various proportional and combination showed physicochemical and mucoadhesive characteristics various formulation shows drug release of valsartan, it can be concluded that such valsartan buccal patches may be provided suspended drug release provided buccal patch delivering for prolonged periods in the management of hypertensive, which can be good way to bypass first pass metabolism.

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