RESEARCH ARTICLE

FORMULATION DEVELOPMENT & EVALUATION OF EFFERVESCENT TABLET OF ALENDRONATE SODIUM WITH VITAMIN D_3

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ABSTRACT:

Alendronate sodium is a bisphosphonates which has antiresorptive effect which is implicated in the prophylaxis and treatment of osteoporosis. The objective of this study was to formulate effervescent tablet of Alendronate sodium with Vitamin D_3 against osteoporosis thereby improving patient compliance. As per revised definition proposed to US FDA, Effervescent tablet is a tablet intended to be dissolved or dispersed in water before administration. Effervescent tablets were formulated using citric acid and sodium bicarbonate as effervescent composition by wet granulation. The drug-excipient compatibility study done by DSC & FTIR analysis and it reveals absence of interaction between the drug and excipients. The flowability study of precompression blend shows good flow properties. Formulation was evaluated for weight variation, thickness, hardness, solution time, pH of solution & content uniformity. All the evaluation parameters were within the limit and complies specifications as per U.S.P. & B.P. From the Stability analysis may be inferred that there was no degradation and change in the formulation. The Effervescent tablet of Sodium Alendronate and Vitamin D_3 is a new pharmaceutical formulation to be taken orally and offering a considerable advantage: avoidance of gastro-intestinal disorders, to the limits of the possible. As compared to the pure drug and marketed tablet, this formulation displayed significantly effective in the oral osteoporosis treatment in post menopausal women.

Keywords: Alendronate sodium, Vitamin D_3, Effervescent tablet, Osteoporosis.

INTRODUCTION:

The oral dosage forms are the most popular way of drug administration despite having some disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form. So, Effervescent tablets acts as an alternative dosage form.[1] As per revised definition proposed to US FDA, Effervescent tablet is a tablet intended to be dissolved or dispersed in water before administration. In addition to active ingredients, it generally contains mixture of acids/acid salts and carbonate and hydrogen carbonates which release carbon dioxide when mixed with water.[2] Effervescence is the evolution of gas bubbles from a liquid, as the result of a chemical reaction.

$$C_6H_8O_7\,(aq) + 3NaHCO_3\,(aq) \rightarrow Na_3C_6H_5O_7\,(aq) + 4H_2O + 3CO_2\,(g)\uparrow$$

Citric acid + Sodium bicarbonate → Sodium citrate + Water + Carbon dioxide [3]

This reaction occurs in presence of water, even with small amount as catalyzing agent, and because water is one of the reaction products, it accelerates the rate of reaction, leading to difficulty in stopping the reaction. For this reason, the whole manufacturing and storage of effervescent products is planned by minimizing the contact with water.[3]

Alendronate sodium is a BCS class III bisphosphonate, used in the treatment of osteoporosis.[5,6] Which acts as a potent, specific inhibitor of osteoclast-mediated bone resorption.[4] Colecalciferol (vitamin D_3) is a secosterol that is the natural precursor of the calcium-regulating hormone calcitriol (1,25-dihydroxyvitamin D_3).[7] Peter C. P. *et al*., examine the possible mechanism for the esophageal adverse events reported with alendronate sodium tablets and the animal studies showed that under low pH conditions alendronate sodium can cause esophageal irritation.[8] This study seeks to formulate effervescent tablet of Alendronate sodium with cholecalciferol, which limits the amount of time in which the bisphosphonate is in contact with the Oesophageal tissue, thus minimizing the risk of irritation[9] and provide vitamin D_3 nutrition during bisphosphonate treatment to facilitate normal bone

formation and mineralization while minimizing the occurrence of or potential for the complications associated with vitamin D insufficiency, such as hypocalcaemia and osteomalacia.[10]

MATERIAL AND METHODS MATERIALS:

Alendronate sodium trihydrate was obtained from Apex Healthcare Ltd., Ankleshwar (Gujarat), as a gift sample. Vitamin D_3, Citric acid, PVP-K30, Sodium bicarbonate, Sodium saccharine, Malic acid, Maltodextrin, Sodium metabisulphite, Boric acid, Sodium benzoate, color and flavor were procured from SciTech Specialities Pvt. Ltd., Sinnar (Maharashtra). All the APIs and excipients used were of analytical grade.

METHODS:

I. DRUG-EXCIPIENT COMPATIBILITY STUDY:

Drug-Excipient Compatibility Study by FTIR: The IR spectrum of drug as well as sample (drug and excipient) was recorded using FTIR spectrophotometer (Bruker, ALPHA, ECO-ATR) with diffuse reflectance principle. Sample was placed in the sample holder and the spectrum was scanned over a frequency range 4000– 400 cm^{-1}.[11,12]

Drug-Excipient Compatibility Study by DSC:

The DSC study was carried out using Mettler Toledo DSC 822e differential scanning calorimeter with thermal analyzer. The samples (drug and excipients) were heated in sealed aluminum pans under nitrogen flow (20 ml/min) at a scanning rate of 10°C/min from 0 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.[11-13]

II. FORMULATION DEVELOPMENT:

Dispense all required materials according to doers-checkers system. Then shift the materials as per the sequence and specified mesh sieves. Mix alendronate sodium with citric acid in octagonal blender (20, Anish Pharma) & granulated with PVP K30 in rapid mixer granulator (20, Anish Pharma). Then it was dried in a Fluidize Bed Dryer (20, Anish Pharma). Also blend 'B' was mixed in an octagonal blender.

Then blend 'A' & 'B' were mixed with each other and blended with lubrication blend. Final blend was compressed with tablet Compression machine (Accura D4, Fluidpack) and packed with strip packaging machine (4 RACK GMP, Vilas Engg.).

Table 1: Composition of formulations F1-F10

Ingredients	Formulation (mg/tab.)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Blend 'A'										
Sod. alendronate	91.37	91.37	91.37	91.37	91.37	91.37	91.37	91.37	91.37	91.37
Citric acid	2000.76	1880.8	1763.59	1658.99	1562.56	1531.49	1651.17	1671.7	1653.13	1672.67
PVP K30	2.15	4.3	6.45	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blend 'B'										
Sod. bicarbonate	1818.87	1880.78	1939.94	1990.79	2031.32	2144.09	1981.41	2006.03	1983.75	2007.21
Sod. saccharine	4.3	8.6	12.9	17.2	21.5	17.2	12.9	17.2	15.05	15.05
Vitamin D_3	2	2	2	2	2	2	2	2	2	2
Malic acid	-	4.3	8.6	12.9	17.2	21.5	25.8	21.5	21.5	21.5
Maltodextrin	172	172	172	172	172	172	172	172	172	172
Sod. metabisulphite	8.6	8.6	8.6	8.6	8.6	8.6	8.6	8.6	8.6	8.6
Sunset yellow color	2.15	2.15	2.15	2.15	2.15	2.15	2.15	2.15	2.15	2.15
Orange flavor	43	86	129	172	215	129	172	129	172	129
Polomint flavor	4.3	8.6	12.9	17.2	21.5	25.8	25.8	23.65	23.65	23.65
Lubrication blend										
Boric acid	129	129	129	129	129	129	129	129	129	129
Sod. benzoate	21.5	21.5	21.5	21.5	21.5	21.5	21.5	21.5	21.5	21.5
Total	**4300**	**4300**	**4300**	**4300**	**4300**	**4300**	**4300**	**4300**	**4300**	**4300**

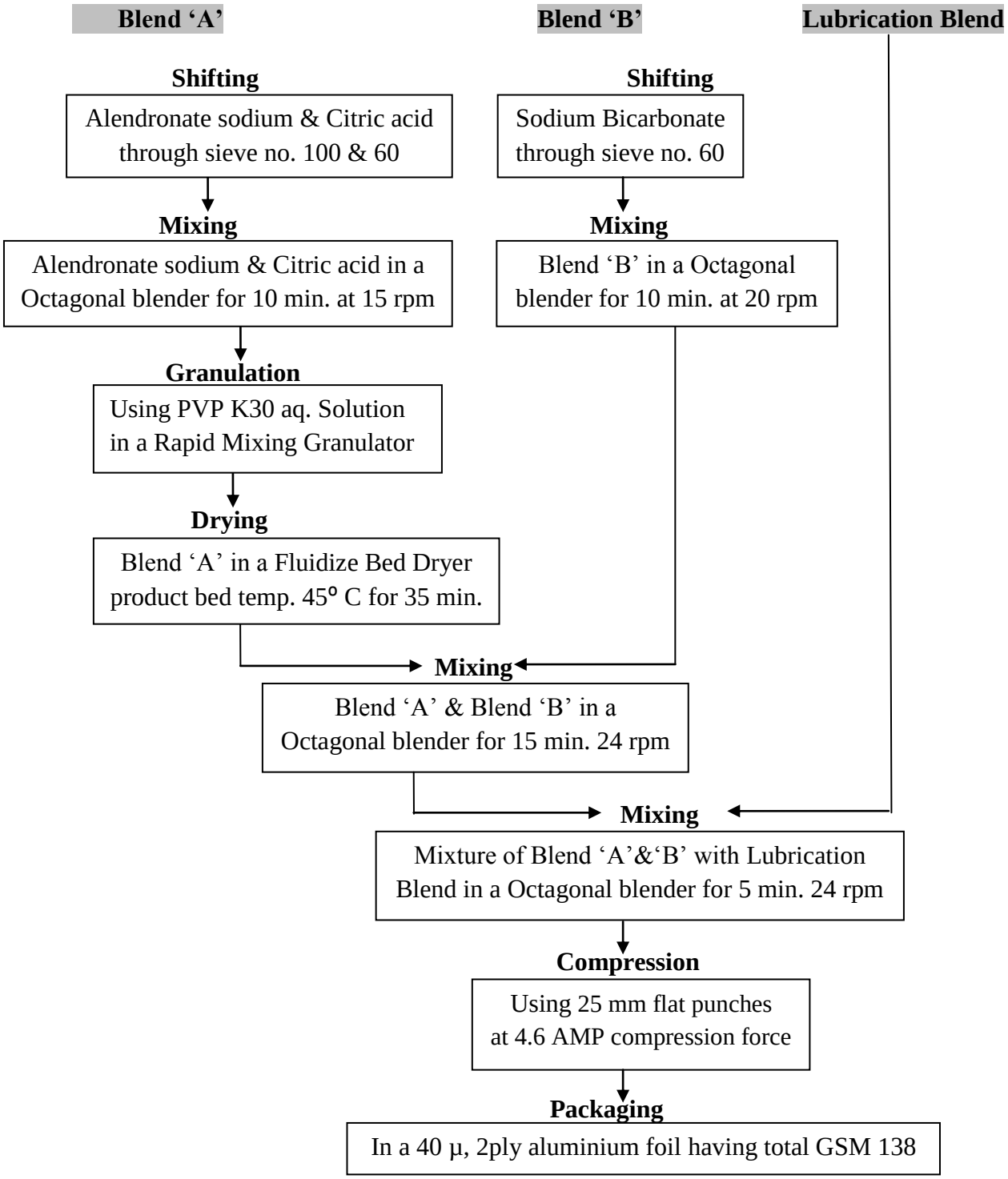

Figure 1: Process flow chart

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III. EVALUATION OF PRECOMPRESSION BLEND:

1) Angle of repose:

It was measured by fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height 'h', above graph paper that was placed on a flat horizontal surface. Granules were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with 'r' being the radius of the base of the conical pile.[14]

$$\tan \theta = h / r$$

Where, θ= angle of repose

2) Bulk density: an accurately weighed sample of granulation was carefully added to the measuring cylinder with the aid of funnel. The level was observed without compacting and noted as apparent volume (V_0).[14,15]

The bulk density was calculated by the formula as given below:

$$\text{Bulk density} = M / V_0$$

Where, M=Mass of powder taken. V_0= Apparent untapped volume.

3) Tapped density: After bulk density measurement the cylinder was placed on the tapped density tester (ETD 1060, Electrolab) and was mechanically tapped. The cylinder was tapped for 500 times initially and the tapped volume (V_1) was measured to the nearest graduated units. The tapping was repeated for additional 750 times and the tapped volume (V_2) nearest to graduated units was noted.[15]

The tapped density was calculated by the formula as given below:

$$\text{Tapped density} = M / V_2$$

Where,

M= Weight of powder. V_2= Tapped volume (after 750 taps).

4) Carr's Index: The percentage compressibility of a powder is direct measure of the potential of powder arch or bridge strength is calculated according to the equation given below:[14-16]

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5) Hausner's ratio: Hausner found that the ratio tapped density/bulk density was related to inter particle friction as such, could be used to predict powder flow properties. The Hausner's ratio was calculated by the formula as given below:[16]

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

IV. EVALUATION OF FORMULATION:

1) Tablet Dimensions:

Ten tablets of each formulation were evaluated for thickness and diameter using a calibrated dial caliper.[1]

2) Weight Variation:

Twenty tablets were selected randomly. Tablets were weighed individually and average weight was calculated. Then deviation of each tablet from average weight was calculated and percent deviation was computed. [17]

3) Tablet Hardness:

The hardness was evaluated using Monsanto (VHT1,Veego) hardness tester.[18]

4) pH of the Solution:

pH solution was determined with one tablet in 200 ml of purified water at 20 ± 1 °C by using pH meter (HI 2211, HANNA), immediately after completing the dissolution time[17]

5) Solution Time:

The solution time is indicating the time required to dissolve the tablet in 200ml of water at 17.5 ± 2.5^{0}C.[18]

6) Drug Content Uniformity:

Drug content analysis of Alendronate sodium:

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing about 25 mg of Alendronate sodium was taken in a 25 ml volumetric flask and dissolved in around 15 ml of distilled water, finally filled up to the mark by distilled water to get a

sample solution of 1 mg/ml. Then appropriate dilutions was done from the sample solution using sodium-1,2-napthoquinone-4-sulphonate reagent and 0.01 M NaOH. Absorbance of the resulting brown colored solution was measured at 525 nm using double beam UV spectrophotometer (1600, shimadzu) against a blank.[19]

Drug content analysis of Vitamin D_3:

Weigh and powder 10 tablets. Weigh accurately about 12.5 gm of the powder into a 100 ml volumetric flask and sufficient amount of Methanol: water (97:3) was added to dissolve properly. Then appropriate dilution was done and analyzed by HPLC instrument (Shimadzu LC-2010A) at 264 nm.

7) Panel Testing (Human Subjects):

In vivo taste evaluation carried out on a trained taste panel of 5 healthy volunteers with organoleptic sense, with their prior consent. On placing the dosage form in mouth for 60 seconds, bitterness recorded against pure drug.[21]

V. STABILITY STUDIES: The optimized formulations sealed in aluminum packaging and kept in the stability chamber (CHM-6S, Remi) maintained at 25ºC/60% RH, 30ºC/65% RH and 40ºC/75% RH conditions for three months. The samples of 20 tablets were randomly withdrawn on initial stage, after one month and three months. These samples were analyzed for the physical appearance, hardness, solution time, pH of solution and drug content.[13,22]

RESULT & DISCUSSION:

I. PREFORMULATION STUDY OF Alendronate sodium & Vitamin D_3:

Alendronate is a white, crystalline, nonhygroscopic powder. Melting point of ALS observed in between 258-262 ^oC, it complies the standard. Colecalciferol is a white, crystalline, odourless powder. Melting point of Colecalciferol observed in between 83-86 ^oC, it complies the standard.

II. DRUG-EXCIPIENT COMPATIBILITY STUDY:

DSC Analysis

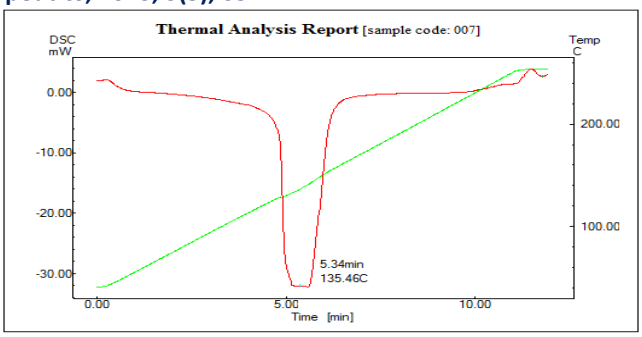

Figure 2: DSC thermogram of Alendronate sodium

The DSC thermogram of Alendronate sodium (figure 2), showed an endothermic peak in the temperature region from 76^{0}C to 115^{0}C. It is followed by an irregular endothermic peak with shoulders at 135.46^{0}C that corresponds to loss of coordinated and crystal water. The third endothermic peak, corresponding to melting of the drug is at 261^{0}C.

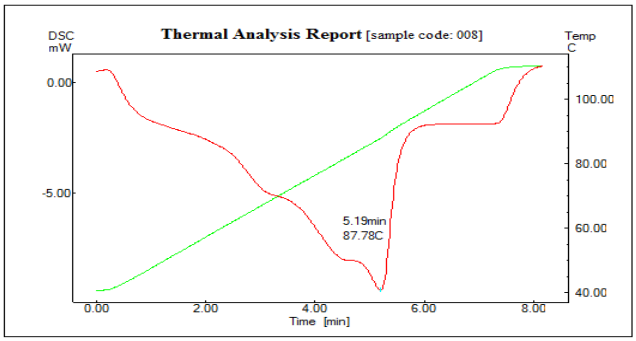

Fig. 3: DSC thermogram of Vitamin D_3

The DSC thermogram of Vitamin D_3 (figure 3), showed endothermic peak, corresponding to melting of the drug is at 87.78^{0}C.

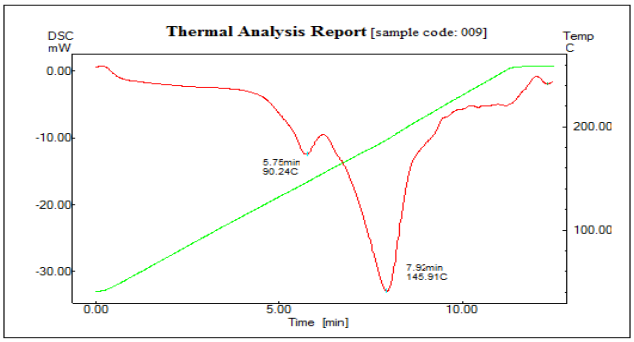

Figure 4: DSC thermogram of Alendronate sodium, Vitamin D_3 & Excipient mixture

The DSC thermogram of Alendronate sodium, Vitamin D_3 & Excipient mixture (figure 4), showed endothermic peak, corresponding to melting of the Vitamin D_3 is at 90.24^{0}C. It is followed by an irregular endothermic peak with shoulders at145.91^{0}C that corresponds to loss of coordinated and crystal water. The third endothermic peak, corresponding to melting of the Alendronate sodium is at 261^{0}C.

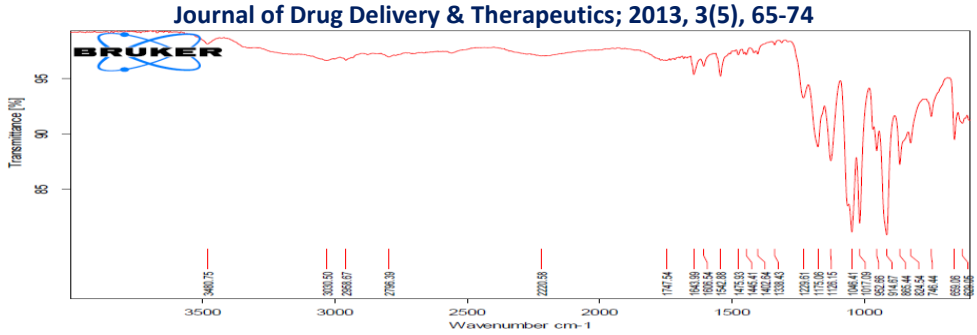

Figure 5: FTIR spectra of Alendronate sodium

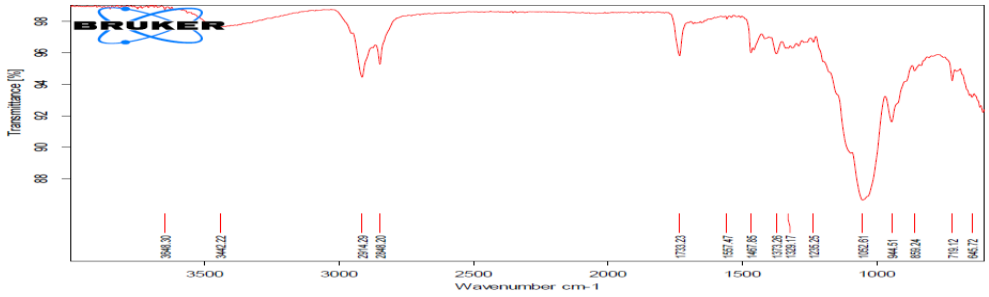

Figure 6: FTIR spectra of Vitamin D_3

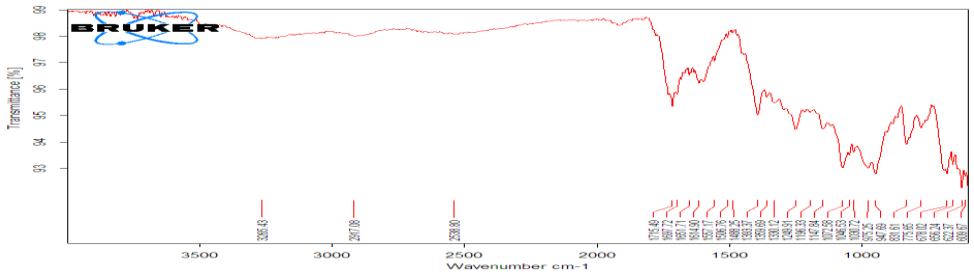

Figure 7: FTIR spectra of Alendronate sodium: VitaminD_3 (1:1) mixture

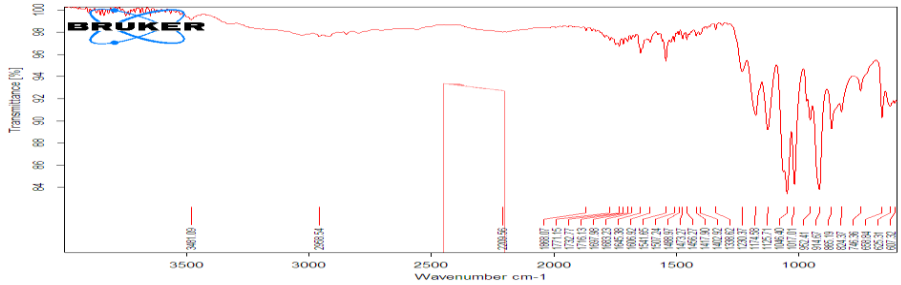

Figure 8: FTIR spectra of Alendronate sodium, Vitamin D_3 & Excipient mixture

Table 2: Interpretation of FTIR

Sr. No.	Functional group	Standard IR range (cm^{-1})	Observed wave number (cm^{-1})
1.	N-H str. Amine	3300-3500	3480.75, 3481.09
2.	C-H str. Alkenes	3010-3100	3030.50
3.	C-N str. Amine	1070-1150	1126.15, 1125.71, 1072.85
4.	O-H str. Amine	3200-3550	3480.75,
5.	C-C str.	1110-1250	1229.61, 1235.25
6.	C-H str. Alkane	2850-2960-	2914.29, 2958.54, 2917.08
7.	O-H str. Alcohol	3200-3550	3442.22, 3481.09, 3265.43

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III. EVALUATION OF PRECOMPRESSION BLEND:

Table 3: Precompression evaluation of blend

Formula-tions	Angle of repose (^{0})	Bulk density (gm/cc)	Tapped density (gm/ cc)	Carr's index (%)	Hausner's ratio
F1	25.56 ± 0.015	0.849 ± 0.001	0.903 ± 0.001	5.98 ± 0.01	1.063 ± 0.002
F2	25.64 ± 0.01	0.852 ± 0.001	0.906± 0.002	5.96 ± 0.03	1.063 ± 0.003
F3	25.76 ± 0.0057	0.854 ± 0.002	0.909± 0.002	6.05 ± 0.04	1.064 ± 0.001
F4	25.84 ± 0.01	0.857 ± 0.002	0.914± 0.001	6.23 ± 0.05	1.066 ± 0.001
F5	25.78 ± 0.015	0.859 ± 0.001	0.917± 0.003	6.32 ± 0.05	1.067 ± 0.003
F6	26.08 ± 0.0057	0.859 ± 0.003	0.911± 0.003	5.7 ± 0.12	1.06 ± 0.002
F7	25.70 ± 0.0057	0.854 ± 0.002	0.909± 0.001	6.05 ± 0.04	1.064 ± 0.002
F8	25.74 ± 0.01	0.857 ± 0.002	0.914± 0.002	6.23 ± 0.10	1.066 ± 0.001
F9	25.83 ± 0.015	0.857 ± 0.001	0.911± 0.003	5.92 ± 0.02	1.063 ± 0.001
F10	26.02 ± 0.0057	0.854± 0.001	0.909± 0.001	6.05 ± 0.04	1.064 ± 0.001

All values are expressed as mean ± SD (n=3)

IV. EVALUATION OF FORMULATION:

Preparation of standard calibration curve of Alendronate sodium:

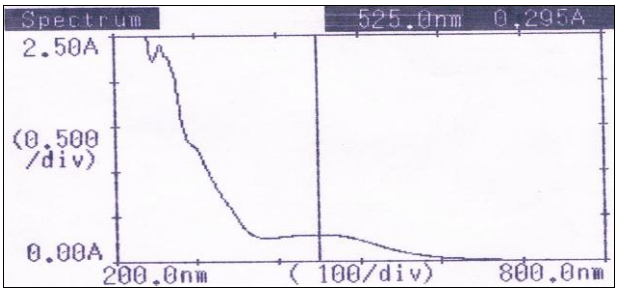

Figure 9: UV- spectrum of Alendronate sodium in distilled water

Table 4: Absorbance data of Alendronate sodium

Sr. No.	Concentrations (µg/ml)	Absorbance
1.	10	0.037
2.	20	0.072
3.	30	0.109
4.	40	0.146
5.	50	0.183
6.	60	0.222

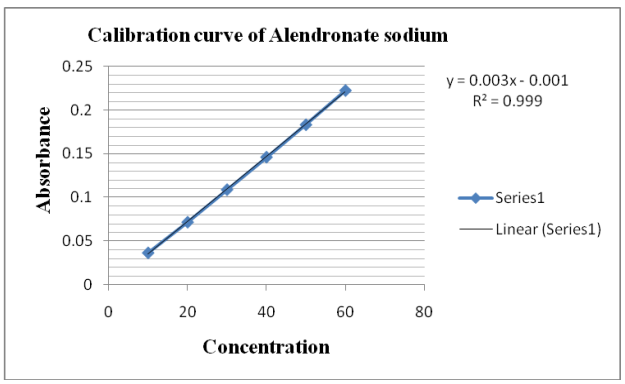

Figure 10: Calibration curve of Alendronate sodium.

Table 5: Evaluation of Thickness, Hardness & Weight variation

Formulations	Thickness (mm)	Hardness (kg/ cm^2)	Wright variation (mg)
F1	5.95 ± 0.005	6.2 ± 0.057	4.328 ± 0.014
F2	5.95 ± 0.01	5.7 ± 0.1	4.305 ± 0.005
F3	5.94 ± 0.015	5.8 ± 0.152	4.3 ± 0.01
F4	5.96 ± 0.01	6.0 ± 0.152	4.29 ± 0.015
F5	5.99 ± 0.021	5.7 ± 0.2	4.303 ± 0.006
F6	6.03 ± 0.015	5.3 ± 0.1	4.336 ± 0.013
F7	5.97 ± 0.02	5.9 ± 0.057	4.315 ± 0.011
F8	5.98 ± 0.005	5.9 ± 0.1	4.338 ± 0.005
F9	5.96 ± 0.01	5.7 ± 0.152	4.325 ± 0.013
F10	6.0 ± 0.005	5.6 ± 0.057	4.314 ± 0.005

All values are expressed as mean ± SD (n=3)

Table 6: Evaluation of chromatograms Vitamin D_3Table 7: Evaluation of chromatograms Vitamin D_3.

Average	Initial	1st Month (^{0}C/RH)			3rd Month (^{0}C/RH)	
		25/60	30/65	40/75	25/60	30/65
STD Area	75867.8	75867.8	75867.8	75867.8	75867.8	75867.8
SPL Area	180596.5	173537	169142.5	162812.5	164843	159485.5
SPL Wt.	11.8512	12.2451	12.1024	11.9845	12.4456	12.3684
Tab.	4.6125	4.6014	4.5987	4.6002	4.5941	4.6102

Table 7: Evaluation of Solution time, pH of solution & Drug content

Formulations	Solution time (sec.)	pH of solution	Drug content (%)	
			ALS	Vit.D_3
F1	60.33 ± 0.079	5.1 ± 0.053	99.70 ± 0.080	198.46 ± 0.028
F2	54.83 ± 0.091	5.04 ± 0.050	99.49 ± 0.069	198.22 ± 0.026
F3	56.09 ± 0.096	5.42 ± 0.025	99.33 ± 0.060	196.34 ± 0.035
F4	58.49 ± 0.09	5.54 ± 0.045	99.17 ± 0.083	196.94 ± 0.036
F5	51.54 ± 0.115	6.03 ± 0.015	99.05 ± 0.092	198.30 ± 0.03
F6	47.46 ± 0.101	5.85 ± 0.030	99.33 ± 0.063	197.04 ± 0.015
F7	42.83 ± 0.110	5.68 ± 0.020	99.38 ± 0.081	196.7 ± 0.020
F8	43.08 ± 0.106	5.58 ± 0.036	99.60 ± 0.072	197.26 ± 0.025
F9	56.42 ± 0.085	5.52 ± 0.025	99.54 ± 0.057	197.7 ± 0.03
F10	57.58 ± 0.090	5.7 ± 0.020	99.65 ± 0.029	199.13 ± 0.026

All values are expressed as mean ± SD (n=3)

Table 8: Taste Analysis of Formulations

Formulations	Volunteer				
	I	II	III	IV	V
F1	Very sour	Very sour	Very sour	Very sour	Very sour
F2	Very sour	Sour	Sour	Very sour	Sour
F3	Slightly sour, good	Slightly sour, good	Sour	Very slightly sour, good	Slightly sour
F4	Good but sweet	Good but sweet	Good but sweet	Good but sweet	Good
F5	Basic, sweet	Basic, very sweet	Basic, very sweet	Basic, very sweet	Basic, very sweet
F6	after metallic	after metallic	after metallic	after metallic	after metallic
F7	after metallic,	after metallic, slightly bitter	after metallic, slightly bitter	after metallic, excess polo	after metallic, slightly bitter
F8	Sweet	ok	Sweet	Sweet	Sweet
F9	Strong orange feel, good	ok	Strong orange feel, good	Strong orange feel, good	ok
F10	ok	ok	ok	ok	ok

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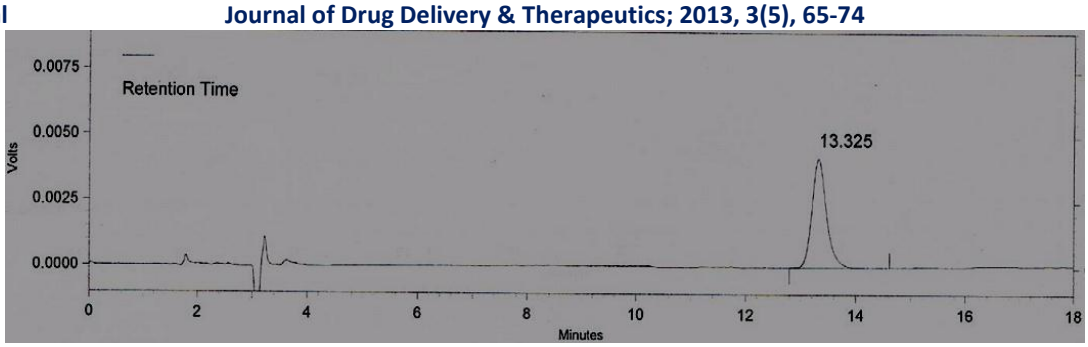

Figure 11: Chromatogram of Vitamin D_3 Standard solution.

V. STABILITY STUDIES:

Table 9: Evaluation of Formulation (F10) after 1st Month

	Appearance	Hardness (Kg/cm^2)	Solution time (Sec.)	pH of solution	% content	
					ALS	Vit. D_3
25ºC/60% RH	Orange colored	5.7 ± 0.1	58.49 ± 0.09	5.72 ± 0.020	99.21 ± 0.015	184.75 ± 0.025
30ºC/65% RH	Orange colored	5.7 ± 0.152	58.76 ± 0.091	5.73 ± 0.030	99.13 ± 0.030	182.09 ± 0.032
40ºC/75% RH	Orange colored	5.7 ± 0.2	58.98 ± 0.115	5.73 ± 0.025	99.01 ± 0.026	177.05 ± 0.028

All values are expressed as mean ± SD (n=3)

Table 10: Evaluation of Formulation (F10) after 3rd Month

	Appearance	Hardness (Kg/cm^2)	Solution time (Sec.)	pH of solution	% content	
					ALS	Vit. D_3
25ºC/60% RH	Orange colored	5.8 ± 0.115	60.33 ± 0.079	5.75 ± 0.020	98.82 ± 0.025	172.39 ± 0.030
30ºC/65% RH	Orange colored	5.8 ± 0.152	60.57 ± 0.079	5.76 ± 0.015	98.69 ± 0.026	168.42 ± 0.025

All values are expressed as mean ± SD (n=3)

DISCUSSION:

The procured sample of Alendronate sodium and Vitamin D_3 was characterized by organoleptic properties, melting point, UV, FTIR and DSC analysis that confirmed the purity of the drug. The DSC analysis showed no significant shift in the endothermic peak & FTIR analysis showed absence of any characteristics peaks of pure drug, which confirms the absence of chemical interaction between drug and excipients. Flowability studies result indicates good-excellent flow properties of the powder mixture. The thickness of the tablet signify uniformity and it was due to uniformity in die fill, good flow properties, uniform pressure and appropriate punch movement. All the formulations are within the limit of weight variation. Hardness was found to be in the range of 5.3 kg/cm^2 to 6.4 kg/cm^2.

Formulations of various effervescent composition show variation in the pH of solutions and In-vivo taste evaluation by panel test, formulation F10 shows more popularity and having better taste than others. Content uniform of Alendronate sodium & Vitamin D_3 is within the limit as per USP specification. It indicates that all formulations have the dose uniformity.[23]

From the stability study results it was observed that there was no significant change in physiochemical properties even after storage at various temperature and humidity conditions for three months. It may be inferred that there was no degradation and change in the formulation.

CONCLUSIONS:

The Effervescent tablet of Sodium Alendronate and Vitamin D_3 is a new pharmaceutical formulation to be taken orally and offering a considerable advantage: avoidance of gastro-intestinal disorders, to the limits of the possible. Another aspect of this invention is that the absorption of the active ingredient is faster when compared to the tablet form; consequently an enhanced bioavailability of the active ingredient is probable. As compared to the pure drug and marketed tablet, effervescent tablet of Alendronate sodium plus Vitamin D_3

displayed significantly effective in the oral osteoporosis treatment in post menopausal women.

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