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Original Article

Design and evaluation of Mucoadhesive Buccal Tablets of an anti-hypertensive drug - Valsartan

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ABSTRACT: Hypertension is a well-established independent risk factor for cardiovascular diseases and stroke. Valsartan is an angiotensin II receptor antagonist used in the management of hypertension. Valsartan is rapidly absorbed following oral administration. Many conventional oral formulations for hypertension offer convenience and ease of use but produce unreliable blood levels and inconsistent response. Buccal route offers several advantages such as rapid absorption, by-passing first pass metabolism and higher blood levels due to high vascularisation of the region and prolonged duration of action. Hence, in the present work mucoadhesive buccal tablets of Valsartan were prepared with the objective of avoiding first pass metabolism and prolonging the duration of action.

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INTRODUCTION

The oral route of drug administration is preferred over other routes because of diverse benefits. The harsh environment to which an oral delivery system is exposed to after administration is a major drawback for drug delivery system e.g. acidity, enzymatic action etc. These drawbacks are the extreme pH variations, gastrointestinal enzymes and others. Such effects can be avoided by using sublingual or buccal route. Buccal cavity presents a milder environment for drug, devoid of the acid hydrolysis and hepatic first pass effect improved drug delivery and bioavailability. Moreover, it has been reported to improve drug delivery through buccal route and dosage form can be removed mechanically by hand in case of toxicity [1].

Hypertension is a well-established independent risk factor for cardiovascular diseases and stroke. In developing countries, heart diseases and stroke resulting from hypertension are the first and third causes of morbidity and mortality.

High blood pressure or hypertension kills around 1.5 million people yearly in South-East Asia which makes it the most important risk factor for non-communicable diseases such as heart attack and stroke, according to the World Health Organization. Many conventional oral formulations for hypertension offer convenience and ease of use but produce unreliable blood levels and inconsistent response [2].

Valsartan is an angiotensin II receptor antagonist used in the management of hypertension. It improves symptoms and quality of life in patients with chronic heart failure. Valsartan is rapidly absorbed following oral administration. It has a systemic availability of 0.25, which is reduced to about 0.15 by food. It is 95% protein bound and is mostly excreted as unchanged drug via the bile. It is given in doses of 40–160 mg once daily; this dosage is reduced in hepatic impairment, intravascular volume depletion, and renal impairment. Therefore, it was selected as a suitable drug candidate for the design of mucoadhesive tablets with a view to improve its oral bioavailability [3,4].

MATERIALS AND METHODS

Materials

Valsartan was obtained as a gift sample from Ranbaxy Ltd., Devas (M.P.). All the other ingredients were procured from S. D. Fine Chemicals Limited, Mumbai. and were of analytical reagent grade.

Method of Preparation of Mucoadhesive tablets: Direct compression method was employed to prepare buccal tablets of Valsartan using carbopol and sodium alginate as polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula. The drug and all the ingredients except lubricant and glidant were taken on a butter paper with the help of a stainless-steel spatula and the ingredients were mixed in the order of ascending weights and blended for 10 min. After uniform mixing of ingredients, lubricant and glidant were added and again mixed for 2 min. The prepared blend of each formulation was compressed using tablet punching machine [4-6].

Table 1: Formulation of Mucoadhesive tablets

INGREDIENTS	FORMULATIONS					
	F1	F2	F3	F4	F5	F6
Valsartan (mg)	40	40	40	40	40	40
Carbopol 934 (mg)	15	30	45	60	75	90
Sodium alginate (mg)	90	75	60	45	30	15
Lactose (mg)	50	50	50	50	50	50
Microcrystalline Cellulose (mg)	30	30	30	30	30	30
Mannitol (mg) or Sodium Saccharin	15	15	15	15	15	15
Magnesium Stearate (mg)	6	6	6	6	6	6
Talc (mg)	4	4	4	4	4	4
Total Weight (mg)	250	250	250	250	250	250

EVALUATION OF MUCOADHESIVE TABLETS

Precompression parameters:

Bulk density (Db): It is ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by;

Db = M/Vo

Where, M is the mass of the powder Vo is the bulk volume of the powder [4-6]

Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml.

Dt =M/Vt

Where, M is the mass of powder, Vt is the tapped volume of the powder [6-9]

Angle of repose (θ): The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane and it is given as [5-8],

Tan θ = h / r; θ = tan-1[h /r]

Where, θ is the angle of repose, h is the height in cm, r is the radius

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Carr's index (I): It indicates the ease with a material can be induced to flow .it is expressed in percentage and is given by [4-6]:

I = Dt –Db /Dt x 100

Where, Dt is the tapped density of the powder, Db is the bulk density of the powder

Table 2: Angle of Repose

S. No	Flowability	Angle of Repose
1	Excellent	$25 - 30^0$
2	Good	$30 - 35^0$
3	Fair	$35 - 37^0$
4	Poor	$37 - 45^0$
5	Very poor	Above 45^0

Table 3: Carr's Index Standard Values

Carr's index %	Type of flow
5 - 15	Excellent
12 – 18	Good
18 – 23	Fair to passable
23 – 35	Poor
35 – 38	Very poor
>40	Extremely poor

Post compression parameters:

1) **Hardness test:** Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated [4-7].
2) **Thickness:** The thickness of three randomly selected tablets from each formulation was determined in mm using a Vernier caliper [4-8].
3) **Friability test:** It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablet was determined by using Friabilator as per IP procedure of friability. It is expressed in percentage (%). Twenty tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of tablets less than 1% is considered acceptable [5-8].

4) **Uniformity of weight:** The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation [4-7].
5) **Uniformity of drug content (%):** Five tablets were powdered in a glass mortar and the powder equivalent to 40 mg of drug was placed in a stoppered 100 ml conical flask. The drug was extracted with 40 ml distilled water with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 1 hour. Then heated on water bath with occasional shaking for 30 minutes and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more distilled water through filter, further appropriate dilution was made and absorbance was measured at 220 nm against blank (distilled water) [6-7].
6) **Surface pH study:** A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 ml of phosphate buffer pH 6.8 for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min [8-9].
7) **Swelling Index (%):** The swelling index of the buccal tablet was evaluated in phosphate buffer pH 6.8 The initial weight of the tablet was determined (W1) and then tablet was placed in 6 ml phosphate buffer pH 6.8 in a petridish and then was incubated at 37±1^{o}C. The tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h) blotted with filter paper and reweighed (W2). The swelling index is calculated by the formula:

Swelling index = 100 (W2-W1) / W1. Where, W1 = Initial weight of the tablet. W2 = Final weight of tablet [10-11].

RESULT AND DISCUSSION

Precompression parameters:

The bulk density and tapped density of all the formulations has found in the range of 0.31 to 0.37 g/c.c and 0.36 to 0.42 g/c.c respectively. From the bulk density and tapped density, the Carr's index was calculated which is an important parameter for flow property.

The angle of repose values was found to be in the range from $25^0.72^1$ to $29^0.83^1$ all the formulations. All the formulations show angle of repose values less than 30^0 indicating excellent flow of the granules

Table 4: Precompression parameters

PARAMETER	F1	F2	F3	F4	F5
Bulk density (g/cc)	0.32	0.36	0.37	0.31	0.33
Tapped density (g/cc)	0.36	0.41	0.42	0.34	0.37
Angle of repose (θ)	$29^O.06^1$	$28^O.25^1$	$25^O.72^1$	$29^O.83^1$	$25^O.26^1$
Carr's index (%)	11.1	12.19	11.90	8.82	10.80

Post compression parameters: The avg. wt. and thickness increase as the as the concentration of Carbopol increases. The hardness of prepared mucoadhesive buccal tablets was increased as the concentration of carbopol was increased.

Table 5: Post compression parameters

Formulation code	Physical parameter		
	Avg. weight ± SD (mg)	Thickness ± SD (mm)	Hardness ± SD (Kg/cm^2)
F1	250.1 ± 0.47	2.42 ± 0.17	4.3±0.15
F2	250.4 ± 0.72	2.36 ± 0.09	4.8±0.12
F3	250.5 ± 0.52	2.38 ± 0.16	5.1±0.17
F4	251.2 ± 0.34	2.58 ± 0.15	5.4±0.11
F5	251.5 ± 0.51	2.69 ± 0.06	5.5±0.16

Drug content (%) & Surface pH study: The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations. The surface pH of the buccal tablets is determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. The results reveal that all the formulations provide an acceptable pH in the range of 6.5 to 6.9 (salivary pH). Hence, they may not produce any local irritation to the mucosal.

Table 6: Post compression parameters continued

Formulation code	Drug Content (%) ± SD	Surface pH± SD
F1	98.65 ± 0.78	5.7±0.21
F2	97.15 ± 0.49	6.9±0.24
F3	98.55 ± 0.32	6.6±0.19
F4	98.93 ± 0.41	6.8±0.32
F5	98.95 ± 0.54	6.5±0.27

Swelling Index (%):

In-vitro water uptake studies are of great significance as variation in water content causes a significant variation in mechanical properties of formulations. The capacity of the formulation to take up water is an important intrinsic parameter of the polymeric system in consideration to the release of the drug on the mucosal surface. Water absorbing capacity of system (SI after 6 hours.) decreased in the following order F6> F5> F4> F3>F2>F1 with decreasing concentration of Carbopol.

When carbopol concentration was increased, the tablets absorbed more moisture and the thickness of the gel layer formed on the surface of tablets increased. Swelling study showed the relative capacities of bioadhesive polymers for moisture absorption and whether the tablets maintained their integrity after swelling.

According to the study, it was concluded that swelling index values of none of the tablets exceeded 76.12% after 8h and different tablets kept their integrity even after swelling. So, it was considered that all tablets had acceptable swelling index.

Table 7: Post compression parameter (Swelling index)

Time (hr)	Swelling index (%)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	08.47	8.74	8.91	9.75	9.81
1	16.82	17.12	19.35	21.16	23.55
2	19.16	20.23	22.21	24.56	27.44
3	25.27	27.17	28.31	29.91	35.34
4	29.11	29.91	30.41	33.71	39.74
5	34.93	36.43	38.13	39.14	45.21
6	41.29	43.21	45.22	51.72	57.28
7	48.38	49.18	53.39	65.31	68.67
8	54.73	59.79	63.15	72.44	76.12

CONCLUSION

The Mucoadhesive buccal tablets were prepared by direct compression method using carbopol 934 and Sodium alginate as mucoadhesive polymer. A total of 05 formulations were prepared. The powder properties like angle of repose, bulk density, tapped density; and Carr‟s index of all the formulations were found to be within the standard limits.

All the post-compression characteristics of the formulations like thickness, weight variation, hardness, friability, drug content and surface pH, *in-vitro* studies like swelling were found to be well within the limits of official standards.

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