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FORMULATION AND *IN-VITRO* EVALUATION OF MUCOADHESIVE BUCCAL TABLET OF VALSARTAN

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ABSTRACT

Drug delivery via the buccal mucosa offers a novel route of drug administration. The route has been tried for systemic delivery of a number of drug candidates since it overcome first pass metabolism, gastrointestinal irritation and bioavailability and also for local delivery of drugs. Valsartan is an antihypertensive agent used to treat the high blood pressure and heart failure. It has half-life 5-9 h. The drug is incompletely absorbing about 23% but most of the absorbed drug reaches to the systemic circulation. Therefore it was planned in this investigation to develop sustain released mucoadhesive buccal tablets containing antihypertensive agent, valsartan to release unidirectionally in buccal cavity for extended period of time for improvement in bioavailability, to reduce dosing frequency and to improve the patient compliance. The effect of two independent variables, Guar gum (X1) and Sodium alginate (X2) at three different levels (-1, 0, +1) on dependent variable including %CDR (Y1), Mucoadhesive strength (Y2) and Swlleng strength (Y3). Using 3 full factorial design. The novel tablet were evaluated in term ofdrug uniformity content , weight variation, thickness, hardness, swelling index, surface pH, mucoadhesion strength and *in-vitro* drug release.

Keywords: Valsartan, Buccal tablet, Guar gum, Sodium alginate.

INTRODUCTION

Mucoadhesive buccal drug delivery systems have turn into immensely interesting in the last 10-15 years. Their capability to bind to mucus membrane concerned awareness as a path for resolving a problem of less bioavailability of traditional drug delivery system employad in the oral route. The route has been tried for systemic delivery of a number of drug candidates since it overcome first pass metabolism, gastrointestinal irritation and bioavailability and also for local delivery of drugs [1, 2]. Many drug delivery systems (DDS) are aimed to sustain drug blood concentration and controlling the rate of drug delivery to the target tissue, but mucoadhesion is one of the most prominent and latest systems in the design of buccal drug delivery systems. It prolongs the residence time of the dosage form at the site of application or absorption and facilitates an intimate contact of the dosage form with the underline absorption surface and thus contributes to improved and / or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, gastrointestinal, rectal and vaginal routes for both systemic and local effects. Valsartan belongs to a class of drugs called angiotensin receptor blockers (ARBs). It works by relaxing blood vessels so that blood can flow more easily. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Valsartan is a BCS class II drug, i.e., low solubility and high permeability. The different mucoadhesive polymers were selected for preparing buccal tablet such as guar gum and sodium alginate.

MATERIALS AND METHODS

Valsartan was obtained from Dr. Raddys Laboratories Ltd, Hydrabad gift sample. All other

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excipients obtained from Blue Cross Laboratory, Ltd, Nashik and Research-Lab Fine Chem. Industry – Mumbai. Characterization of Valsartan

FT-IR Specral Analysis

The infra red spectrum of drug and polymers was recorded with BRUKER OPUS 7.5 over wave number of 4000 to 400 cm^{-1} by using In fra-red spectroscopy.

Drug content uniformity

From each batch three randomly selected tablets were weighed accurately and powdered in a glass mortar with pestle. Powder equivalent to 10 mg of drug was transferred into 10 ml volumetric flask containing 10 ml of pH 6.8 phosphate buffer and kept aside with constant shaking for 24 h to extract the total drug present in the tablet. Then the solution was filtered and the volume was made with pH 6.8 phosphate buffer and analyzed for drug content at λ_{max} of 250 nm against drug devoid phosphate buffer as blank. Averages of triplicate readings were taken. The content of drug was calculated using standard graph [3].

Swelling index

$$\% \text{ Swelling Index} = [W_2 - W_1] / W_1 \times 100$$

Mucoadhesion strength

Goat cheek pouch was obtained commercially; the cheek pouch was collected into a sterile container containing sterile buffer solution of pH 6.75. The cheek pouch brought was stored in a refrigerator until use. The following procedure was used for all the test formulations using the above equipment. The cheek pouch was removed from refrigerator and allowed to attain equilibrium with ambient conditions in the laboratory. The goat cheek pouch was carefully excised, without removing connective and adipose tissue and washed with simulated saliva solution. The tissue was stored in fresh simulated saliva solution pH 6.75. Immediately afterwards the membrane was placed over the surface of lower Teflon cylinder (B) and secured. This assembly was placed into beaker containing simulated saliva solution pH 6.75 at 37 ± 2°C. From each batch, one tablet at a time was taken and stuck to the lower surface of teflon cylinder with a standard cynoacrylate adhesive. The beaker containing mucosal tissue secured upon lower cylinder (B), was manipulated over the base of the balance so that, the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the tablet was wetted with a drop of simulated saliva solution, and then a weight of 20 gm was placed above the expanded cap, left for 10 minutes. After which the tablet binds with mucin. The weight was removed. Then slowly and gradually weights were added on the right side pan till the tablet separates from the mucosal surface/ membrane. The weight required for complete detachment is noted (W_1) (W_1-5.25 gm) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more tablets. Average was computed and recorded. (n=3) [4].

Preparation of tablets containing Valsartan by direct compression

All the ingredients including drug, polymers and excipients were weight accurately according to the batch formula. The drug is thoroughly mixed with mannitol on butter paper with the help of stainless still spatula. Then all the ingredients except lubricant mixed in the order of ascending weights and blended for 10 min. After uniform mixing of ingredients, lubricants was added and against for 2 min. Then tablets were prepared using drug and excepient mixture by direct compression. The formula is shown in table No. 1.

EVALUATION OF VALSARTAN MUCOADHESIVE TABLETS

All the prepared tablets were evaluated for weight variation, thickness, hardness, drug content, surface pH, swelling index, mucoadhesive strength, in-vitro dissolution study and IR spectroscopy.

***In-vitro* Dissolution studies**

The drug release profile was studied using USP dissolution testing apparatus II using a paddle at 50 rpm. 900ml dissolution fluid, pH 6.8 phosphate buffer, was used and a temperature of 37 ±0.5°C was maintained. The oral buccoadhesive tablet is attached to glass disk with cynoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. 5ml of aliquots were withdrawn at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12 h respectively and the same volume was replaced with pH 6.8 phosphate buffer. Absorbance was measured at λmax 250nm and from which percentage of drug release was calculated using calibration curve. The procedure was repeated for three more tablets similarly and average was computed.

Table 1. Composition of Valsartan mucoadhesive tablet

Ingredients	**Formulation code**								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Valsartan	40	40	40	40	40	40	40	40	40
Guar gum	**20**	**30**	**40**	**20**	**30**	**40**	**20**	**30**	**40**
Na. Alginate	**20**	**20**	**20**	**30**	**30**	**30**	**40**	**40**	**40**
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2

Manitol	56	46	36	46	36	26	36	26	16
Lactose	60	60	60	60	60	60	60	60	60
Total	200	200	200	200	200	200	200	200	200

Table 2. Evaluation of Rheological properties

Formulation code	Bulk density (g/cm^3) Mean± S.D	Tapped density (g/cm^3) Mean± S.D	Compressibility index (%) Mean± S.D	Hausner's ratio Mean± S.D	Angle of repose(θ) Mean± S.D
F1	0.3560±0.002	0.4160±0.002	14.67±0.50	1.169±0.003	29.93±0.668
F2	0.3654±0.002	0.4237±0.002	13.74±0.371	1.159±0.01	30.52±0.652
F3	0.3721±0.001	0.4086±0.009	8.702±0.30	1.096±0.004	29.17±0.454
F4	0.3866±0.002	0.4366±0.001	11.44±0.163	1.129±0.002	25.76±0.538
F5	0.3810±0.003	0.4440±0.003	14.11±0.7941	1.163±0.001	27.95±0.647
F6	0.3650±0.007	0.4322±0.004	12.19±0.633	1.184±0.031	26.80±0.527
F7	0.3790±0.005	0.4601±0.005	14.20±0.85	1.20±0.010	28.12±0.728
F8	0.3754±0.002	0.4048±0.003	7.250±0.178	1.058±0.003	26.28±0.713
F9	0.3820±0.003	0.4490±0.005	15.0±0.508	1.178±0.006	28.07±0.731

Table 3. Evaluation of Mucoadhesive tablet of Valsartan

Formulation code	Hardness(kg/cm^2)	Thickness(mm)	Weight variation(mg)	%Drug content
F1	3.73±0.01	2.82±0.01	198.6±1.1	90.84±0.49
F2	4.30±0.02	2.92±0.02	197±1.5	93.66±0.5
F3	4.11±0.01	2.95±0.08	196±1.0	92.95±0.60
F4	3.42±0.02	2.73±0.02	195±1.3	95.06±0.70
F5	4.69±0.01	2.92±0.01	196±1.5	91.89±0.50
F6	4.58±0.01	2.89±0.04	198±1.2	94.48±0.61
F7	4.81±0.01	2.99±0.02	197±1.5	91.19±0.70
F8	4.21±0.02	2.92±0.04	196±1.5	93.42±0.61
F9	3.84±0.02	2.81±0.02	198±1.7	95.88±0.60

Table 4. Evaluation of Mucoadhesion strength of Valsartan tablet

Formulation code	Surface pH	Swelling Index	Mucoadhesion strength (N)
F1	6.3±0.2	81.35±0.47	0.0637±0.03
F2	6.5±0.40	107.77±0.69	0.1011±0.010
F3	6.8±0.15	128.5±0.52	0.1268±0.070
F4	6.6±0.14	88.40±0.65	0.0699±0.025
F5	6.6±0.15	112.2±0.42	0.1055±0.020
F6	6.5±0.01	135.5±0.50	0.1420±0.010
F7	6.7±0.05	92.26±0.22	0.0788±0.015
F8	6.8±0.05	120.34±0.06	0.1112±0.025
F9	6.7±0.05	158.2±0.51	0.1680±0.01

Fig 1. Bioadhesion equipment (Fabricated)

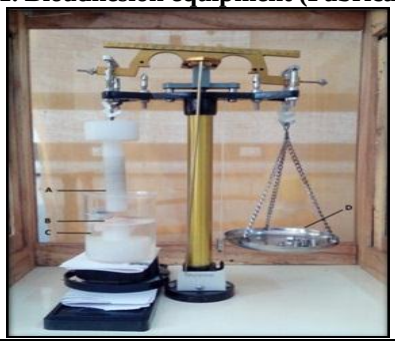
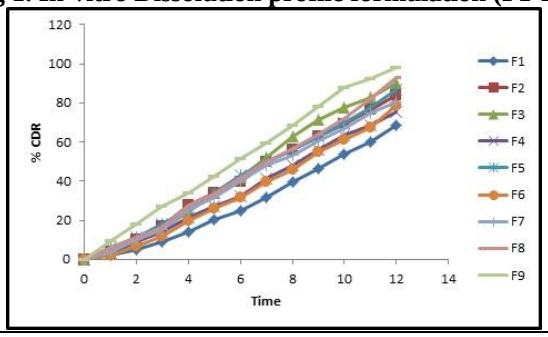


Fig 1. In-vitro Dissolution profile formulation (F1-F9)



RESULT AND DISCUSSION

It could be observed that all that all the prepared tablet fulfills the IP requirements for physicochemical properties and results are given in Table 2. The hardness of prepared tablets was found to be in the range 3.42 to 4.81 kg/cm^2. The thickness and weight of buccal tablet were found to be in the range 2.73 to 2.95 mm and 195 to 198.6 mg respectively. The average drug content of the buccal tablet was found to be within the range of 90.84 to 95.88%. The surface pH of all formulations was found to be in the range of 6.3 to 6.8. Hence it is assumed that these formulations cause no any irritation in the oral cavity. The swelling profile of different batches of tablets. The swelling index of the tablets increased with increasing amount of guar gum and sodium alginate. The mucoadhesivity of tablets was found to be maximum in case of formulation F9 i.e. 0.1680 N. It may be due to fact that the combination and higher concentration of guar gum and sodium alginate. The result is given in table .3. In-vitro drug release data of the all the buccal tablet formulations of valsartan was subjected to goodness-of-fit test by test by linear regression analysis according to Zero order, first order kinetics and according to Higuchi's and Korsmeyer-peppas equestion to assertion mechanism of the drug release shown in fig.1. The formulation F9 show drug release 96.29% within 12 h are shown in fig.1. The FTIR studies revealed that there was no physicochemical interaction between Valsartan.

CONCLUSION

It can be concluded that the mucoadhesive buccal tablets of Valsartan can be prepared by using natural polymers to control the drug release and also to avoid the first pass metabolism. The formulation F9 was found to be promising, which shows an in vitro drug release of 96.29% in 12 h along with satisfactory mucoadhesive strength.

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Nil

CONFLICT OF INTEREST

No interest

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