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Research Article

Design and Evaluation of Gastro-Retentive Floating Tablets of Ibandronic acid

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Abstract

The objective of this study is Preparation and evaluation of gastro-retentive floating tablets of Ibandronic acid by direct compression method polymers or combination. In this study, Ibandronic acid, the most commonly used biphosphonate for treating osteoporosis, was formulated as gastro retentive dosage form (GRDF) tablets to enhance its oral bioavailability. GRDDs are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. GRDF tablets of Ibandronic acid (200 mg) were characterized with the effects of Carbopol 934P, HPMC 4KM and Na-CMC at various ratios on swelling, floating, physical integrity. A prolonged dissolution profile of Ibandronic acid GRDF tablets developed in this study was observed for its thickness, friability, hardness, drug content and in-vitro drug release. Formulated Floating tablets of Ibandronic acid gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation and content uniformity. Sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K4M has predominant effect on total floating time and drug release. From the study it is evident that a promising controlled release floating tablets of Ibandronic acid can be developed to increase gastric residence time and thereby increasing its bioavailability. Both doses significantly reduced the occurrence risk of new vertebral fractures by 50–52 percent when compared to the effects of the placebo drug.

Keywords: Gastro retention, Ibandronic acid, floating tablet, Carbopol, GRDF, GRFT.

INTRODUCTION

Osteoporosis is a progressive bone disease that is characterized by a decrease in bone mass and density which can lead to an increased risk of fracture. In osteoporosis, the bone mineral density (BMD) is reduced, bone micro-architecture deteriorates, and the amount and variety of proteins in bone are altered. Osteoporosis can occur at any age, although the risk for developing the disease increases as you get older. [1,2]

Bones affected by osteoporosis may become so fragile that fractures occur spontaneously or as the result of Minor falls, such as a fall from standing height that would not normally cause a break in a healthy bone, Normal stresses such as bending, lifting, or even coughing.[3]

Ibandronic acid is not recommended for people with severe renal impairment.[4] Ibandronic acid is a bisphosphonate medication used in the prevention and treatment of osteoporosis and metastasis-associated skeletal fractures in people with cancer. It may also be used to treat hypercalcemia (elevated blood calcium levels). It is typically formulated as its sodium salt Ibandronate sodium.[5-13]

Ibandronic acid', which suppresses the activity of osteoclasts and makes the bone stronger. Ibandronic acid may reverse bone loss by increasing bone mass and stopping more bone loss.[7]

Gastro retentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several important drugs. GRDFs greatly improves the pharmacotherapy of stomach by releasing the drug locally and thus results into high concentration of drug at the gastric mucosa which can be sustained over a longer duration of time. GRDDS has advantages of increasing gastric residence time and Better therapeutic effect of short half-life drugs.[14,15]

MATERIALS AND METHODS

Materials and their role in formulation

Ibandronic acid was procured as gift sample from Okasa Pharmaceuticals, Satara. HPMC obtained by Colorcon Asia Ltd, Goa., Sodium CMC was purchased from S.D. fine chemicals Mumbai. All other solvents and reagents were used of analytical grade. [16]

METHOD

Direct compression method was used for preparation. Binder, fillers and disintegrants were used in direct compression method. [17]

FORMULATION OF FLOATING TABLET

Each floating tablets containing 50 mg Ibandronic acid were prepared by direct compression method. Ibandronic acid pure drug was mixed with required quantity of HPMC K4M, sodium CMC, Carbopol 934P, sodium bicarbonate and lactose by

geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate in mortar and pestle for 2 min. The lubricated blend was compressed into tablets using 12 mm flat face round tooling on CLIT Pilot Press rotary tablet machine. Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm2 with 4.0 mm tablet thickness (Table no.1 &2).

EVALUATION

Fourier transform infrared analysis: Fourier transform infrared spectroscopy is mostly used to identify organic, polymeric, functional group, and some inorganic materials as well. FT-IR measurement of pure drug, polymer and drug loaded formulations are obtained by using this technique. The pellets are prepared on kbr press under hydraulic pressure of 150kg/cm2 and the spectra are scanned over the wave number range of 3600-400cm-1 at ambient temperature. [14,18]

Differential scanning calorimetry: DSC are performed to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations are obtained using DSC instrument equipped with an inter cooler zinc standards are used to calibrate the DSC temperature and enthalpy scale. The sample preparations are sealed in aluminium pan and heated at a constant rate of 10ºC/min over a temp range 25ºC-65ºC. [14,18]

Evaluation of effervescent floating tablet formulations

Evaluation of Powder blends:

The flow properties of granules (before compression) were characterized in terms of angle of Repose, tapped density, bulk density, Carr's index and Hausner ratio. Physical evaluation of Ibandronic acid floating tablets two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator).[15]

Evaluation of Granules

A. Angle of repose

The angle of repose of Ibandronic acid was determined by fixed funnel method. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using measuring cylinder. **[15]**

$$\tan \theta = h/r \quad \text{..... [1]}$$

Bulk density = Weight of the powder / Bulk volume of powder .....[2]

B. Compressibility Index

The Carr's index (%) and the Hausner ratio were calculated using following equations. **[15]**

$$\textit{Carr's Index} = \frac{TBD - LBD}{TBD} \times 100$$

$$\textit{Hausner Ratio} = \frac{TBD}{LBD} \times 100$$

C. Evaluation of Tablets

Physical properties like Weight variation, Hardness, Thickness, Friability and Drug content of tablet performed and results shown in Table No.3. [18]

D. Thickness

Thickness of tablets was determined using Vernier caliper. Three tablets from each batch were used, and average values were calculated.

E. Average weight

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

F. Drug content

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then suitable dilutions were made and absorbance at 525 nm wavelength was taken by using a UV spectrophotometer. Drug content was calculated by using absorbance at wavelength 525 nm.

G. Hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

H. Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined. [18]

$$\textbf{\% loss} = \frac{\text{Initial wt.of tablets} - \text{Final wt.of tablets}}{\text{Initial wt.of tablets}} \times 100$$

I. Determination of swelling index

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37±0.5^{0}C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation shows relationship between swelling index and time. [15]

$$\textbf{WU \%} = \frac{\text{IWeight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial wt.of tablets}} \times 100$$

J. *In Vitro* Release Studies

The *in vitro* dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in 0.1 N HCl for 12 h in 900 ml of dissolution media, maintained at 37±0.5^{0}C and agitated at 50 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The concentration of Ibandronic acid was measured spectrophotometrically at 525 nm. [15]

K. Buoyancy determination

The buoyancy test of tablet was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 900 ml 0.1N HCl, maintained at 37±0.5^{0}C and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation. [15]

RESULTS

IR spectrum of Ibandronic acid

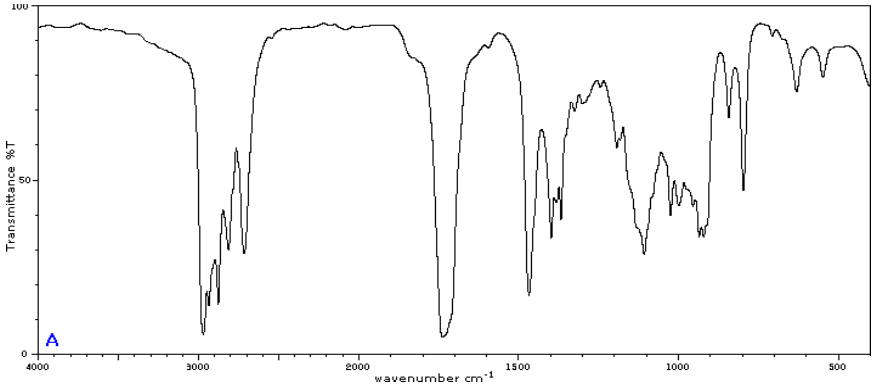

Figure 1: IR spectrum of Ibandronic acid

IR spectra of mixture of Ibandronic acid + HPMC K4M

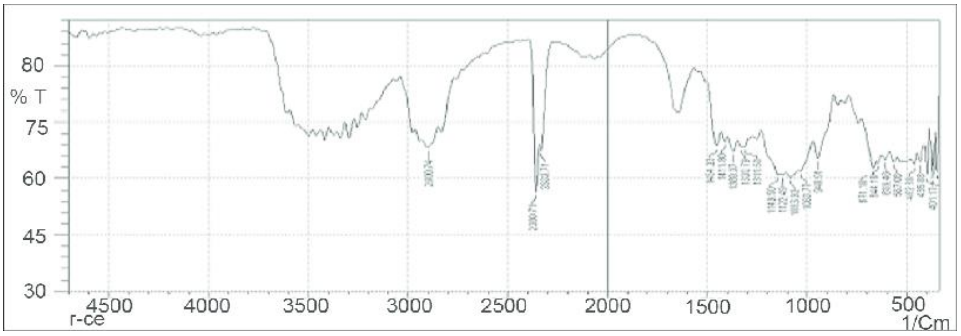

Figure 2: IR spectra of mixture of Ibandronic acid + HPMC K4M

Infrared spectrum of Hydroxypropylmethyl cellulose K4M

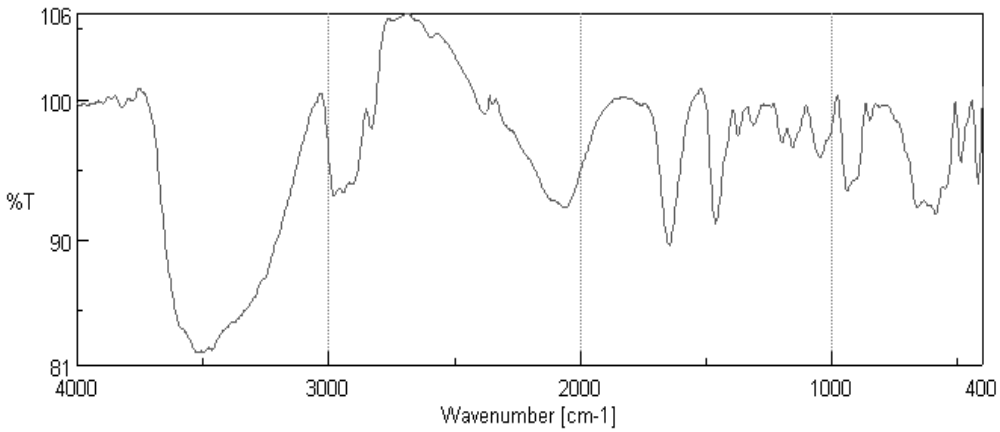

Figure 3: Infrared spectrum of Hydroxypropylmethyl cellulose K4M

Infrared spectrum of Carbopol 934

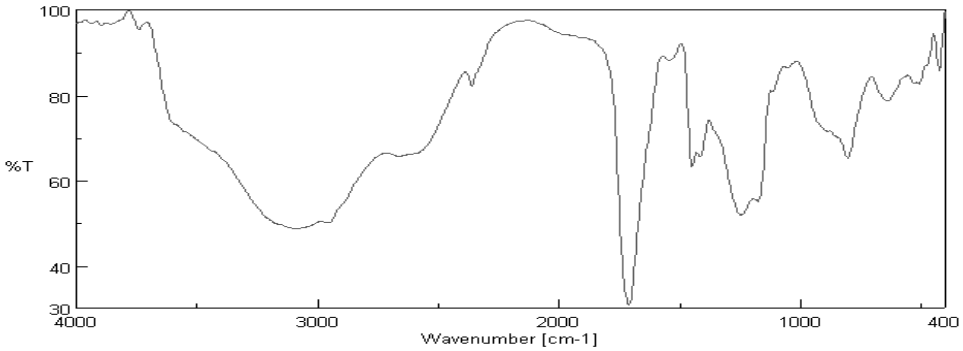

Figure 4: Infrared spectrum of Carbopol 934

FTIR spectrum of the CMC sample

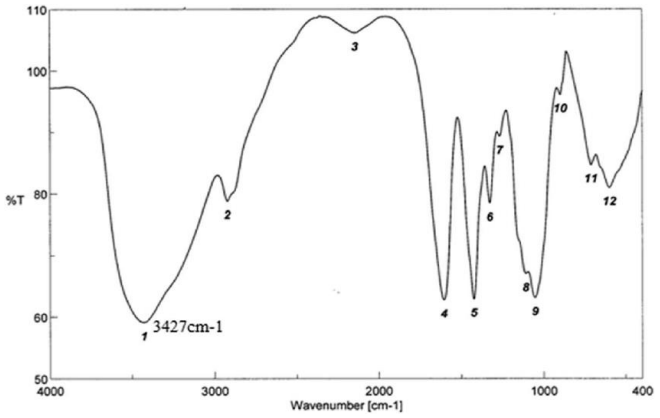

Figure 5: FTIR spectrum of the CMC sample

DSC thermograms Ibandronic acid

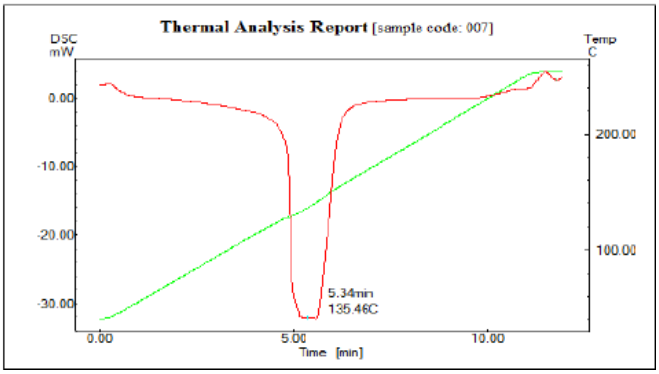

Figure 6: DSC thermograms Ibandronic acid

DSC thermograms (A) Ibandronic acid (IA) (B) IA+HPMC K4M + sodium bicarbonate

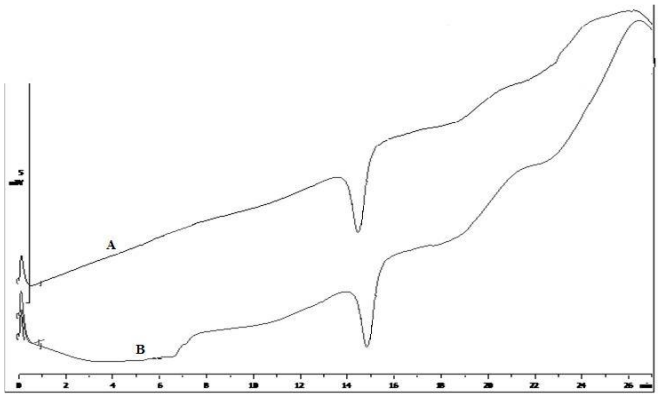

Fig. 7: DSC thermograms (A) Ibandronic acid (IA) (B) IA+HPMC K4M + sodium bicarbonate

DSC curve of the Na-CMC film from 50 to 250⁰C.

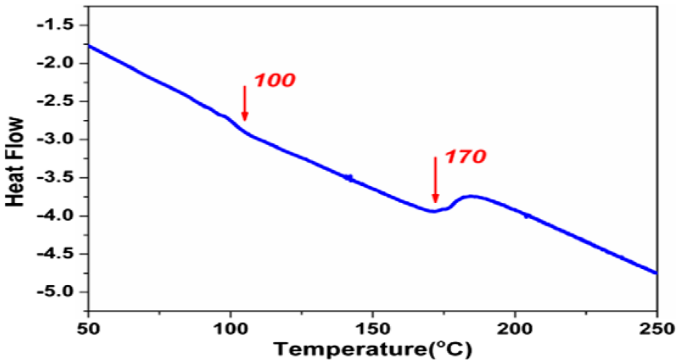

Figure 8: DSC curve of the Na-CMC film

Parameters of Ibandronic acid formulation A1-A7

Table 1: Result of study of physical parameters of Ibandronic acid formulation A1-A7

Formulation	Angle of Repose ( ) (n=3)	Bulk Density (g/cm^3) (n=3)	Tapped Density (g/cm^3) (n=3)	Carr's Index (%) (n=3)	Hausner ratio H_R (n=3)
A1	29.2±0.62	0.584±0.008	0.736±0.006	20.86±0.74	1.28± 0.06
A2	31.2±0.34	0.584±0.006	0.736±0.004	24.74±0.62	1.28± 0.02
A3	30.8±0.18	0.576±0.004	0.726±0.004	21.48±0.52	1.26±0.04
A4	29.6±0.44	0.574±0.004	0.726±0.006	23.58±0.44	1.28±0.06
A5	28.6±0.66	0.584±0.006	0.738±0.008	18.14±0.64	1.32±0.06
A6	28.4±0.48	0.586±0.006	0.734±0.008	19.33±0.76	1.36±0.05
A7	26.6±0.66	0.584±0.002	0.744±0.006	23.24±0.10	1.34±0.02

Composition of Floating tablets of Ibandronic acid

Table 2: Composition of Floating tablets of Ibandronic acid

Ingredient (mg)	A1	A2	A3	A4	A5	A6	A7
Ibandronic acid	50	50	50	50	50	50	50
HPMC K4M	100	100	100	100	100	100	100
Sodium CMC	30	30	30	_	30	30	30
Carbopol 934P	50	45	40	30	35	25	20
Lactose	109	109	109	144	104	109	109
Sodium bicarbonate	55	60	65	70	75	80	85
Magnesium stearate	6	6	6	6	6	6	6
Total weight of tablets	400	400	400	400	400	400	400

Physicochemical properties of Ibandronic acid floating tablets

Table 3: Physicochemical properties of Ibandronic acid floating tablets

Batch code	Average wt. (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
A1	400	4.18 ± 0.06	12.18 ± 0.06	7.6± 0.04	0.68±0.18	104.06 ± 0.18
A2	405	3.96 ± 0.04	12.18 ± 0.04	8.6± 0.08	0.78±0.14	99.64 ± 0.16
A3	395	4.08 ± 0.06	12.16 ± 0.06	9.8± 0.06	0.78±0.13	104.88 ± 0.24
A4	400	4.16 ± 0.04	12.18 ± 0.08	7.6± 0.04	0.98±0.17	106.16 ± 0.18
A5	410	4.14 ± 0.06	12.16 ± 0.06	7.8± 0.04	0.72±0.14	104.48 ± 0.12
A6	395	4.06 ± 0.04	12.16 ± 0.08	8.8± 0.04	0.66±0.13	106.44 ± 0.12
A7	405	4.28 ± 0.08	12.14 ± 0.06	7.8± 0.06	0.76±0.16	96.66 ± 0.22

Dissolution drug release data

Table 4: Dissolution drug release data of batch A1 to A7

Time (min)	Cumulative % drug release					
	A1	A2	A3	A5	A6	A7
0	0.000	0.000	0.000	0.000	0.000	0.000
30	6.788	10.348	13.546	15.362	19.936	13.548
60	7.916	12.508	17.084	22.658	29.446	17.994
120	10.526	16.138	19.372	26.256	34.788	21.656
180	15.876	20.516	24.498	35.976	40.658	25.888
240	19.338	24.016	28.646	38.274	44.976	32.326
300	23.456	27.146	32.518	40.824	52.126	38.476
360	28.275	31.994	36.696	45.608	54.944	44.276
420	32.624	36.368	39.262	48.148	58.532	51.708
480	34.895	39.664	43.491	52.514	62.584	56.788
540	40.476	45.267	50.126	58.546	64.478	62.334
600	46.033	50.848	52.448	64.014	66.966	68.738
660	48.748	54.598	57.124	66.728	69.878	75.218
720	52.166	59.034	62.936	72.234	74.576	79.430

All values are expressed as mean ± SD, n=3, A1-A7=code of formulations

Swelling index

Table 5: swelling index of batch A1 to A7

Time (min)	% Swelling index						
	A1	A2	A3	A4	A5	A6	A7
0	0	0	0	0	0	0	0
15	38.18	38.14	39.66	32.16	40.38	37.16	31.54
30	54.48	52.98	48.14	35.72	51.94	40.16	53.74
60	68.63	72.15	64.16	55.36	69.26	68.54	72.24
120	84.52	84.64	84.96	76.86	88.48	86.18	101.86
180	106.11	101.94	106.66	91.12	116.24	107.42	122.24
240	116.48	118.23	128.32	102.78	123.08	125.94	142.64
300	121.24	126.92	132.12	112.82	134.64	133.34	157.44
360	134.72	136.54	137.72	116.28	150.24	140.78	161.12
420	138.78	142.32	143.42	124.22	153.88	142.68	175.98
480	145.68	144.84	150.65	122.65	160.36	148.68	178.78
540	154.64	158.84	157.56	116.84	171.16	153.74	181.46
600	154.29	152.18	151.94	106.66	170.46	151.86	182.46
660	148.18	148.18	152.94	104.78	168.46	150.16	185.98
720	138.12	138.18	142.15	102.56	160.44	140.16	194.90

Floating ability of various Ibandronic acid tablet formulations

Batch Code	Floating Lag time (min)	Floating duration (min)	Integrity
A1	Not float	Not float	Intact
A2	Not float	Not float	Intact
A3	34	22	Intact
A4	28	43	Broken after 6-8Hrs
A5	22	63	Intact
A6	42	>720	Intact
A7	51 sec	>724	Intact

All values are expressed as mean ± SD, n=3, A1-A7= Formulation codes.

DISCUSSION

The reported melting point value for Ibandronic acid is in the range of 118-121^{0}C. The observed melting point ranged between 120-124^{0}C. The absorption maxima of the standard solution were scanned between 400-800 nm region on shimadzu 1800 spectrophotometer. The absorption maxima were found to be 525 nm. Infrared spectrum shows all prominent peaks of Ibandronic acid. IR spectrum indicated that characteristics peaks belonging to measure functional group such as principle peak.

The infrared spectrum of physical mixture of polymers (HPMC K4M) and Ibandronic acid was studied and confirmed that there is no interaction with each other. The spectra show all the prominent peaks of drug as well as polymer. IR spectrum indicated characteristics peaks belonging to measure functional group such as principle peaks.

Hence it can be concluded that there were no any significant changes in the physical mixture of Ibandronic acid and HPMC K4M. DSC thermogram of Ibandronic acid shows endothermic peak at 272^{0}C.where as HPMC K4M shows melting endothermic at 34.40^{0}C.

Result of study of physical parameters of Ibandronic acid formulation A1-A7 is summarized in table no. 1. Composition of Floating tablets of Ibandronic acid is summarized in Table no. 2 .

All formulation from A1 to A7 was evaluated with thickness and diameter of tablets measured by Vernier caliper. Thickness and diameter was in range of 3.98 ±0.02 to 4.22±0.07.The hardness

was in range of 7.2±0.03 to 9.0±0.02kg/cm ^{2}, which was measured on Monsanto hardness tester.

Drug content release was in the range of 96.33±0.12 to 107.48±0.10 shown in (Table 4).

The percentage drug release was found 50% after 7 hrs. For all the formulations A1-A7. After12 hrs. It showed 79.40% drug release shown in Table no.4.

The swelling index was calculated with respect to time. As time increase, the swelling index was increased because weight gain by tablet was increased proportionally with rate of hydration, later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed as shown in, (Table no.5).

The drug release profile of all 7 formulations from A1 to A7 shown in (Table 4).

The release rate can be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug. In view of this absorption characteristics, the hypothesis of current investigation is that if the gastric residence time of Ibandronic acid containing formulation is prolonged and allow to float in the stomach for a long period, the oral bioavailability might be increased hence the present research work was to study systematically the effect of formulation variable on the release and floating properties of Ibandronic acid drug delivery system.

For floating drug delivery system, the polymers used must be highly swellable in shortest time. Hence, HPMC was chosen as a main swellable polymeric material. In order to get the longer duration of floating time the high viscosity polymer selected, HPMC K4M was chosen and it was found that, increased viscosity of a polymer prolongs the drug delivery from the dosage form. In order to retain the dosage form in the stomach for a long period of time and to avoid gastric emptying dosage form, carbopol 934P was included.

It was reported earlier that, Carpool belongs to the class of sellable and adhesive polymers and to utilize this property of carbopol, it was included in the formulation with the intention of adhering the dosage form to the inner wall of the stomach and also possibly to control the release of Ibandronic acid from the dosage form. In the 7 series formulation batch A7 given the highest floating time as compare to A6,A5,A4,A3,A2 and A1 (Table no.6).

Total floating time depends upon the amount of HPMC as the polymer content increased the floating time was increased due to the formation of thick gel which entrapped the gas formed due to $NaHCO_3$ firmly. Due to high viscosity and content of the polymer bursting effect of the tablet was decreased and float for longer duration of time. From the result of floating lag time it was concluded that, as the concentration of gas generating agent increase the floating lag time get shortens this finding were supported by study of Park et al., reported that as the concentration of gas generating agent ($NaHCO_3$) was increased the floating lag time get shortened and at the same time floating ability get increased.

Carbopol was used as a swelling agent, which also helped in gastric retention due to its adhesive properties. But carbopol affected floating properties. Physicochemical evaluation i.e. the prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the formulations.

Results of Water uptake study showed that the order of swelling in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymer was achieved up to 10 hrs and then gradually decreased due to erosion.

CONCLUSIONS

Drugs like chlorpheniramine maleate which is locally used in the treatment of Helicobacter Pylori requires longer residence time in the stomach which can be achieved by designing gastro-retentive dosage forms.

Over the last two decades, various gastro-retentive dosage forms have been designed to increase the gastric retention time. Nevertheless, there are opportunity and potential for the development of effective GRDDS with a improving bioavailability of the drugs that have absorption window in the proximal and mid GIT. Based on the literature survey, it can be concluded that GRDDs offers various potential advantages for drugs with poor bioavailability. Drug absorption in the gastro intestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. The control of gastro intestinal transit of orally administered dosage forms using GRDD systems can improve the bioavailability of drugs that exhibit site specific absorption.

Due to unpredictability of human GIT development of efficient GRDFs is a real challenge to pharmaceutical technology as the drug delivery system must remain for a sufficient time in the stomach which is not compatible with normal physiology. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life.

The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half-life. [120]

Formulated Floating tablets of Ibandronic acid gave satisfactory results for various physicochemical parameters like hardness, friability, thickness, weight variation and content uniformity. Sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K4M has predominant effect on total floating time and drug release. Carbopol 934P also shows significant effect on drug release which was given extra adhesion property and helped to maintain the integrity of the tablet. Lactose also shows significant effect on the drug release. Sodium CMC has given extra adhesion property and helped to maintain the integrity of the tablet.

From the study it is evident that a promising controlled release floating tablets of Ibandronic acid can be developed to increase gastric residence time and thereby increasing its bioavailability. All the formulations found to be stable over the storage period and conditions tested. Further detailed investigations are required to establish efficacy of these formulations and fix the required dose.

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Authors Contributions: All the authors have contributed equally.

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