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Formulation Development and *In-vitro* Characterization of Alendronic Acid Immediate Release Tablets

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Abstract: Alendronate is an antiresorptive agent used in prophylaxis and in the treatment of osteoporosis. The purpose of the study is to prepare Alendronic Acid immediate release tablets using direct compression technique in order to avoid the interaction between Alendronic acid and glycosidic hydroxyl group of sugar resulting in brown coloration in case of wet granulation process. The tablet blends were prepared and analyzed for various physiochemical properties. In order to get the best and optimized product six different formulations were developed. Various physical evaluation like weight variation, thickness, hardness, friability, disintegration, assay of the tablets were studied. All the parameters were found within the specified limit. *In-vitro* dissolution study was done in PH 6.8 phosphate buffer. F6 was selected as the optimized formulation on the basis of dissolution (99% in 15 min). Final formulation was subjected to FTIR and DSC studies to confirm for absence of any polymeric transition in the drug.

Key words: Osteoporosis · Direct Compression Method · Sodium Alendronate

INTRODUCTION

Osteoporosis is a disabling condition of thinning and weakening of bones. Drugs of choice in chronic treatment of osteoporosis are biphosponates and its analogs. Etidronate and Medronate are first generation anti resorptive drugs showing clinical efficacy but pharmacokinetic shortcomings like low oral bioavailability, short half life, least potency and sometimes showing bone demineralization leads to development of second generation antiresportive drugs. Alendronate, Promidonata and Ibandronate are second generation antiresorptive drugs, 10-100 times more potent than first generation antiresorptives. Alendronate has been officially indicated for treatment and prevention of osteoporosis in post menopausal women, to increase bone mass in men with osteoporosis, glucocorticoid induced osteoporosis in men and treatment of paget's disease of bone in man and women. Alendronate act by inhibiting an enzyme farnesyl pyrophosphate synthetase which helps in the biosynthesis of isoprenoid lipids (FPP and GGPP) reducing osteoclast function and bone resorption. The aim of present work is to prepare a stable oral formulation of Alendronic acid tablets since it interacts with glycosidic hydroxyl group of sugar resulting in formation of brown pigment which ultimately leads to discoloration, instability and potency loss. The present work was undertaken to develop a stable and optimize immediate release tablet formulation by direct compression method using various grades of excipients to avoid such interaction [1-3].

MATERIAL AND METHODS

Materials: Sodium Alendronate (Micronised) was obtained from Ipca Lab. Ltd, Microcrystalline Cellulose (Avicel- PH101, Avicel- PH112) from Signet Chemical Corporation, Pvt. Ltd, Lactose Anhydrous (Pharmatose DCL 21) from Kawarlal and sons and Cross carmellose sodium (Ac-di-Sol) and Magnesium stearate from Signet Chemical Corporation Pvt.Ltd.

Preformulation Study

Micromeritic Properties: The loose bulk density and tapped density were determined using density apparatus (Mac Bulk Density Apparatus, IP). The angle of repose was determined using the fixed funnel method. Carr's Index and Housner's ratio were calculated (Table 1).

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Preparation of System

Calculation of API: Mol. Wt of Alendronic acid (249.1) ~ Mol. Wt. of Sodium Alendronate trihydrate (325.12)

For 70mg of Alendronic acid

- = 325.12/249.1 *70 =91.37 mg of sodium Alendronate trihydrate

Method: The composition of tablet is given in Table 2. The drug blend of Sodium Alendronata, Avicel PH 102, Lactose anhydrous, Cross carbamelose sodium and others were sifted through sieve no.40. Magnesium stearate was added to the above blend and further mixed. The lubricated material was compressed using direct compression technique in single punch tablet press (Single station tablet compression machine, Cadmach, India) using 9mm normal concave punch [4].

Physicochemical Characterization of Tablets [5-8]: Diameter and Thickness of the tablets (n =3) were measured using "Vernier-caliper" (Mitutoyo Dogmatic, CD-8" CSX) and average was calculated. The hardness of the tablets (n=10) was determined using (Dr. Schleuniger Hardness Tester, 8M). The friability (%) of tablets (n=10) was determined using Roche Friabilator (Electrolab, EF-1W). Weight variation test of the tablets (n=20) was carried out as per the official method. Disintegration time was determined by using USP device (Electrolab, Double unit, ED-2). To perform disintegration test, one tablet was placed in each tube and the basket arch was positioned in a 900 ml beaker of water at 37°C ± 2°C.

Assay: Estimation of drug content was done by HPLC method at ambient condition using column 25CM *4.1 MM containing packing L-21, PLRP-S 1000A°. Sample was analyzed using UV Visible detector at 266 nm. Flow rate was kept 1ml/min with injection volume 50 micro liters. Run time was 10 min, showing retention time of 5.6 min. Buffer having PH 8 1500 ml, acetonitrile 400 ml and methanol 100ml were thoroughly mixed and degassed to be used as mobile phase.

***In vitro* Dissolution Test:** Dissolution study of tablets was performed in USP II (paddle) dissolution test apparatus (Lab India Disso-2000, Electrolab TDT O8L) using 900 ml of water as dissolution media. The tablets were loaded into each basket of dissolution apparatus; the temperature of dissolution media was maintained at 37±0.5°C with stirring speed of 50 rpm throughout the study. The samples were withdrawn at suitable interval of time and analyzed by HPLC (Waters-2489) with UV-Visible detector along with derivatization technique at 266 nm using water as blank. Buffer having PH 8 1500 ml, acetonitrile 400ml and methanol 100 ml were thoroughly mixed and degassed to be used as mobile phase

FTIR Study: The identification of pure drug and drug excipient compatibility study was done by KBr pellet technique using Jasco FT/IR-4100. The standard spectrum was correlated with the reference IR spectra.

DSC Study: The experiment was performed in (Mettler Toledo DSC 823e) with a non-hermetically sealed aluminum pan. The sample of 4 gm was sealed in the aluminum pan and heated at a rate of 10°C/min from 40°C to 325°C with an empty pan a reference. The peak and the onset temperature and the enthalpy of fusion reported are the mean of three determinations.

Polymorphic Study (XRD): The change of the polymorph was determined by X-Ray diffraction study. In this method, the intensity of X-ray diffraction from a sample is measured as a function of diffraction angles. The X-ray powder diffraction patterns were obtained by using (X'pert Pro MPD / Cubic Fast) with Cu Ka (λ = 1.54056Å) radiation and a crystal monochromator, voltage: 45 mv and current: 20 amps. The diffraction angles were run at 1°/min in terms of 2θ angle.

RESULT AND DISCUSSION

The results for micromeritic properties are shown in Table 1. For direct compression of materials, it is required good flow and compacting properties. The drug Alendronate exhibited angle of repose of 33.43±0.01 indicating poor flow property. The Carr's index (28.15) and Housner's ratio (1.39) values were also very high. The prepared formulation mixture showed good flow properties as indicated by low values of angle of repose, Carr's index and Housner's ratio.

Different tablet formulations (Table 2) of Alendronic acid were prepared by direct compression technique with an average weight ranging from 347.5-353.5 mg. The tablets of different batches showed uniform thickness (4.58 ± 0.05 to 4.69 ± 0.01) mm and diameter (12.82 ± 0.04 to 12.90 ± 0.03 mm).

Table 1: Powder flow properties

Formulations	Bulk density (gm/ ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
FD-1	0.588±0.02	0.776±0.03	24.22	1.32	30.12±0.02
FD-2	0.592±0.04	0.784±0.02	24.48	1.32	30±0.03
FD-3	0.597±0.03	0.800±0.01	25.37	1.34	30.4±0.02
FD-4	0.563±0.03	0.733±0.04	23.19	1.30	29.08 ±0.04
FD-5	0.571±0.02	0.740±0.04	22.83	1.29	28.04±0.03
FD-6	0.571±0.05	0.733±0.02	22.10	1.28	28±0.02
Pure drug	0.684±0.02	0.952±0.03	28.15	1.39	33.43±0.01

Mean ± S.D., n=3

Table 2: Formula of Alendronic Acid immediate release Tablets

		Formulations					
Sl. No	Ingredients	FD1	FD2	FD3	FD4	FD5	FD6
1	Sodium Alendronate (Micronized)	91.37	91.37	91.37	91.37	91.37	91.37
2	Microcrystalline Cellulose (Avicel PH-102)	113.03	118.23	118.23	--	59.12	29.55
3	Microcrystalline Cellulose (Avicel PH-112)	--	--	--	118.23	59.12	88.68
4	Lactose Anhydrous (Pharmatose Dcl-21)	123.50	113.40	113.40	113.40	113.40	113.40
5	Crosscarmellose Sodium (Ac-Di-Sol)	20.0	24.0	24.0	24.0	24.0	24.0
6	Magnesium Stearate	2.10	3.0	3.0	3.0	3.0	3.0
	Total tablet weight(mg)	350	350	350	350	350	350

Table 3: Physical characteristics of Alendronic Acid immediate release tablets

formulations	Weight Variation (mg)	Length (mm)	Width (mm)	Thickness (mm)	Hardness (kp)	D.T (min-sec)	friability (%)	Assay (%w/w)
FD1	349.3- 353.2	12.85± 0.05	7.07±0.03	4.58± 0.05	13.6-16.4	3.32-3. 57	0.412	98.685±1.02
FD2	347.5-352.8	12.82± 0.04	7.04±0.01	4.61± 0.03	13.5-15.6	1.55 -2. 42	0.440	99.963±0.93
FD3	349.0-353.5	12.84± 0.04	7.10±0.04	4.62± 0.03	13.2-15.4	1.47-2.10	0.517	99.924±0.89
FD4	348.7-352.6	12.88±0.04	7.05±0.03	4.62± 0.02	13.3-15.2	1.25 -2.10	0.343	100.531±0.78
FD5	348.5-351.9	12.85±0.03	7.08±0.02	4.64± 0.04	13.0-15.1	1.17-1.54	0.361	99.984±0.96
FD6	349.4-353.0	12.83±0.02	7.06±0.03	4.69± 0.01	13.2-14.8	1.10 -1.46	0.352	101.003±0.85

Mean ± S.D., n=3

Tablets are studied for hardness, disintegration, friability. The hardness was found to be 13.2 to 16.4 Kp. The percentage friability was ranging from 0.343 to 0.517 which is within the official limit (< 1 %). Disintegration time was found to be in 1.10-3.57 min, which was maximum for FD1 and varying the proportion of superdisintegrant the disintegration time decreased for FD6. FD6 was showing maximum drug content of 101.003% which was within the range of 90 to 100% for Alendronic acid. All the data's were shown in Table 3. FD1 showed slow drug release within 30min, hence in order to get rapid release, the superdisintegrant concentration was increased and proportion of excipients was varied. FD6 containing the MCC 102 and MCC 112 in the ratio1:3 found to be showing good release profile of 100.9 % in 30mins, suitable for immediate release tablets (Fig. 1).

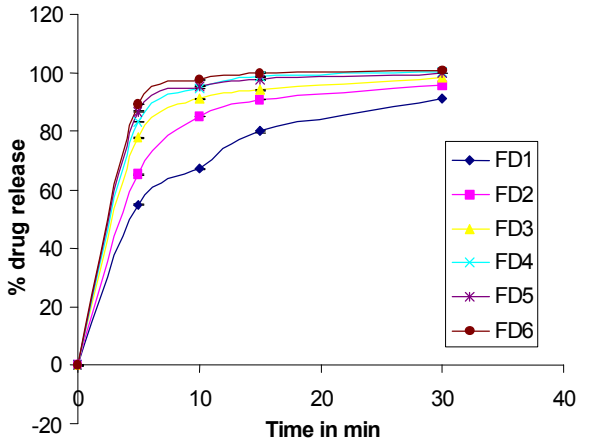

Fig. 1: Comparative dissolution profile in PH 6.8 Phosphate buffer

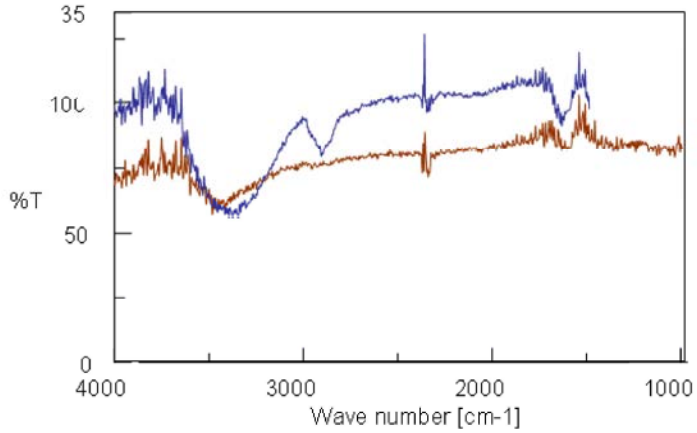

Fig. 2: FTIR spectrum of pure drug and FD6

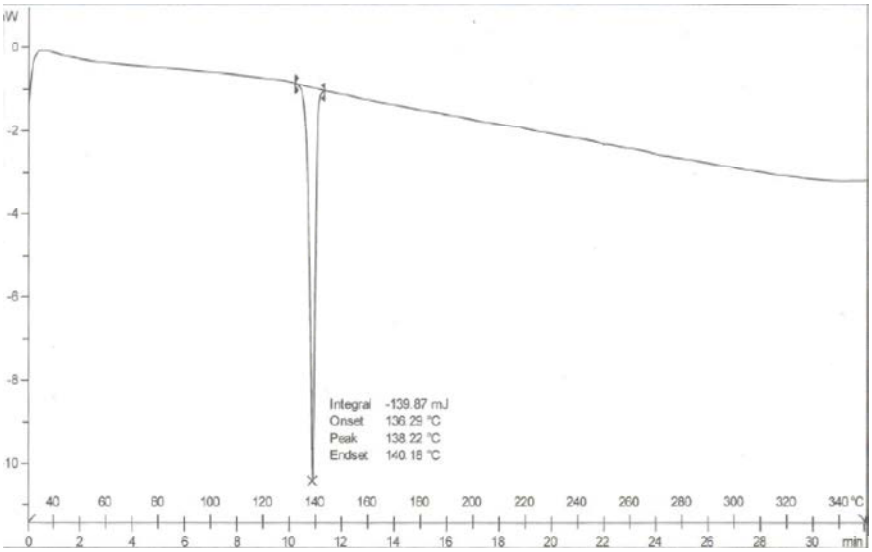

Fig. 3: DSC thermogram of Sodium Alendronate

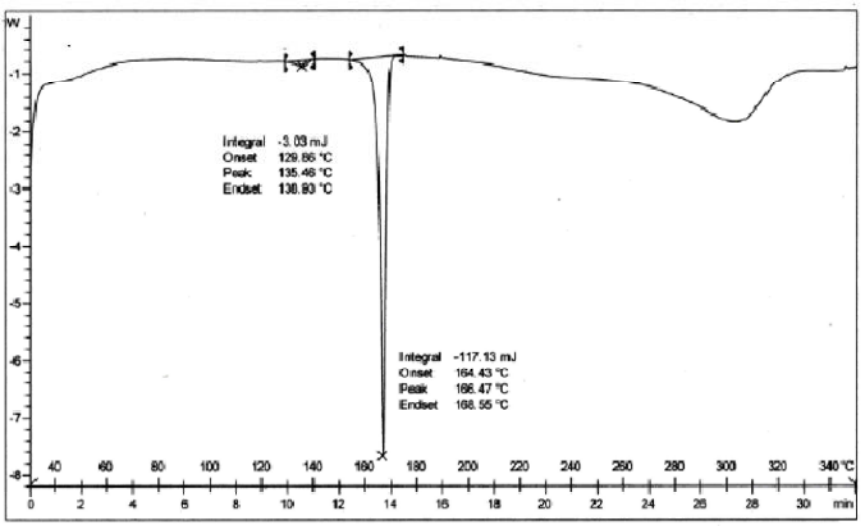

Fig. 4: DSC thermogram of FD6

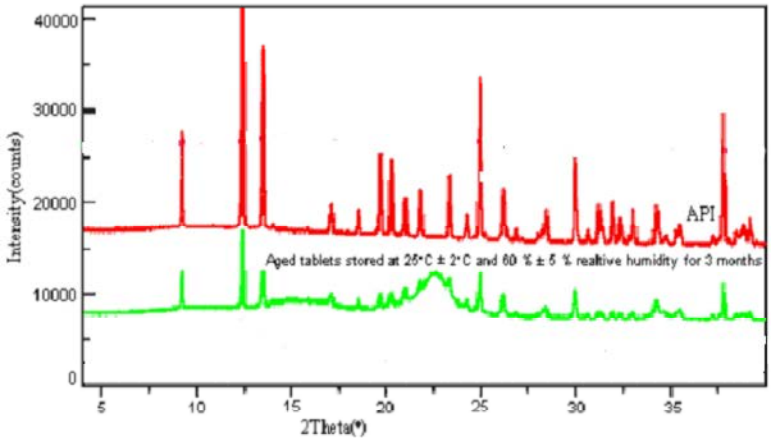

Fig. 5: XRD thermogram of pure drug and FD6

The IR absorption spectra of the pure drug and its mixture with each of the excipients used individually was taken in the range of 4000-1000 cm^{-1} using KBr disc method. The major peaks were reported for evaluation of purity as shown in Fig. 2. [9-10].

The absence of any significant change or there was no shift in the peaks of the drug out of its range in the IR spectral pattern in the formulations indicating the absence of any interaction between the drug and the excipients.

DSC studies revealed that endothermic peak for pure sodium alendronate was obtained at 138.22°C and the melting range was (onset to end of peak) 136.29°C to 140.18°C. The thermogram of the optimized formulation gave the melting endotherms at 135.46°C and 166.47°C. Thus from the DSC study as shown in Fig. 3 and 4 was confirmed that there was no change in the endothermic peak of the drug and hence the drug and the excipients were well compatible with each other.

The presence of numerous distinct peaks in the X-Ray diffraction pattern of sodium alendronate indicate it to be a crystalline powder with characteristic diffraction peaks at a diffraction angle of 2θ at 9.1, 12.5, 13.75, 19.5, 20.4, 24.7, 30.0 and 37.8 as shown in Fig. 5. The formulation also exhibited a distinct pattern with diffraction peaks at diffraction angle of 2θ at similar values as found for the pure drug. Overall diffraction pattern revealed that there is no change in polymorphic properties of the drug and the drug is well distributed through out the formulations. [11].

CONCLUSION

The study was undertaken with the aim of preformulation and formulation development of to develop a non-infringing stable oral solid dosage form of BCS class III drug Sodium Alendronate. The stable immediate release tablet formulation of Sodium Alendronate developed had physiochemical characteristic and *in vitro* drug release within pharmacopoeial limits. Moreover, the developed product was less complex with regards to formulation components and processing aspects.

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