EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 10
382-388
Year: 2020

FORMULATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING TABLETS OF RISEDRONATE SODIUM

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Article Received on 23/07/2020 **Article Revised on 13/08/2020** **Article Accepted on 03/09/2020**

ABSTRACT
Aim: The present study is planned with the brief objectives to preparation of gastro-retentive floating tablets of Risedronate Sodium by direct compression method polymers or combination of these. **Material & Methods: In methodology,** gastro-retentive floating tablets of Risedronate Sodium by direct compression method polymers or combination of these were made. The evaluation of gastro retentive formulation was done by the many parameters i.e. angle of repose, bulk density, porosity, weight variation, hardness, friability, swelling index, water uptake etc. **Result:** Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm^2 with 4.0 mm tablet thickness. 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 3.99 ±0.02 to 4.24±0.07& 12.06 ±0.04 to 12.16±0.05 respectively. The hardness was in range of 7.4±0.03 to 9.0±0.06kg/cm^2, which was measured on Monsanto hardness tester. Drug content release was in the range of 98.33±0.12 to 108.96±0.16 shown in Table (no. 3). The percentage drug release was found 58% after 7 hrs. for all the formulations A1-A7. 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. **Conclusion:** In the present era, gastro retentive dosage forms (GRDF) receive great attention because they can improve the performance of controlled release systems. This retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner, and finally is easily metabolized in the body.

KEYWORDS: Osteoporosis, Chronic pain, Peak bone mass, Gastro-Retentive Floating, Risedronate Sodium.

INTRODUCTION
Osteoporosis is a disease where decreased bone strength increases the risk of a broken bone. It is the most common reason for a broken bone among the elderly. Bones that commonly break include the back bones, the bones of the forearm, and the hip. Until a broken bone occurs there are typically no symptoms. Bones may weaken to such a degree that a break may occur with minor stress or spontaneously. Chronic pain and a decreased ability to carry out normal activities may occur following a broken bone.[1]

Osteoporosis may be due to lower than normal peak bone mass and greater than normal bone loss. Bone loss increases after menopause due to lower levels of estrogen. Osteoporosis may also occur due to a number of diseases or treatments including alcoholism, anorexia, hyperthyroidism, surgical removal of the ovaries, and kidney disease. Certain medications increase the rate of bone loss including some antiseizure medications, chemotherapy, proton pump inhibitors, selective serotonin reuptake inhibitors and steroids. Not enough exercise and smoking are also risk factors. Osteoporosis is defined as a bone density of 2.5 standard deviations below that of a young adult. This is typically measured by dual-energy X-ray absorptiometry at the hip.[2]

Certain drugs like alendronate, etidronate, risedronate, raloxifene and strontium ranelate can be helpful for the preventing of osteoporotic fragility fractures in postmenopausal women with osteoporosis.[3-5]

The present study is planned with the brief objectives to preparation of gastro-retentive floating tablets of Risedronate Sodium by direct compression method polymers or combination of these.

MATERIALS AND METHODS
Materials and their role in formulation[6]
Risedronate Sodium 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.

DIRECT COMPRESSION[7]

Preparation of DC-vehicles

As we have already discussed that DC excipients are speciality products prepared by modification of normal ingredients, these modification can be done in two ways:

1. Chemical modification: Ethyl cellulose, Methyl cellulose, HPMC, Na-CMC, Cyclodextrins

2. Physical modification: Dextrates or compressible sugars, sorbitol, DCP etc.

3. Spray drying: MCC, Emdex, Spray dried Lactose etc.

4. Crystallization: Dipac etc.

5. Granulation: Tabletose (granulated lactose) etc.

6. Co-processing: Cellactose: MCC, Lactose.

Ludipress: Lactose, PVP, Crosspovidone.

Starlac: Lactose, Maize starch.

Celocol: MCC, Calcium phosphate.

Prosolv: MCC, Colloidal Silica.

Di-Pac**:** Sucrose, modified dextrins.

Xylitab: Xylitol, Na CMC.

Pharmatose: Anhydrous lactose, lactitol.

Avicel CE 15: MCC, Guar Gum.

Advantose FS 95: Fructose, starch.

Barcoft CS 90: Calcium carbonate, Starch.

Plasdone S-630: Vinyl acetate, vinyl pyrrolidone.

Carbofarma G10: Calcium Carbonate.

Carbofarma G11: Maltodextrins.

Some other examples for DCVs includes Avicel(pH-101, 102), Cab-O-Sil, Explotab, Emcocel, Ac-bi-Sol etc.

(f.) Examples of drugs suitable for direct compression

Aspirin, Caffeine, Acetaminophen, Propoxyphen.napsylate, Ascorbic acid, Sodium ascorbate, Thymine HCl, Pyridoxine HCl, Pyrillamine maleate, Sodium chloride, Calcium lactate, Doxylamine lactate, Amytriptylline HCl, Quinidine HCl, Chlorpromazine, Isosorbide dinitrate etc.

Evaluation methods of Floating Drug delivery system

1. Fourier transform infrared analysis[8]

The pellets are prepared on kbr press under hydraulic pressure of 150kg/cm^2 and the spectra are scanned over the wave number range of 3600-400cm^{-1} at ambient temperature.

2. Differential scanning calorimetry[8]

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.

3. Evaluation of powder blend[9]

a) Angle of repose

Angle of repose is defined as "the maximum angle possible between the surface of the pile of powder and the horizontal plane." Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base(r) with ruler.

$$\text{Tan } \theta = h/r \quad \text{..... 1}$$

b) Bulk density

Bulk density denotes the total density of the material. It includes the true volume of inter-particle spaces and intra-particle pores. The packing of particles is mainly responsible for bulk .Bulk density is defined as:

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

c) Percentage porosity

Whether the powder is porous or nonporous, the total porosity expression for the calculation remains the same. Porosity provides information about hardness, disintegration, total porosity etc.

% porosity, € = void volume

4. Evaluation of floating tablets[10]

a) Measurement of buoyancy capabilities of the FDDS

The floating behaviour is evaluated with resultant weight measurements. The experiment is carried out in two different media, deionised water and simulated meal. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionised water.

b) In Vitro floating and dissolution behaviour

The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states "the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started".

c) *Weight variation:* The USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit, and if no tablet differs by more than 2 times the percentage limit.

d) Hardness & friability

Normally, a pre-weighed tablet sample is placed in the friabilator which is then operated for 100 revolutions. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable. Most of the effervescent tablets undergo high friability weight losses, which accounts for the special stack packaging, that may be required for these types of tablets.

5. Swelling systems[9]

a) Swelling Index

After immersion of swelling dosage form into SGF at 37^{0}C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

b) Water Uptake

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as weight Gain.

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

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

Wo = initial weight of dosage form.

RESULTS

Evaluation of effervescent floating tablet formulations

Evaluation of Powder blend

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 Risedronate Sodium 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).

Formulation of Floating Tablet

Each floating tablets containing 35 mg Risedronate Sodium were prepared by direct compression method. Risedronate Sodium 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 2min.The lubricated blend was compressed into tablets using 12 mm flatface round tooling on CLIT Pilot Press rotary tablet machine. Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm^2 with 4.0 mm tablet thickness (Table no.1 & 2).

A. Evaluation of Granules

The angle of repose of Risedronate Sodium was determined by fixed funnel method. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using measuring cylinder**.**

B. Compressibility Index

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

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

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

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.

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 263 nm wavelength was taken by using a UV spectrophotometer. Drug content was calculated by using absorbance at wavelength 263 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.

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

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.

$$WU\ \% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

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 Risedronate Sodium was measured spectrophotometrically at 263 nm.

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.

Table no.1: Result of study of physical parameters of Risedronate Sodium formulation A1-A7.

Formulation	Angle of Repose ( ) (n=3)	Bulk Density (g/cm^3) (n=3)	Tapped Density (g/cm^3) (n=3)	Carr'sIndex (%) (n=3)	Hausner ratioH_R (n=3)
A1	28.1±0.64	0.584±0.008	0.735±0.008	20.85±0.78	1.29± 0.06
A2	30.3±0.36	0.584±0.004	0.732±0.008	24.73±0.6	1.28± 0.02
A3	31.6±0.18	0.578±0.004	0.726±0.006	22.46±0.52	1.24±0.02
A4	29.5±0.42	0.572±0.008	0.726±0.004	24.56±0.44	1.26±0.02
A5	29.5±0.66	0.582±0.006	0.734±0.006	18.13±0.62	1.38±0.02
A6	28.4±0.48	0.586±0.006	0.734±0.008	20.33±0.76	1.36±0.06
A7	26.5±0.66	0.584±0.002	0.744±0.006	24.24±0.12	1.34±0.02

Table 2: Composition of Floating tablets of Risedronate Sodium.

Ingredient (mg)	A1	A2	A3	A4	A5	A6	A7
Risedronate Sodium	35	35	35	35	35	35	35
HPMC K4M	100	100	100	100	100	100	100
Sodium CMC	30	30	30	–	30	30	30
Carbopol 934P	55	45	40	30	35	25	20
Lactose	109	114	114	144	114	114	114
Sodium bicarbonate	65	70	75	80	85	90	95
Magnesium stearate	6	6	6	6	6	6	6
Total weight of tablets	400	400	400	400	400	400	400

Table 3: Physicochemical properties of Risedronate Sodium floating tablets.

Batch	Average wt	Thickness			Diameter	Hardness
Code	(mg)	(mm)	(mm)	(kg/cm2)	Friability (%)	Drug content (%)
A1	400	4.17 ± 0.04	12.16 ± 0.05	7.6± 0.02	0.88±0.08	104.06 ± 0.16
A2	405	3.99 ± 0.02	12.08 ± 0.02	8.6± 0.06	0.88±0.04	99.66 ± 0.16
A3	395	4.08 ± 0.08	12.06 ± 0.04	9.0± 0.06	0.78±0.03	105.78 ± 0.22
A4	400	4.16 ± 0.02	12.08 ± 0.08	7.4± 0.03	0.96±0.07	108.96 ± 0.16
A5	410	4.14 ± 0.06	12.08 ± 0.02	7.8± 0.02	0.72±0.04	108.48 ± 0.10
A6	395	4.08 ± 0.02	12.08 ± 0.09	8.8± 0.04	0.66±0.03	108.44 ± 0.14
A7	405	4.24 ± 0.07	12.06 ± 0.05	7.6± 0.03	0.78±0.06	98.33 ± 0.12

Table 4: Dissolution Risedronate Sodium 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	5.788	11.346	14.548	15.366	19.934	13.546
60	8.918	12.508	18.084	22.656	30.444	18.992
120	12.528	17.136	19.370	26.256	34.078	21.656
180	15.875	20.514	24.496	36.974	40.656	25.888
240	20.338	24.001	29.648	39.274	43.976	33.324
300	22.456	28.148	32.508	42.824	52.106	38.474
360	27.276	31.996	36.694	45.606	54.942	44.076
420	31.624	36.368	39.264	49.148	58.532	52.708

480	36.896	40.666	44.492	56.512	63.584	56.778
540	40.476	46.266	50.026	59.546	64.476	62.336
600	46.032	50.840	52.448	62.014	66.964	68.734
660	49.746	54.594	57.104	66.722	69.876	75.210
720	55.166	59.032	62.934	72.234	73.574	80.404

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

Table 5: Swelling index of Risedronate Sodium batch A1 to A7.

Time			% Swelling index				
(min)	A1	A2	A3	A4	A5	A6	A7
0	0	0	0	0	0	0	0
15	38.13	38.12	39.65	32.14	40.38	38.14	31.52
30	54.48	52.92	50.14	35.71	51.92	40.12	53.72
60	67.63	72.15	64.15	56.35	69.23	68.52	72.22
120	85.51	84.62	86.96	76.86	86.46	85.18	102.85
180	104.11	102.92	106.66	92.07	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	138.12	138.12	142.15	102.55	162.44	140.16	194.96

Table 6: Floating ability of various Risedronate Sodium 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	27	44	Broken after 6-7Hrs
A5	22	66	Intact
A6	44	>725	Intact
A7	55 sec	>726	Intact

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

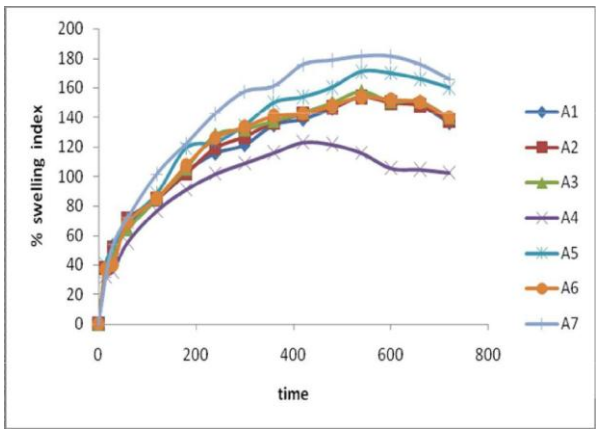

Fig. 1: Relationship between swelling index and time of A1 to A7.

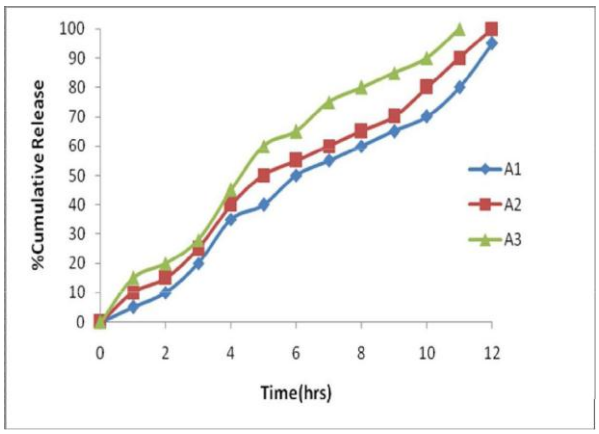

Fig 2: Drug release Profile of A1, A2, A3.

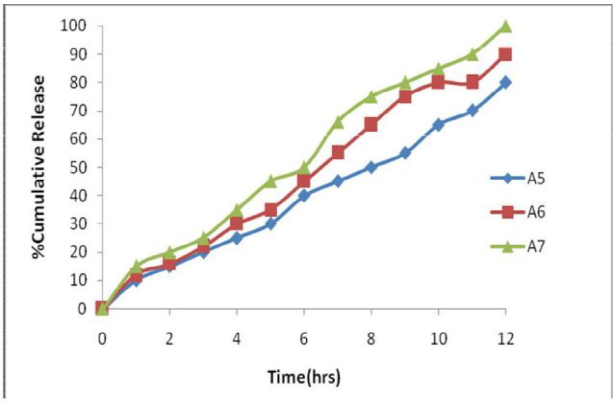

Fig. 3: Drug release Profile of A5, A6, A.

DISCUSSION

The reported melting point values for Risedronate Sodium were in the range of 252-262^{0}C. The observed melting point ranged between 254-264^{0}C.

UV, Shimadzu 1800 recording spectrophotometer equipped with a pair of 1 cm quartz matched cells used for all spectral measurements. Absorption spectra of samples are recorded between 200-400 nm. A consort pH meter was used for checking the pH of buffer solutions. The absorption maxima were found to be 263 nm.

Result of study of physical parameters of Risedronate Sodium formulation A1-A7 is summarized in table (no. 1) and Composition of Floating tablets of Risedronate Sodium 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 3.99 ±0.02 to 4.24±0.07& 12.06 ±0.04 to 12.16±0.05 respectively.

The hardness was in range of 7.4±0.03 to 9.0±0.06kg/cm ^{2}, which was measured on Monsanto hardness tester.

Drug content release was in the range of 98.33±0.12 to 108.96±0.16 shown in Table (no. 3). The percentage drug release was found 58% after 7 hrs. for all the formulations A1-A7. After 12 hrs. it showed 80.40% 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).

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 Risedronate Sodium 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 Risedronate Sodium 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, Carbopol belongs to the class of swellable 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 Risedronate Sodium 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 NaHCO3 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 (NaHCO3) 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

In the present era, gastro retentive dosage forms (GRDF) receive great attention because they can improve the performance of controlled release systems. An optimum GRDF system can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner, and finally is easily metabolized in the body. Physiological barriers like gastric motility and gastric retention time (GRT) act as obstacles in developing an efficient GRDF. Gastro retention can be achieved by developing different systems like high density systems, floating drug delivery systems (FDDS), muco-adhesive systems, expandable systems, superporous systems, and magnetic systems. All these systems have their own merits and demerits. This study focused on the various aspects useful in development of GRDF including the current trends and advancements.

ACKNOWLEDGEMENTS

It's my privilege to express profound sense of gratitude and cordial thanks to our respected Chairman **Mr. Anil Chopra**, Vice -Chairperson **Ms. Sangeeta Chopra** & Pro – Chairman **Mr. Prince Chopra**, St. Soldier Group of Educational Society, Jalandhar for providing necessary facilities to complete this research work.

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