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Design and Evaluation of Mucoadhesive Buccal Tablets of Alendronate Sodium

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ABSTRACT

The aim of this work was to design and evaluate mucoadhesive buccal tablets of the Alendronate sodium via buccal mucosa. Buccal tablets of Alendronate sodium were designed to release drug at mucosal site for extended period of time without washout of drug by saliva. Alendronate sodium is an antiresorptive effect which is implicated in the treatment of osteoporosis. The tablets were prepared using carbopol-934P as a primary polymer because of its excellent mucoadhesive property and secondary polymers like HPMCK4M, Ethyl cellulose and guar gum by direct compression method. The formulations were evaluated for pre compression evaluation of powder blend such as angle of repose, compressibility index and Hausener's ratio as well as post compression evaluation of tablets like hardness, thickness, friability, weight variation, assay, determination of surface pH, swelling index, an*ex vivo*residence time,*in vitro* drug release. The formulation F6 showed an *ex vivo*residence time 6.52±0.31hr. The surface pH of the optimized formulation F6 was found to be 6.83±0.28;the *in vitro* drug release profile of the optimized formulation (F6) was 97.30 % of the drug in 6 hrs. Thus conclusion can be made that the stable mucoadhesive buccal tablets of Alendronate sodium can be designed for the sustained release.When the polymer proportion in the formulation was increased with increased swelling index, drug release was decreased significantly.It follows the zero order release. The mechanism of drug release is further confirmed by the Korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

Keyword: Alendronatesodium, Carbopol, Mucoadhesive buccal tablet, Sustainedrelease.

INTRODUCTION

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface[1]. The concept of the mucoadhesive polymer has been accepted as a promising strategy to prolong the residence time and to improve localization of drug delivery systems on various membranes[2]. Buccal delivery of drugs is an alternative to oral route of drug administration; this buccal route has numerous advantages like good convenience, the toughness of epithelium, sudden removal of dosage form in case of need, relatively low enzymatic activity, prevent drug degradation in gastro intestinal tract by avoiding hepatic first pass metabolism[3]. Alendronate sodium is a second generation bisphosphonate that is used for the treatment of some forms of osteoporosis and Paget's disease. It exhibit poor bioavailability (NLT 1%) and low biological half life (2 hrs) due to high first pass metabolism[4]. The aim of the present work wastodesign and evaluatemucoadhesivebuccal tablets of Alendronate sodium in order to investigate thesuitability of different types of polymers (Carbopol with HPMCK4M, Ethyl cellulose, and guar gum) in differentratios on the parameterslike swelling index (%), *ex-vivo* residence time, surface pH, *in vitro* drug release rate.

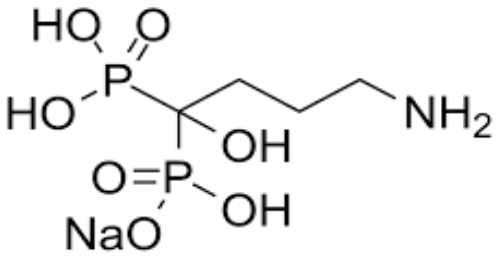

Figure 1: Structure of Alendronate sodium

MATERIALS AND METHODS

Alendronate sodium was obtained as a gift sample from Aurobindo Ltd., (Hyderabad). Hydroxy Propyl Methyl Cellulose (HPMC K4M) (Rohm Pharma GmbH, Germany), Carbopol (CP) were used as polymers. Mannitol, Spray dried lactose Micro Crystalline Cellulose (SD Fine Chemicals) served as diluents. Aspartame, Magnesium stearate is obtained from SD Fine Chemicals.

Formulation of mucoadhesive buccaltablets of Alendronatesodium:
In this work, directcompressionmethod has been employed to preparebuccaltablet with different polymersbecause with the dry granulationand wetgranulation the hardness of tabletshaveincreased because of which rate of drugrelease got decreased. For one tablet accurately weighed 250mg was used in the formulation. All the ingredients were accurately weighed andpassed through mesh#60. In ordertomixallingredients thoroughly drug, polymers, microcrystalline cellulose, aspartame were blended geometrically in mortar &pestle for 10minutes then magnesium stearate and talc were mixed for 1-2 min[5].

Table1: Formulation of Alendronate sodium mucoadhesive buccal tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Alendronate sodium	40	40	40	40	40	40	40	40	40
Carbopol 934P	30	20	10	30	20	10	30	20	10
HPMCK4M	10	20	30	-	-	-	-	-	-
Ethyl cellulose	-	-	-	10	20	30	-	-	-
Guar gum	-	-	-	-	-	-	10	20	30
PVP-K30	8	8	8	8	8	8	8	8	8
Aspartame	2	2	2	2	2	2	2	2	2
Pine apple flavor	5	5	5	5	5	5	5	5	5
Magnesium stearate	8	8	8	8	8	8	8	8	8
Talc	5	5	5	5	5	5	5	5	5
MCC	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Total (mg)	250	250	250	250	250	250	250	250	250

Evaluation of mucoadhesive buccal tablets
Compatibility Studies: The drug excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra-red spectra of pure drug and optimized formulation were recorded.

Selection of wavelength for analysis of Granisetron: the prepared concentration of 10 µg/ml and it was used for initial spectral scan in the UV range of 200-400 nm to detect maximum wavelength and further dilutions for linearity were prepared from the stock solution by allegation method[6, 7].

Pre-compression parameters
The blends for mucoadhesivebuccal tablets were characterizedwith respect to angle of repose, bulk density, tappeddensity, Carr's index, and Hausner's ratio[8].

Post compression parameters

Thickness:

The thickness of the tablets was measured by micrometer and it is expressed in mm[9].

Hardness:

Tablets require strength or hardness to withstand mechanical shocks of handling in manufacture, packing and shipping. Tablet hardness was measured by Monsanto hardness tester and results are expressed in Kg/cm^2[10].

Weight variation test:

20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight[11].

Friability:

It was performed in Rochefriabilator[12].

Determination of drug content (assay)

Twenty tablets were taken and triturated well. The quantity equivalent to 100mg of Alendronatewas dissolved in 100ml of phosphatebufferpH 6.8 solutions on rotary shaker overnight[13].

Surface pH study

The tablets were allowed to swell for 2 hours in 2ml of pH 6.8 PBS and measured by using ph meter[14].

Swellingindex

Each tablet was weighed (W1) and placed in petridish with 5ml of phosphate buffer pH 6.8. After placing the formulation for specified time, the tablets were wiped off to remove excess of surface water by using filter paper and again reweighed (W2). Where, W1=Initial weight of the tablet. W2= Weight of tablet after swelling time interval[15].

Determination of the *Ex- vivo* residence time

The *Ex- vivo* residence time was found using a locally modified USP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.8phosphatebuffer maintained at 37°C. The sheep buccal tissue was tied with thread to the central stand[16].

***In Vitro* drug release study:**

In vitro drug release study of mucoadhesivetablets were performed using standard USP dissolution apparatus type II. For each time interval 5ml sample was withdrawal and replacement of fresh medium at predetermined time interval. The samples were analyzed for drug content using double beam UV spectrophotometer at 238nm[17].

RESULTS AND DISCUSSION

Compatibility study: From the FT-IR study, the drug was found to be compatible with all the excipients, as shown in Figure 2&3.

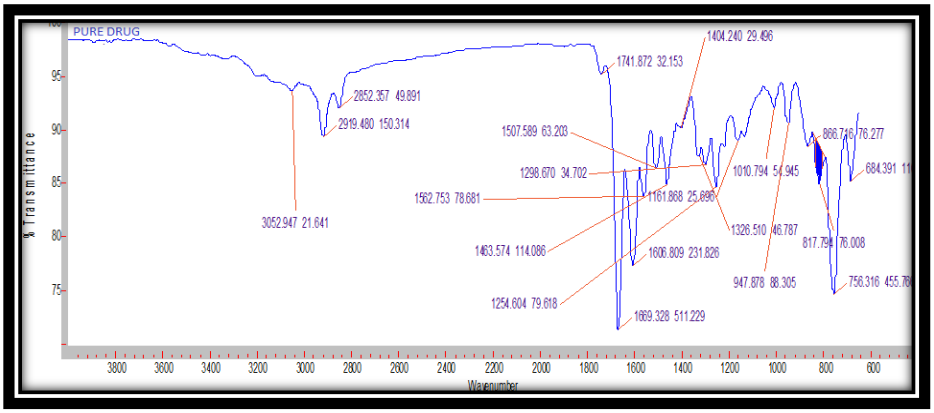

Figure 2: FTIR of pure drug Alendronate sodium

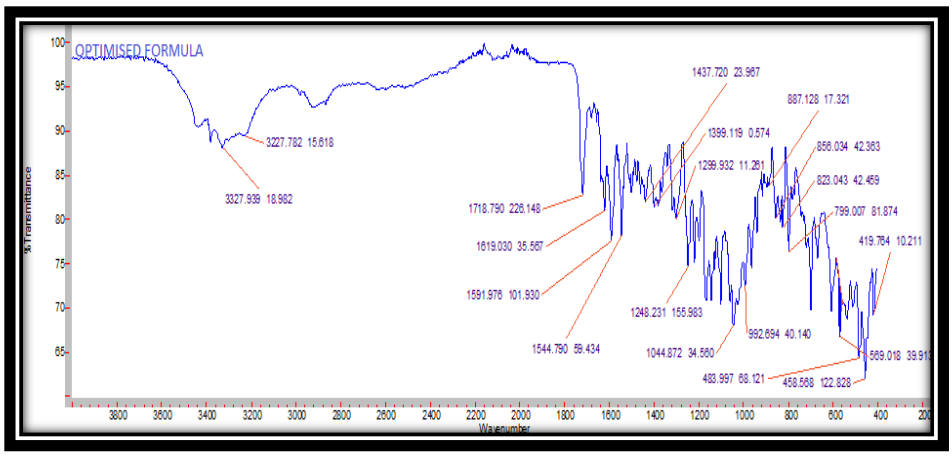

Figure 3: FTIR of optimized formulation of Alendronate sodium

Table 2: Flow properties of mucoadhesive buccal tablets of Alendronatesodium

Formulation code	Angle of repose (^{o})	Bulk density (gm/cm^3)	Tapped bulk density (gm/cm^3)	Carr's Index (%)	Hausener's ratio
F1	19º79´ ±0.12	0.71±0.06	0.64±0.28	9.86±0.18	0.962 ±0.08
F2	19º73´±0.03	0.73±0.16	0.63±0.13	13.70±0.21	0.98±0.21
F3	20º21´±0.09	0.77±0.14	0.68±0.22	11.69±0.07	0.933±0.11
F4	20º14´ ±0.06	0.81±0.28	0.71±0.19	12.35±0.02	0.892 ±0.01
F5	21º61´ ±0.12	0.77±0.15	0.66±0.25	14.29±0.16	0.8 ±0.22
F6	19º74´±0.10	0.76±0.18	0.65±0.33	14.47±0. 21	0.7 ±0.12
F7	19º79´ ±0.11	0.78±0.14	0.65±0.12	16.67±0.29	0.962±0.16
F8	19º73´±0.14	0.73±0.19	0.64±0.19	12.33±0.06	0.98 ±0.05
F9	20º21´ ±0.07	0.72±0.14	0.66±0.22	11.49±0.06	0.933 ±0.08

*****All values represent Mean±SD: n=3

Flow properties of batches were evaluated by measuring the angleofrepose, Carr's index and Hausener's ratio. Thus, angle of repose and compressibility index are indicates of good flow properties of powder blend mucoadhesive buccal tablets of Alendronate sodium.

Table3: Evaluation of buccal tablets of Alendronatesodium

Formulation code	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Assay (%)
F1	Passes	4.20±0.02	0.09±0.23	3.1±0.10	98.74±0.19
F2	Passes	4.30±0.22	0.17±0.14	3.1±0.08	99.03±0.16
F3	Passes	4.37±0.23	0.08±0.21	3.2±0.12	97.69±0.37
F4	Passes	4.33±0.21	0.07±0.11	3.4±0.10	98.74±0.09
F5	Passes	4.40±0.01	0.24±0.25	3.9±0.14	99.04±0.11
F6	Passes	4.37±0.14	0.31±0.12	3.4±0.23	99.03±0.11
F7	Passes	4.30±0.13	0.42±0.11	3.5±0.22	98.75±0.28
F8	Passes	4.37±0.14	0.08±0.09	3.9±0.12	98.75±0.31
F9	Passes	4.30±0.22	0.08±0.10	3.3±0.09	99.69±0.27

*****All values represent Mean±SD: n=3

The weight of the tablets passed within the limit as per IP standards, the thickness was found to be in the range of 3.1±0.08 to 3.9±0.14mm. The hardness of the tablets was in the range of 4.20±0.02-4.40±0.01kg/cm², and the friability was in the range of 0.07±0.11to 0.42±0.11. All these parameters were within acceptable limits. The drug content of all

formulated found to be an average of 98.74±0.09 to 99.69±0.27mg.All 9 formulations were tested for physical parameters like weight variation, thickness, hardness, friability and found to be within pharmacopoeial limits.

Table 4: Evaluation of buccal tablets ofAlendronatesodium

Formulation code	*Ex- vivo* residence time (hrs)	Surface pH	Disintegration time (min)
F1	5.34±0.26	5.57±0.22	184.16 ± 0.48
F2	6.68±0.31	6.63±0.20	180.33 ± 0.16
F3	5. 10±0.24	5.57±0.28	171.50 ± 0.04
F4	6.34±0.22	5.87±0.26	198.17 ± 0.75
F5	5.12±0.14	6.20±0.24	170.50 ± 0.83
F6	6.52±0.31	6.83±0.28	126.67 ± 0.21
F7	5.64±0.32	5.63±0.20	217.17 ± 0.98
F8	5.52±0.16	5.83±0.25	191.34 ± 0.21
F9	6.26±0.26	6.50±0.28	188.17 ± 0.75

*****All values represent Mean±SD: n=3

The *ex-vivo* mucoadhesion time for the prepared buccal tablets varies from 5 h to more than 6 h. The difference between the values of the *ex-vivo* mucoadhesion time for buccal tablets can be attributed to the combination of the various amounts of the polymer which affect the mucoadhesion. Moreover, Carbopoland HPMCK4M owing to its solubility in water and the observed high swelling rate and extent, resulted in lower mucoadhesion time. The surface pH of the formulations was found to be 5. 10±0.24 to 6.68±0.31, and the pH was found to be near to the neutral. These results recommended that the formulation is suitable for oral application and they were not irritant to the buccal mucosa. Surface pH values for all the formulations are shown in Table 4.

According to the IP, buccal tablet should disintegrate within 4 h. All though all the formulations disintegrated within a given time. The disintegration time was found to be in the range of 217.17 ± 0.98 to 126.67 ± 0.21 min for F1-F9. The least disintegration time was observed with F6 containing a lower concentration of Carbopol causes fast disintegration of tablet due lack of gel-forming ability in the water and highest disintegration time was observed in F7 containing a higher concentration of Carbopol and guar gum in combination has ability to seal the pores during compression, resulting from higher hardness and higher disintegration time.

Table5: Evaluation of swelling index of buccal tablets ofF1-F3

Time (hr)	F1	F2	F3
0	0	0	0
0.5	52±0.16	34.6±0.16	65±0.12
1	69±0.19	42.32±0.12	83.5±0.13
2	72±0.16	55.41±0.10	90.3±0.11
3	84±0.18	68.23±0.19	103.5±0.12
4	96±0.12	71.18±0.18	110.8±0.11
6	98±0.07	79.21±0.19	115.8±0.12

*****All values represent Mean±SD: n=3

Table 6: Evaluation of swelling index of buccal tablets ofF4-F6

Time (hr)	F4	F5	F6
0	0	0	0
0.5	48.01±0.21	40.8±0.15	70.1±0.22
1	60.01±0.19	52.3±0.12	89.5±0.20
2	74.6±0.20	65.6±0.11	99.6±0.18
3	86.1±0.21	78.3±0.20	111.5±0.19

4	90.1±0.22	81.8±0.18	119.3±0.21
6	94.8±0.18	87.1±0.19	123.2±0.20

*****All values represent Mean±SD: n=3

Table 7: Evaluation of swelling index ofbuccal tablets ofF7-F9

Time (hr)	F7	F8	F9
0	0	0	0
0.5	38.6±0.20	40.16±0.21	44.6±0.21
1	46.30±0.19	48.62±0.12	52.32±0.20
2	59.51±0.22	62.46±0.18	65.41±0.19
3	64.26±0.18	68.13±0.20	70.23±0.16
4	72.10±0.19	75.28±0.21	72.18±0.17
6	75.34±0.22	79.21±0.22	80.21±0.18

*****All values represent Mean±SD: n=3

Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drugs and proper bioadhesion. The mucoadhesive polymers (HPMCK4M, Ethyl cellulose and guar gum with Carbopol) used in the study were hydrogel that swelled upon contact with water and retained a large amount of water.

Table 8: *In vitro* drug release data for F1-F6 formulations

Time (hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
0.5	68.54	57.37	64.25	44.09	42.41	36.14	50.76	45.16	39.12
1	71.79	64.79	78.15	44.93	56.26	48.22	69.40	58.20	54.13
2	82.66	68.88	83.95	58.62	63.25	51.70	72.39	62.64	58.87
3	93.54	79.39	85.88	72.44	78.16	66.67	80.12	70.45	62.24
4	97.25	80.78	89.26	83.63	89.04	72.49	99.30	89.89	86.15
5	-	92.88	96.38	95.15	98.26	86.56	-	97.4	94.05
6	-	-	99.5	-	-	97.30	-	-	98.56

In-vitro drug release studies were conducted in phosphate buffer pH 6.8, and the studies revealed that the release of Alendronate sodiumfrom different formulations varies with characteristics and composition of polymers, as shown in Table 8.The *in vitro* drug release profile of the optimized formulation (F6) was 97.30 % of the drug in 6 hrs. It means the release of drug from optimized formulation was sustained release.

Mathematical Release Kinetics:

Table 9: Drug release kinetics

	R^2 values				n values
Optimized Formulation	Zero order	First order	Higuchi	Korsmeyer – Peppas	Korsmeyer Peppas (n)
F6	0.989	0.834	0.960	0.670	0.982

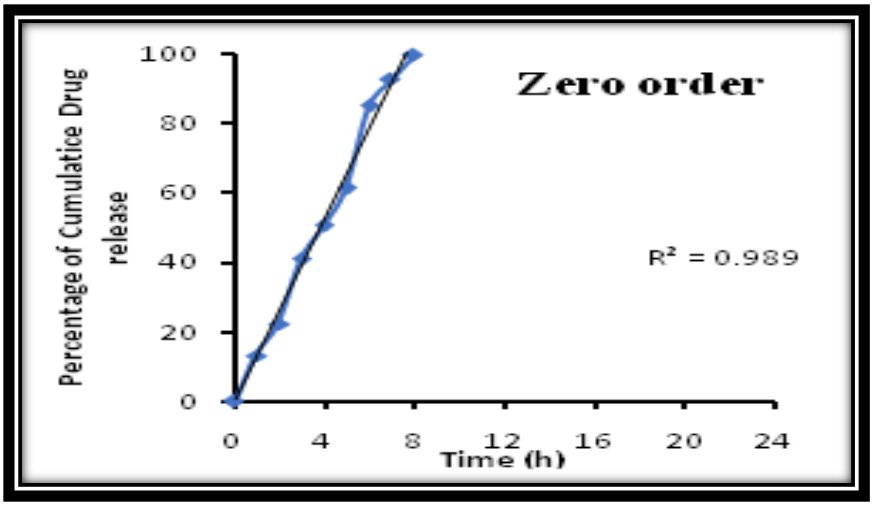

Figure4: Drug release Kinetics of Optimized formulation of F6

The *in vitro* dissolution data for best formulation F6 were fitted in different kinetic models i.e, zero order, first order, Higuchi and Korsmeyer-Peppas equation. Optimized formulation F6 shows R^2 value 0.989. As its value nearer to the '1' it is confirmed as it follows the zero order release. The mechanism of drug release is further confirmed by the Korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The mechanism of release is anomalous, that is both diffusion and erosion are involved and the data was shown in the table 9.

CONCLUSION

The mucoadhesive buccal tablets of Alendronatesodium could be prepared using HPMC K4M, Ethyl cellulose, Guargum and Carbopol934p by direct compression method. The formulation F6 showed the tablets were in acceptable range in all evaluation parameters. The formulation F6 showed an *ex vivo* residence time 6.52±0.31hr. The surface pH of the optimized formulation F6 was found to be 6.83±0.28;the*in vitro* drug release profile of the optimized formulation (F6) was 97.30 % of the drug in 6 hrs. Thus conclusion can be made that the stable mucoadhesive buccal tablets of Alendronatesodium can be designed for the sustained release. When the polymer proportion in the formulation was increased with increased swelling index, drug release was decreased significantly. It follows the zero order release. The mechanism of drug release is further confirmed by the Korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

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