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DEVELOPMENT, IN VITRO AND IN VIVO EVALUATION OF RISEDRONATE SODIUM FLOATING MICROBALLOONS

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ABSTRACT

The present investigation is concerned with the formulation and evaluation of Risedronate Sodium floating microballoons to extend gastric residence time (GRT) and to prolong the release of the drug. In the present work by solvent evaporation process, floating microballoons of Risedronate sodium were formulated. The prepared microballoons were subjected for both *In vitro* and *In vivo* evaluation. Out of all formulations the formulation (RSF10) with *E*udragit RS 100, Eudragit S 100 in 1:1 ratio has noticed maximum amount of drug release hence, considered as the optimized formulation. The *in vitro* release kinetics demonstrated that the optimised formulation releases the drug in a zero-order manner based on the regression values of kinetic models. For *in vivo* assessment, the optimised formulation was subjected to *in vivo* radiographic analysis and in vivo pharmacokinetic analysis. The optimized formulation remained buoyant in the stomach for up to 5.5 h and the oral bioavailability of the improved formulation was substantially higher than that of the formulations put on the market. The improved bioavailability may be due to the longer-lasting floating function of the dosage form in the stomach.

KEYWORDS: Risedronate sodium, Floating microballoons, Solvent Evaporation, Gastric residence time, *Invitro* evaluation, *Invivo* evaluation.

INTRODUCTION

The oral route has gained the most interest among the various routes of drug administration, partially due to the ease of administration and the considerable versatility in the configuration of the dosage type. Sadly, in most situations, the significant heterogenesity of the physiology of the gastrointestinal tract and its transit time contributes to unpredictable bioavailability and therapeutic results that are not reproducible.[1,2] Gastric emptying of dosage forms is an incredibly complex process and the potential for dosage forms that remain in the stomach for a longer period of time than traditional dosage forms to extend and monitor emptying time is a valuable advantage.[3,4] In developing controlled release mechanisms for improved absorption and enhanced bioavailability, many difficulties are encountered.[7] The failure to confine the dosage form to the appropriate region in the gastrointestinal tract is one of these difficulties.[8] Conventional drug delivery systems may not overcome all these issues imposed by the gastrointestinal tract. Hence, Gastro Retentive Drug Delivery System was developed.

Microballoons are considered as one of the most favourable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere.[8] The novel techniques involved in their preparation include simple solvent evaporation method[9], emulsion-solvent diffusion method, single emulsion technique, double emulsion technique, phase separation coacervation technique, polymerization technique, spray drying and spray congealing method and hot melt encapsulation method.[10] The slow release of drug at desired rate and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polylactic acid, Eudragit® S and hydroxy propyl methyl cellulose, cellulose acetate are used in the formulation of hollow microspheres, and the release of drug can be modulated by optimizing polymer concentration and the polymer -plasticizer ratio.

Risedronate sodium, is a pyridinyl bisphosphonate that inhibits the osteoclast-mediated bone resorption and modulates the metabolism of the bone. It is a drug used to treat Paget'sdisease and the effects of osteoporosis triggered by menopause or steroid usage. Risedronate sodium has an affinity for the bone crystals of hydroxyapatite and serves as an anti resorptive agent and also prevents osteoclasts at the cellular level.[9]

MATERIALS AND METHODS

Risedronate sodium was purchased from Yarrow chem. Products, Mumbai, India. Eudragit RS100, Ethylcellulose, HPMCK4M, Ethanol, Eudragit S100, Dichloromethane chemicals of Laboratory-grade from SD Fine chemicals Pvt.Ltd., was used.

Formulation of Risedronate sodium floating microballoons

The floating microballoons were formulated using the technique of solvent evaporation. In an organic solvent, the polymer is dissolved and the drug is dissolved or dispersed in the formed polymer solution. The drug-containing solution is then added into an aqueous phase containing the required additive (polymer/surfactants) to create oil in water emulsion. Once the stable emulsion has formed, the organic solvent is evaporated either by continuous stirring for 6 h under 3 blade propellers at 500rpm or by increasing the temperature to 40°C under pressure. The solvent removal roots precipitation of polymer at the interface of oil / water droplets, which makes microballoons hollow and imparts floating properties.[10] Thecollectedmicroballoons are dried at room temperature.

Table 1: Composition of floating microballoons of Risedronate.

S. No.	Materials	RS F1	RS F2	RS F3	RS F4	RS F5	RS F6	RS F7	RS F8	RS F9	RS F10	RS F11	RS F12	RS F13	RS F14	RS F15
1	Risedronate Sodium	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35
2	Eudragit RS 100	35	35	35	70	70	70	35	35	70	70	NA	NA	NA	NA	NA
3	Eudragit S 100	35	70	105	35	70	105	105	105	70	70	NA	NA	NA	NA	NA
4	HPMC K4M	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	35	35	35	70	70
5	Ethylcellulose	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	35	70	105	35	70
6	Ethanol	15	15	15	15	15	15	20	10	20	10	15	15	15	15	15
7	Dichloromethane	15	15	15	15	15	15	10	20	10	20	15	15	15	15	15

***In vitro* Evaluation Methods**

Scanning Electron Microscope (SEM)

Scanning Electron Microscope was used to analyze the surface morphology and surface properties of the right formulation (SEM). An electron microscope with a fine coat and an ion sputter are used to screen and examine microballoons. The sample was mounted on a copper sample holder and sputtered with carbon before being coatedwithgold.[11,12]

Particle Size Measurement: Particle size of prepared microballoons was estimated by an optical microscope and the mean particle size was calculated with the help of a calibrated ocular microscope by measuring 100 particles.[11]

Percentage yield: The prepared microballoons were weighed accurately. The cumulative percentage yield of floating microballoons was calculated by dividing the weighed quantity of microballoons by the total number of all excipients and medication used in their preparation.[11]

It was calculated by using following formula,

Percentage yield=Actual yield of product/Total weight of excipients and drug

Entrapment Efficiency: The over all drug content and the unentrapped drug of the floating microballoons were used to measure the volume of entrapped drug in the microballoons. The unentrapped drug was determined by taking one dose equivalent of floating microballoons and washed with 0.1NHCl to remove the free drug on the surface. By dispersing 50 mg of microballoons in 10 ml of 0.1 N HCl, the drug concentration in microballoons was measured and the microballoons are agitated with a magnetic stirrer for 12 h to extract the drug by dissolving the polymer. Both the solutions of unentrapped drug and total drug were filtered through a whattman filter paper and the drug concentration was determined spectrophotometrically at 264 nm by making desired dilution with 0.1N HCl.[11,12]

Percentage Entrapment Efficiency was calculated as follows:

% Entrapment efficiency = (Total drug content– unentrapped drug)*100/Total drug content.

***Invitro* buoyancy:** Microballoons were spread over the 900ml of 0.1N HCl placed in USP dissolution apparatus type II. With the help of paddle rotating at 50rpm the medium was agitated for12h. The floating microballoons and the settled microballoons were collected separately and dried. Then they are weighed. From the ratio of the mass of the microballoons that are floating and the total mass of the microballoons buoyancy percentage was calculated.([11,12])

$$\% \text{ Buoyancy} = Qf*100/(Qf+Qs)$$

Where

Qf =floatingmicroballoonsweight

Qs=settledmicroballoonsweight.

Drug content: Spectro photometric analysis was used to assess the drug quality of each dosage equal to a unit dose (35mg). Each formulation was finely powdered in a glass mortar and dissolved for 6 hours in 0.1 N HCl with absorbance measured at 264nm.

***In vitro* release study:** The *invitro* drug release was carried out by using USP basket type dissolution apparatus containing 900 mL of 0.1N HCl (pH 1.2) as a dissolution medium at 37 ± 0.5 ºCat 50 rpm. At predetermined time intervals such as 0, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12hrs, 5 mL of sample was with drawn and the samples were filtered through whatmann filter paper, diluted suitably and analyzed spectrophotometrically with UV-Visible spectr-photometer at λ_{max} 264 nm. After the test sample was withdrawn, an equivalent volume of fresh dissolution medium was applied automatically to keep the dissolution medium at 900 ml. The average percentage drug release was determined after the dissolution analyses were completed.[28,31]

Drug release kinetic studies

The mechanism of drug release was determined by fitting the release data to the following kinetic models like as zero-order kinetics, first-order kinetics, Higuchi, Korsmeyer-Peppas models and calculate the R^2 values of the drug release profiles corresponding to each model using PCP Dissov3 software.[11,12]

Stability studies: Stability studies were conducted according to international conference on harmonization (ICH) guidelines. Optimized Microballoons (RSF10) were enclosed in polyethylene covers and placed in desiccators containing saturated sodium chloride solution (75%RH). The desiccators was stored at 40°C for 3months. After every month, microballoons were evaluated for physical appearance, drug content and percentage of drug release for12hr. Finally microballoons were tested for any statistical difference using the student paired t –test the differences were considered to be significant at $p < 0.05$.[11,12]

***Invivo* Evaluation of Gastric Residence Timein Rabbits**

The Institutional Animal Ethical Committee has reviewed the experimental protocol for conducting *in vivo* radiographic studies and has given permission i.e., (Registration No. IAEC/22/UCPSC/2018). *Invivo* floating behavior of optimized floating microballoons formulation was studied in healthy albino rabbits, weighing 1.5 kg to 2 kg. The study was based on the principle of monitoring radiological activity. Animals were maintained under standard laboratory conditions (Temperature 25 ± 2^0C).Rabbits were held in an animal house for one week to acclimate them to the environment and fed a normal diet. Three healthy male albino rabbits were used to study the in vivo transit activity of the formulated microballoons. Before the research began, all of the animals were visually tested. Any animal which did not meet the health and weight criteria were excluded from the study. Animals with any inflammation, dermatitis, infection or apparent abnormalities of the urinary tract were excluded from the study. None of the animals should have symptoms or past history of gastro-intestinal disease. First X- ray was taken for all the rabbits to ensure absence of radio opaque material in the stomach. During the study food was not allowed to eat by animal's but provided with water. Radio opaque microballoons were made by incorporating 500 mg of barium sulfate into a polymeric solution

and using a similar process to create an improved formulation. Rabbits are given an optimized formulation containing $BaSO_4$ and a suitable amount of water. X-ray study was conducted both in fed and unfed state.

Fasting state

The BaSO4 loaded microballoons were administered orally with sufficient amount of water through a mouth gag introduced in between the two jaws of rabbit. During the study animals were not allowed to take food but provided with water ad libitum and in between the radiographic imaging animals were not allowed to take any food but freed and Permitted to move and carry out normal activities.

Fed state

All the rabbits were fasted for 12h before initiating the study and fed with a lowcalorie diet. Half an hour later, BaSO4 loaded microballoons were administered orally with sufficient amount of water through a mouth gag introduced in between the two jaws of rabbit and at different time intervals rabbits were exposed to X-ray imaging and floating behavior was studied.[11,12] For radiographic imaging rabbits were physically restrained and by placing the animals in front of X-ray machine location of the dosage form in the stomach was monitored. The distance between the animal and the X-ray source is maintained same during the imaging process. Gastric radiography is done at the time intervals of 0.5, 2.5, 4.5, 5.5 hrs and in between the radiographic imaging animals were not allowed to take any food but freed and permitted to move and carryout normal activities.

***In Vivo* Pharmacokinetic evaluation of The Optimized Microballoons**

Good interpretation of the *invitro* and *invivo* performance of the dosage form is a fundamental objective in the pharmaceutical product development. *In vitro* studies may not give complete information about *in vivo* performance due to poor correlation exist between *in vitro* and *in vivo* performance due to various unpredictable physiological factors that affect drug release and absorption particularly in case of oral controlled drug delivery system. In the present investigation floating microballoons were developed to release the drug through upper part of the GIT resulting in the improved bioavailability compared to conventional dosage forms. The *in vivo* performance of the optimized formulation (RSF10) was evaluated bypharmaco kinetic study on healthy albino rabbits obtained from Mahaveera Enterprises, No. 203, Harsha Homes 2-2-185/55/E, Hyderabad-500013, Telangana, India, and made comparison with the marketed formulation (Actonel 35 mg).

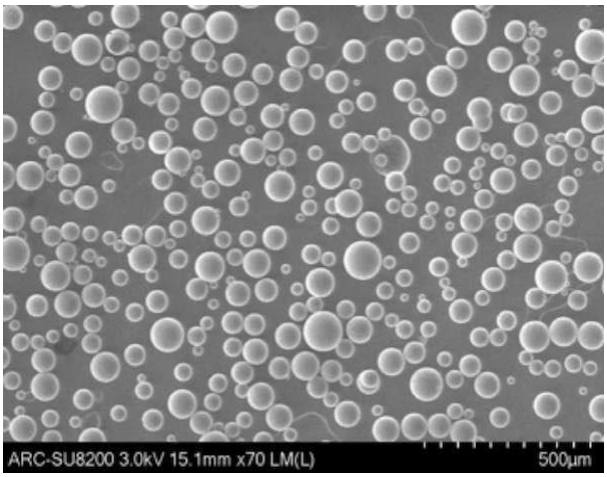

Figure 1: Scanning electron micrographs of optimized floating microballoons of Risedronate sodium.

Table 2: *In vitro* evaluation parameters of prepared microballoons of Risedronate Sodium.

Formulation Code	% Yield	% EE	% B
RSF1	86.4	83.4	77.8
RSF2	83.4	93.2	85.4
RSF3	82.6	94.6	85.1
RSF4	76.8	90.6	81.6
RSF5	81.2	90.2	85.5
RSF6	83.4	93.5	86.5
RSF7	81.4	90.7	82.9
RSF8	82.4	88.5	84.5
RSF9	81.6	90.5	81.2
RSF10	86.5	93.6	88.5
RSF11	71.5	69.8	66.5
RSF12	66.8	66.5	66.9
RSF13	65.4	63.5	65.3
RSF14	65.4	63.5	64.9
RSF15	60.2	62.3	63.8

Table 3: % Drug Release Data of Microballoons.

Time (Hr)	% Drug Release														
	RSF1	RSF2	RSF3	RSF4	RSF5	RSF6	RSF7	RSF8	RSF9	RSF10	RSF11	RSF12	RSF13	RSF14	RSF15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	24.6± 0.12	18.5± 0.36	14.7± 0.71	19.6± 0.78	5.7± 0.65	5.1± 0.57	15.8± 0.45	15.6± 0.25	6.5± 0.69	5.3± 0.10	6.4± 0.98	5.4± 0.54	4.2± 0.59	5.9± 0.15	8.2± 0.24
1	43.8± 0.13	33.5± 0.75	24.8± 0.15	36.2± 0.29	10.2± 0.36	7.8± 0.69	25.6± 0.20	23.4± 0.43	10.2± 0.54	9.8± 0.21	10.2± 0.35	9.5± 0.11	6.5± 0.1	11.6± 0.19	15.3± 0.32
2	63.8± 0.19	50.3± 0.54	43.5± 0.26	56.4± 0.56	18.6± 0.24	11.4± 54	41.5± 0.06	43.6± 0.85	15.8± 0.35	18.5± 0.32	16.4± 0.49	11.6± 0.18	11.3± 0.16	16.8± 0.21	19.5± 0.5
3	86.9± 0.23	62.8± 0.25	57.6± 0.38	64.5± 0.51	24.6± 0.59	19.5± 32	56.7± 0.12	58.6± 0.29	24.5± 0.78	24.6± 0.52	21.2± 0.12	16.7± 0.25	13.5± 0.23	23.8± 0.26	21.5± 0.6
4	97.6± 0.56	73.6± 0.85	65.7± 0.79	74.5± 0.29	33.5± 0.16	28.5± 0.29	65.3± 0.56	68.5± 0.75	36.8± 0.42	35.6± 0.75	27.5± 0.91	21.3± 0.36	16.5± 0.2	29.6± 0.41	26.9± 0.2
6	100.2± 0.89	83.7± 0.68	73.6± 0.54	86.5± 0.67	51.2± 0.19	44.5± 0.17	71.5± 0.28	71.3± 0.64	54.6± 0.76	55.9± 0.69	41.2± 0.87	36.5± 0.14	26.5± 0.35	43.5± 0.48	41.3± 0.65
8	100.1± 0.58	100.1± 0.75	85.6± 0.47	98.5± 0.82	63.7± 0.21	56.4± 0.25	83.5± 0.26	85.6± 0.45	65.4± 0.25	66.5± 0.79	46.8± 0.74	41.3± 0.65	36.9± 0.45	51.2± 0.31	49.8± 0.61
10	100.2± 0.45	100.1± 0.23	100.1± 0.26	100.2± 0.38	81.5± 0.31	66.7± 0.36	97.8± 0.87	100.2± 0.75	84.6± 0.78	87.9± 0.26	66.8± 0.69	56.5± 0.5	46.8± 0.54	72.5± 0.8	61.5± 0.71
12	100.2± 0.28	100.1± 0.49	100.1± 0.45	100.1± 0.54	100.1± 0.88	73.6± 0.89	100.2± 0.56	100.1± 0.98	100.1± 0.54	100.3± 0.71	73.5± 0.32	66.5± 0.6	57.9± 0.72	1.5± 0.95	71.5± 0.15.

Table 4: Release kinetic parameters of Risedronate Sodium.

Formulationcode	Release Kinetics Parameters				
	Zeroorder	Firstorder	Higuchimodel	Korse-meyerpeppas	Hixon -crowell
RSF1	0.100	0.991	0.804	0.827	0.952
RSF2	0.587	0.992	0.966	0.959	0.985
RSF3	0.744	0.989	0.985	0.978	0.979
RSF4	0.507	0.992	0.954	0.956	0.979
RSF5	0.998	0.938	0.868	0.998	0.964
RSF6	0.988	0.979	0.879	0.990	0.990
RSF7	0.747	0.986	0.988	0.982	0.974
RSF8	0.733	0.984	0.979	0.969	0.973
RSF9	0.996	0.939	0.870	0.986	0.967
RSF10	0.996	0.938	0.871	0.987	0.966
RSF11	0.984	0.976	0.896	0.989	0.985
RSF12	0.990	0.973	0.870	0.990	0.983
RSF13	0.994	0.972	0.849	0.993	0.981
RSF14	0.988	0.966	0.889	0.991	0.981
RSF15	0.961	0.977	0.930	0.986	0.979

Table 5: Stability data of optimized microballoons formulation (RSF10) of Risedronate Sodium.

Optimized formulation RSF10	Bulk density	Tappeddensity	Compressibility index	Angle of repose	% Buoyancy	Drug content	Mean particle Size (µm)
1st Month	0.77±0.12	0.68±0.01	10.31±0.10	13.1±0.21	81.2±0.30	98.01±0.51	129.01±2.39
2nd Month	0.76±0.11	0.67±0.03	10.28±0.11	12.8±0.10	80.1±2.10	97.06±0.48	129.01±1.99
3rd Month	0.75±0.08	0.66±0.04	10.19±0.13	12.5±0.09	80.1±1.10	97.02±0.47	128.02±1.56

Table 6: Percentage drug release of optimized microballoons formulation (RSF10) of Risedronate Sodium during stability studies.

RSF10	1st Month	2nd Month	3rd Month
0	0	0	0
0.5	5.1±0.9	4.9±0.1	4.6±0.2
1	9.7±0.19	9.6±0.13	9.1±0.09
2	18.4±0.31	17.9±0.29	16.9±0.21
3	24.4±0.50	24.1±0.47	23.8±0.42
4	35.2±0.71	34.8±0.69	33.3±0.61
6	55.8±0.67	54.7±0.61	54.1±0.58
8	66.1±0.76	65.4±0.62	65.9±0.59
10	87.7±0.22	87.1±0.19	87.5±0.12
12	100.2±0.69	100.0±0.59	100.8±0.51

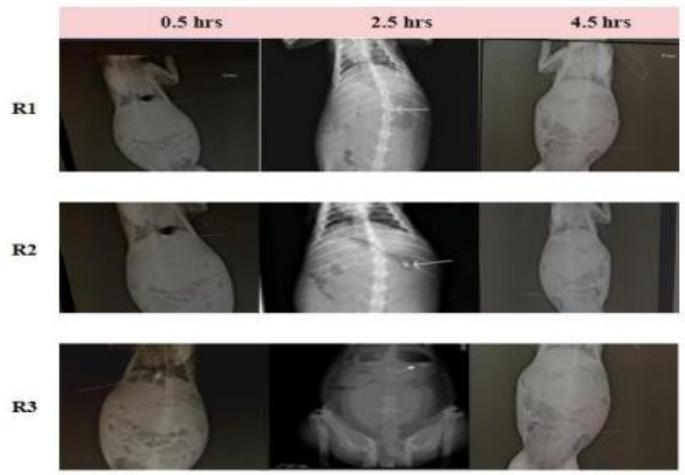

Figure 02: X-ray images of optimized formulation of Risedronate Sodium microballoons in the gastric region of rabbit during unfed state at 0.5 hrs, 2.5 hrs, 4.5hrs.

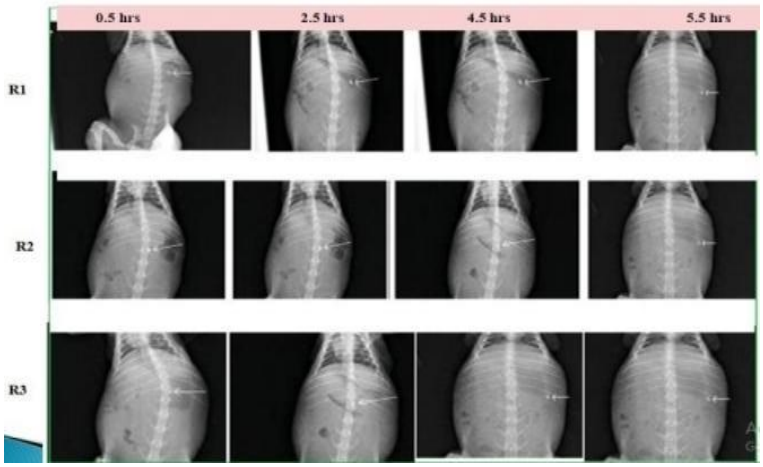

Figure 03: X-ray images of optimized formulation of Risedronate Sodium microballoons in the gastric region of rabbit during fed state at 0.5 hrs, 2.5 hrs, 4.5hrs, 5.5hrs.

Table 7: Mean pharmacokinetic parameters of Risedronate Sodium as reference and test tablets in rabbits (n=6).

Pharmacokinetic parameter	Unit	Reference	Test
Cmax	ng/mL	84.21	93.86
tmax	h	3	8
AUC0-t	ng/mL×h	1023.01	1652.21
AUC0-α	ng/mL×h	1548.60	2939.76
t1/2	h	15.38	17.96

DISCUSSION

In vitro Evaluation of Risedronate sodium Microballoons

Scanning electron microscope (SEM)

Scanning electron microscope was used to study the surface morphology of the microballoons. The surface morphology of optimized formulation (RSF10) was shown in the Figure 5. It is evident from the SEM micrographs that the sodium filled microballoons of Risedronate were mainly spherical in appearance. The surface was found to be flat, compact and less brittle, where the inner center was extremely porous and irregular with multiple depressions expressing water, ethanol and dichloromethane evaporation. The less porous outer surface and highly porous internal surface supported controlled release of drug from the microballoons and good buoyancy.

Physico chemical properties of prepared microballoons

The average particle size of floating microballoons was found to be in the range of 120-180µm. The calculated tapped mass, bulk density, compressibility index, and angle of repose are all within acceptable limits, indicating that microballoons have strong flow properties. Both of the prepared formulations had drug content that was within the permissible range of 95.0-100.0%. All these values obtained for all the formulations are given in Table 1& 2. Thepercentage yield was in the range of 60-90 % for all the formulations. It was found to be lessthan 70% yield with ethyl cellulose and HPMC K4M and for optimized formulation the yieldwas 86.5 %.

All of the formulations had an entrapment efficiency of 60-90%, with the optimized formulation having an entrapment efficiency of 93.6%. The entrapment efficiency was low with formulations prepared with ethyl cellulose and HPMC K4M. There was no effect of solvent ratio was observed in the percentage entrapment efficiency. The percentage buoyancy was in the range of 60-90%for all the formulations and was found to be 88.5% for optimized formulation. The high buoyancy of the microballoons is mainly due to the presence of pores and cavities which were formed during solvent evaporation which can be seen in Figure 6 and all these results were shown in Table 3.

Invitro drug release study

Dissolution studies of all the formulations were carried out using USP basket type dissolution apparatus. Thedissolution profiles were compared among different formulations. The cumulative percentage drug release was decreased with increase in the polymer concentration. Based on the results of *in vitro* drug release studies it was found that (RSF10) has shown sustained drug release for 12h with zero order drug release. The results of the *invitro* drug release studies are shown in the dissolution profiles in the Figure7to 9.

Release Kinetics of Floating Microballoons

The drug release mechanism was calculated by comparing the release data to the following kinetic models, such as zero-order kinetics, first-order kinetics, Higuchi, Korsmeyer-Peppasmodels, and determining the R2 values of the drug

release profiles corresponding to eachmodelusingPCPDissov3software.The *invitro* drug release kinetics based on the regression values reveals that the optimized formulation (RSF10) releases the drug in zero order manner (Table 4).

Stability studies

The stability study was conducted for 3 months and the results were analyzed. No significant change was observed in particle size, flow properties, drug content, percentage buoyancy and percentage drug release of microballoons. Microballoons were found to be stable at storage conditions for three months (Table 5 &6).

***Invivo* Evaluation of Risedronate Sodium Micro-balloons**

***Invivo* floating behaviour**

The optimized floating microballoons formulation prepared was tested for *in vivo* floating behavior in health yalbinorabbits. Radiographic images obtained at 0.5hrs, 2.5hrs, 4.5hrs & 5.5 hrs are shown in Figure 10 &11. It was observed from the images that the formulation was remained buoyant for up to 5.5 hrs in the stomach indicating the uniform distribution of formulation in the stomach. But in unfed state the formulation remained buoyant in the Stomach only upto 2.5 hrs this is because in fasting condition myoelectric migrating contractions forces the contents to duodenum from stomach. The forceful waves will remove all the contents of stomach including dosage form. This will not take place in fed state. Therefore from these studies, it was clearly observed that the floating microballoons should be given to patients after a standard diet.

***Invivo* Pharmacokinetic study**

The *in vivo* pharmacokinetic study was conducted in healthy albino rabbits. In this study, the pharmacokinetic parameters of Risedronate Sodium floating microballoons were compared with marketed tablet (Actonel).The mean Plasma concentration – time profile obtained from the study is shown in Figure 12. Various pharmacokinetic parameters were estimated such asCmax, tmax, AUC and relative bioavailability are given in Table 7. The importance of the disparity between the treatments was measured via the student paired t- test using Graphpad Prism. The findings revealed that the discrepancy between both SR and Floating Microballoon pharmacokinetic parameters was statistically significant ($p<0.050$).

The mean comparison formulation tmax was 3 hrs. This suggests that the release of the drug from the reference formulation was rapid while the mean tmax was 8 hrs in the research formulation.This revealed that the test formulation was successful in delaying the peak plasma concentration, while demonstrating that the floating microballoons had a prolonged plasma concentration of Risedronate sodium.

The mean biological half-life(t1/2) from the research and reference formulations of Risedronate sodium was 17.96 h and 15.38 h respectively. The distinction found here is that there is a prolonged constant release of the drug into the blood stream due to prolonged ingestion of the test formulation.

The mean area under the plasma time curve AUC 0-t and AUC 0-total of the reference formulation was 1023.01ng/ml h and 1548.60 ng/ml h, and while AUC 0-t and AUC 0-total of the test formulation were 1652.21ng/ml h and 2939.76 ng/ml h, this suggests that the totalabsorption of Risedronate sodium at the same dosage was higher in the test formulation relative to the reference product. The findings revealed that the oral bioavailability of the optimised formulation (RSF10) was substantially enhanced relative to the formulation sold. Relative bioavailability was found to

be 189.8 with respect to the advertised formulation due to extended gastric residence time of floating microballoons of Risedronate sodium.

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