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Design and Evaluation of Gastro-Retentive Floating Tablets of Etidronate disodium

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Abstract

Osteoporosis raises the chance of breaking a bone strength. It is the most frequent cause of fractures in the elderly. The hip, forearm, and back bones are among the bones that break most frequently. Usually, there are no symptoms until a broken bone happens. In order to target site-specific drug release in the upper GIT for a local or systemic effect, GRDDs are a method of extending the gastric residence time. For a very long time, gastro retentive dosage forms (GRDFs) have been used to enhance treatment with a number of significant medications. Paget's disease is a particular kind of bone disease that is treated with etidronate disodium.Bones are weakened and deformed by this disease. To improve its oral bioavailability, etidronate disodium, the most widely used biphosphonate for osteoporosis treatment, was made into gastro retentive dosage form (GRDF) tablets. Carbopol 934P, HPMC 4KM, and Na-CMC at different ratios were used to characterize the effects of GRDF tablets of Etidronate disodium (200 mg) on swelling, floating, and physical integrity. The thickness, friability, hardness, drug content, and in-vitro drug release of the Risedronate GRDF tablets produced in this study were all found to have a prolonged dissolution profile. Oral drug delivery is still the most popular method despite significant advancements in the field because it is simple to administer, therapy is inexpensive, and patient compliance is high.

Keywords: Gastro retention, Etidronate disodium, Carbopol 934P, HPMC 4KM, Na-CMC, GRDF, GRFT.

INTRODUCTION

Reduced bone mass and microarchitecture changes are marks of osteoporosis, a bone condition that makes bones more brittle and more prone to fractures. A bone mineral density (BMD) at the hip and/or spine that is at least 2.5 standard deviations lower than the mean peak bone mass of young, healthy people as assessed by dual-energy X-ray absorptiometry (DXA) is considered osteoporosis, according to the World Health Organization (WHO)[1]. As people age, the prevalence of osteoporosis increases continuously, and it is expected to climb significantly as a result of the global demographic shift. In the US, osteoporosis is thought to be the cause of 1.5 million fractures per year[2]. Because oral controlled release drug delivery systems release drugs at a predefined, predictable, and regulated rate, they have attracted a lot of attention. However, due to inadequate absorption or GIT breakdown, several medications exhibit low bioavailability[3]. Consequently, in order to address these issues, gastro-retentive drug delivery systems are made to increase the duration of the medications' gastric retention, which include:

- Locally active in the stomach
- unstable in the intestinal environment
- Having a limited window for absorption in the gastrointestinal tract.
- Have poor solubility in areas with high pH.

A number of strategies, such as floating drug delivery systems (FDDS), mucoadhesion or bioadhesion systems, high density systems, expansion systems, magnetic systems, superporous huydrogel, raft forming systems, and floating ion exchange resins, have been put forth to improve the stomach residency of the drug delivery. Etidronic acid is a bisphosphonate that is utilized in pharmaceuticals, cosmetics, detergents, and water treatment. A salt of etidronic acid is called an etidronate.[4] The Pharmacokinetic of drugs show that bioavailabity 3%, Metabolism is nil, Biological half laife 1 to 6 hours and Excretion Renel and fecal.A bisphosphonate called etidronic acid is used to treat osteoporosis, Paget's disease of the bone, and to build bone. In the long term, bisphosphonates strengthen bone by shifting the balance

between bone resorption and formation to the formation side by reducing osteoclastic activity, which inhibits bone resorption. In contrast to other bisphosphonates, etidronate also inhibits the calcification of bones. A bisphosphonate called etidronic acid is used to treat osteoporosis, Paget's disease of the bone, and to build bone. In the long term, bisphosphonates strengthen bone by shifting the balance between bone resorption and formation to the formation side by reducing osteoclastic activity, which inhibits bone resorption. In contrast to other bisphosphonates, etidronate also inhibits the calcification of bones.

MATERIALS AND METHODS

Materials [5]

Etidronate disodium was obtained 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.

Evaluation of powder blend [6]

Angle of repose

"The maximum angle possible between the surface of the pile of powder and the horizontal plane" is the definition of angle of repose. Better flow characteristics result from a smaller angle of repose. By using a ruler to measure the pile's height (h) and the base's radius (r), one can determine the angle of repose.

$\tan \theta = h/r$

Bulk density

The material's overall density is indicated by its bulk density. The actual volume of intra-particle pores and inter-particle spaces is included. Bulk is mostly caused by the way the particles are packed. The definition of bulk density is:

Bulk density = Weight of the powder / Bulk volume of powder

There may be a significant number of gaps between particles when they are densely packed. As a result, powder trapping enables the particles to move and eliminate voids to the lowest possible volume. The bulk volume is the volume that the powder occupies under these circumstances.

Evaluation of floating tablets

Measurement of buoyancy capabilities of the FDDS:

The resulting weight measurements are used to assess the floating behavior. Two distinct media—simulated food and deionized water—are used in the experiment. The findings demonstrated improved floating behavior in higher molecular weight polymers with slower rates of hydration, which was more noticeable in simulated meal medium than in deionized water.

In Vitro floating and dissolution behaviour:

USP dissolution equipment is typically used to conduct the dissolution tests on a variety of medications. According to USP 28, "before the blade rotates, the dosage unit is allowed to sink to the bottom of the vessel." When Pillay et al. applied a helical wire sinker to theophylline's swellable floating system—which is only weakly soluble in water—they found that the wire helix prevented the system from swelling and slowed down the release of the drug. The floating drug delivery system was completely submerged beneath a ring or mesh assembly in order to get around this restriction, and an increase in drug release was seen. It was also demonstrated that the approach was more consistent and repeatable. GRDDS is positioned similarly to other conventional tablets, and the USP apparatus with paddle is typically used for the in vitro dissolution test. However, in some cases, a much smaller paddle force acts on the floating dosage form, which typically floats on the surface, because the vessel is large and the paddles are at the bottom. Because floating dosage forms don't rotate, they might not produce accurate or repeatable results. Similar issues arise with swellable dosage forms because the hydrogel may adhere to the paddle or vessel surface and produce unreproducible results. The following are some of the different modifications made to the dissolution assembly to avoid such issues.

Weight variation

During the compression process, composite samples of tablets—typically ten—are taken and weighed. Although the composite weight divided by 10 yields an average weight, there is an issue with the averaged value. The United States Pharmacopeia (USP) establishes allowable weight variations for individual tablets as a percentage of the sample's average weight in order to help mitigate this issue. By weighing 20 tablets separately, figuring out the average weight, and comparing the weights of each tablet to the average, the USP offers the weight variation test. If no more than two tablets deviate from the percentage limit and if no tablet deviates more than twice from the limit, the tablets pass the USP test.

Hardness & friability:

The "force required to break a tablet in diametric compression test" is the definition of hardness. For this reason, hardness is also known as tablet crushing strength. Monsanto testers, Pfizer testers, and strong Cobb testers are a few tools used to measure hardness. The Roche Friabilator is the name of the laboratory friability tester. This includes a device that uses a plastic chamber that rotates at 25 rpm to subject several tablets to the combined effects of shock and abrasion. With each revolution, the tablet is dropped six inches. Typically, a tablet sample that has been previously weighed is put inside the friabilator and spun 100 times. Generally speaking, conventional compressed tablets that lose less than 0.5% to 1.0% of their weight are acceptable. The majority of effervescent tablets experience significant weight losses due to friability, which explains why these tablets may need special stack packaging.

Swelling systems:- [6]

Swelling Index:-

Following the swelling dosage form's immersion in SGF at 37 degree C, it is periodically removed, and the

dimensional changes—such as the increase in tablet thickness or diameter over time—are measured.

Water Uptake:-

It measures the swellable matrix's swelling property indirectly. Here, the dosage form is taken out on a regular basis, and weight changes over time are calculated. Thus, weight gain is another name for it.

Water uptake = WU = (Wt – Wo) * 100 / Wo

Where, Wt = weight of dosage form at time t.

Wo = initial weight of dosage form.

RESULTS & DISCUSSION

Evaluation of effervescent floating tablet formulations

Evaluation of Powder blend:

Prior to compression, the granules' flow characteristics were described using the Hausner ratio, Carr's index, bulk density, tapped density, and angle of repose. Etidronate disodium floating tablets are examined physically. Organoleptic characteristics, including color, taste, shape, and odor, were assessed after two tablets were chosen at random from each formulation. Vernier calipers were used to measure the diameter and thickness of ten tablets. 20 tablets were used to test the prepared floating tablets for weight uniformity, 10 tablets were used to test for friability (using a Roche type friabilator), and 20 tablets were used to test for hardness (using a Monsanto tester).

***Formulation* of Floating Tablet**

Etidronate disodium 200 mg was prepared in each floating tablet using the direct compression method. In a mortar and pestle, etidronate disodium pure drug was geometrically mixed with the necessary amounts of lactose, sodium bicarbonate, carbopol 934P, HPMC K4M, and sodium CMC for ten minutes. For two minutes, magnesium stearate was used to lubricate the aforementioned powder in a mortar and pestle. The CLIT Pilot Press rotary tablet machine was used to compress the lubricated blend into tablets using 12 mm flat face round tooling. Tablets with a hardness of 6–9 kg/cm2 and a thickness of 4.0 mm were obtained by adjusting the compression force (Table Nos. 1 & 2).

Evaluation of Granules

Angle of repose

Etidronate disodium's angle of repose was ascertained using the fixed funnel method. A measuring cylinder was used to calculate the tapped bulk densities (TBD) and loose bulk densities (LBD).

Compressibility Index

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

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

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

Evaluation of Tablets

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

Thickness

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

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.

Drug content

Twenty tablets were crushed and dissolved in 0.1 N HCl to create a powder equal to the tablet weight. After that, appropriate dilutions were prepared, and a UV spectrophotometer was used to measure absorbance at a wavelength of 243 nm. Absorbance at 243 nm was used to calculate the drug content.

Hardness

The hardness of tablets determines their resistance to breakage or shipping under storage, transportation, and handling conditions prior to use. A Monsanto hardness tester was used to measure each formulation's tablet hardness. The unit of measurement for hardness was kg/cm^2.

Friability

The strength of a tablet is measured by its friability. The following process was used to test the friability using a Roche type friabilator. After being precisely weighed, twenty tablets were put in the tumbling device, which rotates at 25 rpm and drops the tablets six inches at a time. The tablets were weighed after four minutes, and the weight loss as a percentage was calculated.

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

Determination of swelling index

By putting the tablet matrices in the dissolution test apparatus and rotating the paddle at 50 rpm in 900 ml of distilled water at 37 ± 0.5^0C, the swelling characteristics of HPMC matrices containing the drug were ascertained. Periodically, the tablets were taken out of the dissolving medium. These were blotted with paper to remove any remaining water, and their weight gain was measured. According to the equation that illustrates the relationship between swelling index and time, swelling characteristics were expressed as a percentage of water uptake (WU%).

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

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 Etidronate disodium was measured spectrophotometrically at 243 nm.

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.

Table 1: Result of study of physical parameters of Etidronate disodium formulation A1-A7

Formulation	Angle of Repose (θ) (n=3)	Bulk Density (g/cm^3) (n=3)	Tapped Density (g/cm^3) (n=3)	Carr'sIndex (%) (n=3)	Hausner ratio H_R (n=3)
A1	28.1±0.64	0.586±0.008	0.736±0.008	21.86±0.78	1.30± 0.06
A2	32.3±0.36	0.586±0.004	0.734±0.008	24.78±0.6	1.28± 0.02
A3	33.6±0.18	0.578±0.004	0.726±0.006	23.48±0.52	1.26±0.02
A4	29.5±0.42	0.576±0.008	0.726±0.004	24.58±0.44	1.28±0.02
A5	29.5±0.66	0.584±0.006	0.738±0.006	19.18±0.62	1.38±0.02
A6	29.4±0.48	0.588±0.006	0.738±0.008	21.38±0.76	1.36±0.06
A7	28.5±0.66	0.588±0.002	0.748±0.006	24.26±0.12	1.36±0.02

Table 2: Composition of Floating tablets of Etidronate disodium

Ingredient (mg)	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	
Etidronate disodium	200	200	200	200	200	200	200	
HPMC K4M	50	50	50	50	50	50	50	
Sodium CMC	30	30	30	30	30	30	30	
Carbopol 934P	55	45	40	30	40	25	20	
Lactose	109	119	124	164	124	139	144	
Sodium bicarbonate	50	50	50	50	50	50	50	
Magnesium stearate	6	6	6	6	6	6	6	
Total weight of tablets	500	500	500	500	500	500	500	

Table 3: Physicochemical properties of Etidronate disodium floating tablets

Batch code	**Average wt (mg)**	**Thickness (mm)**	**Diameter (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**Drug content (%)**
A1	500	5.17 ± 0.04	16.16 ± 0.05	7.6± 0.02	0.88±0.08	97.06 ± 0.16
A2	505	4.99 ± 0.02	16.08 ± 0.02	8.6± 0.06	0.88±0.04	99.66 ± 0.16
A3	495	5.08 ± 0.08	16.06 ± 0.04	9.0± 0.06	0.78±0.03	96.78 ± 0.22
A4	500	5.16 ± 0.02	16.08 ± 0.08	7.4± 0.04	0.96±0.07	98.96 ± 0.16
A5	510	5.14 ± 0.06	16.08 ± 0.02	7.8± 0.02	0.72±0.04	95.48 ± 0.10
A6	495	5.08 ± 0.02	16.08 ± 0.09	8.8± 0.04	0.66±0.03	98.44 ± 0.14
A7	505	5.24 ± 0.07	16.08 ± 0.05	7.6± 0.03	0.78±0.06	98.33 ± 0.12

Table 4: Dissolution Etidronate disodium release data of batch A1 to A7

Time (min)	Cumulative % drug release						
	A1	A2	A3	A4	A5	A6	A7
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
30	6.788	12.346	13.548	14.302	16.366	19.934	14.546
60	8.918	13.508	16.084	18.203	22.656	32.444	18.992
120	11.528	16.136	19.370	22.032	26.256	34.078	22.656
180	16.875	20.514	26.496	28.050	37.974	41.656	25.888
240	21.338	24.001	29.648	31.056	40.274	43.976	34.324
300	23.456	29.148	30.508	37.025	42.824	53.106	38.474
360	28.276	32.996	36.694	40.015	45.606	55.942	44.076
420	32.624	36.368	39.264	49.052	50.148	58.532	54.708
480	36.896	42.666	46.492	51.023	56.512	63.584	56.778
540	42.476	46.266	50.026	55.055	60.546	64.476	64.336
600	46.032	52.840	52.448	58.708	62.014	66.964	68.734
660	49.746	54.594	58.104	60.025	66.722	70.876	76.210
720	56.166	60.032	63.934	68.102	71.234	74.574	81.404

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

Table 5: swelling index of Etidronate disodium batch A1 to A7

Time (min)	% Swelling index						
	A1	A2	A3	A4	A5	A6	A7
0	0	0	0	0	0	0	0
15	39.13	38.12	39.65	30.14	40.38	38.14	31.52
30	55.48	52.92	50.14	36.71	51.92	41.12	53.72
60	68.63	72.15	65.15	56.35	69.23	68.52	74.22
120	86.51	84.62	86.96	76.86	86.46	85.18	102.85
180	104.11	102.92	106.66	94.07	120.24	108.44	122.22
240	115.48	118.23	128.32	101.78	124.07	125.92	144.62
300	122.25	126.91	134.11	110.92	134.61	134.33	158.42
360	134.71	136.53	137.72	116.28	150.22	142.74	161.11
420	138.76	144.31	143.39	123.21	155.84	144.66	175.92
480	146.64	146.84	152.05	122.65	160.35	148.66	178.77
540	153.64	153.84	157.69	115.84	172.15	153.72	181.48
600	151.29	152.19	150.94	105.65	170.45	152.85	182.44
660	148.13	148.16	150.94	103.77	166.46	150.15	185.92
720	139.12	138.12	140.15	102.55	160.44	140.16	194.96

Table 6: Floating ability of various Etidronate disodium 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	35	23	Intact
A4	28	46	Broken after 6-7Hrs
A5	23	68	Intact
A6	45	>725	Intact
A7	58 sec	>726	Intact

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

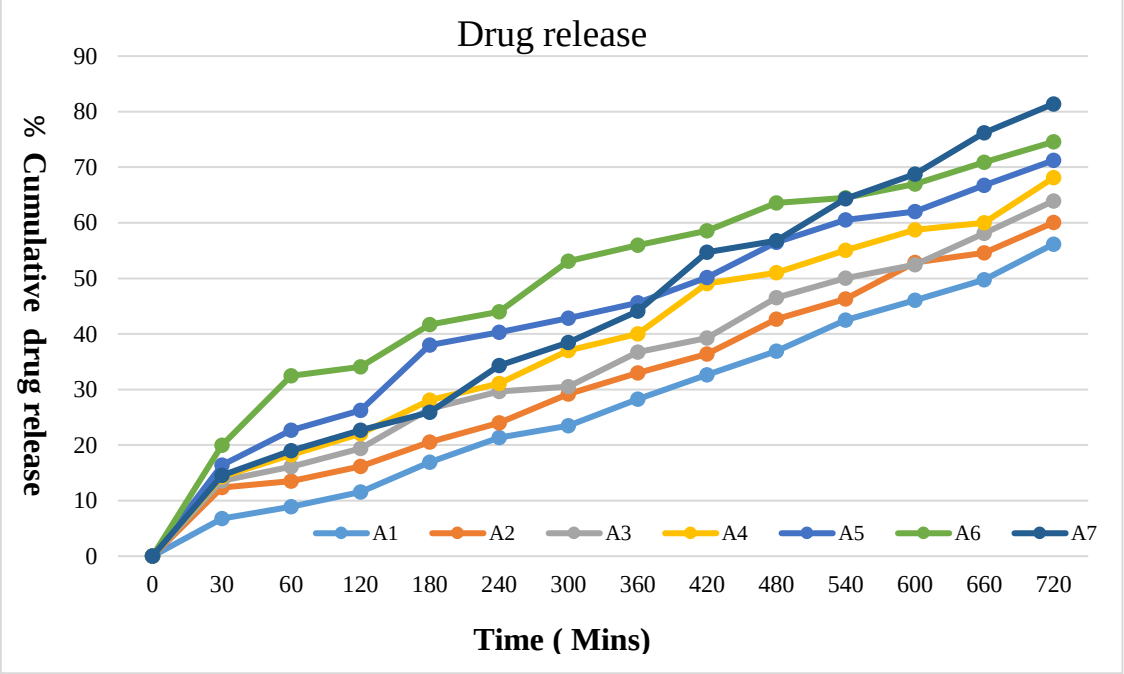

Figure 1: Dissolution Etidronate disodium release data of batch A1 to A7

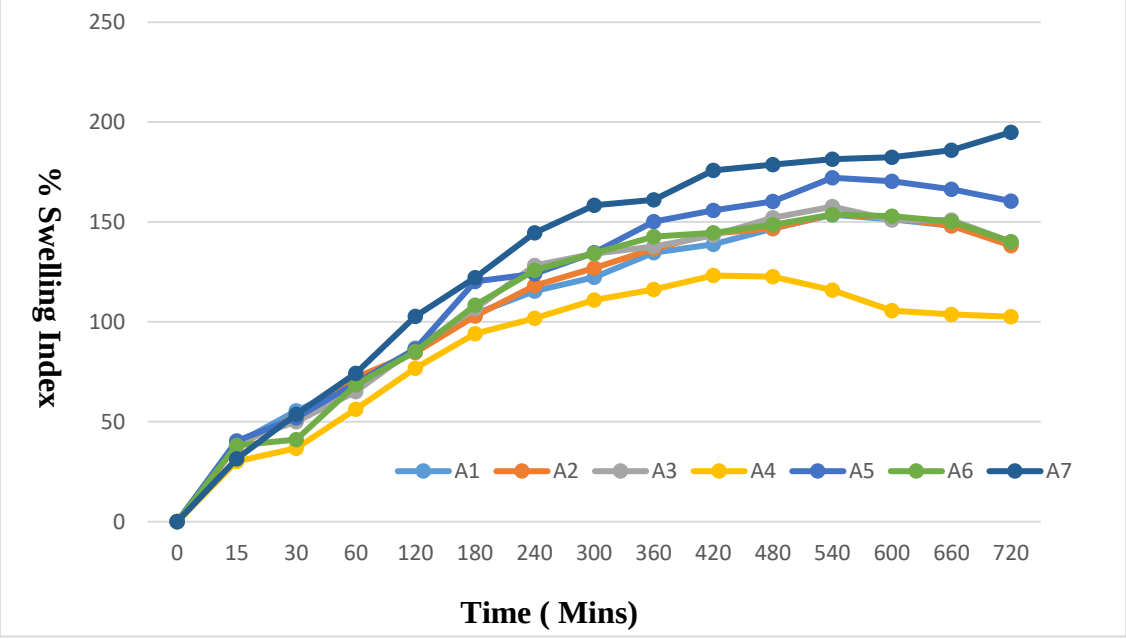

Figure 2: Swelling index of Etidronate disodium of batch A1 to A7

Figure 3: The buoyancy test of Etidronate disodium tablet

CONCLUSIONS AND DISCUSSIONS

The escalating prevalence of osteoporosis and its burdensome clinical correlates urge health professionals to abandon the old notion of osteoporosis as a mere "natural byproduct" of aging. Rather, the medical community is called to promote an adequate awareness on the subject and put in place large-scale screening and diagnostic procedures in order to identify people with osteoporosis or at risk of developing the condition. This would allow the early correction of risk factors for osteoporosis and the prompt institution of anti-osteoporotic treatments. In this regard, it needs to be considered that therapeutic decision-making should be based not solely on BMD, but on comprehensive fracture risk assessments. A relatively large number of medications is currently available. Each drug (or class of drugs) possesses specific advantages and side effects and should therefore be prescribed or avoided in selected patient populations. New and potentially highly effective agents are currently under development which may offer novel therapeutic tools to counteract what has rightly been called the osteoporosis epidemic.

From the study it is evident that a promising controlled release floating tablets of Etidronate disodium 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.

Result of study of physical parameters of Etidronate disodium formulation A1-A7 is summarized in table (no. 1) and Composition of Floating tablets of Etidronate disodium 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 4.99 ±0.02 to 5.24±0.07 & 16.06 ±0.04 to 16.16±0.04 respectively. The hardness was in range of 7.4±0.04 to 9.0±0.06kg/cm^2, which was measured on Monsanto hardness tester. Drug content release was in the range of 95.48±0.10 to 99.66±0.16 shown in Table (no. 3). The percentage drug release was found 32.62 % - 58.53% at 7 hrs. for all the formulations A1-A7. After 12 hrs. it showed 56.16% - 81.40% 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 (Fig.1), (Table no.5). The drug release profile of all 7 formulations from A1 to A7 shown in (Fig. 2 & 3).

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