World Journal of Pharmacy and Biotechnology
ISSN: 2349-9087 | www.pharmaresearchlibrary.com/wjpbt
W. J. Pharm. Biotech., 2019, 6(2): 62-67
DOI: https://doi.org/10.30904/j.wjpbt.2019.4079

Formulation and *In-vitro* Evaluation of Risedronate Effervescent Floating Tablets

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A B S T R A C T

Risedronate, is a bisphosphonate used to strengthen bone, treat or prevent osteoporosis, and treat Paget's disease of bone. In the present research work effervescent floating matrix formulation of Risedronate by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared with Methocel K4 M retarded the drug release up to 12 hours in the concentration of 75 mg (F3).The formulations prepared by using Methocel K15M were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Locust bean gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order mechanism of drug release.

Keywords: Risedronate, effervescent floating matrix, Methocel

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Article History
Received : 10 May 2019
Revised : 20 June 2019
Accepted : 15Aug 2019
Published : 29 Dec 2019

Citation: Kamera Kishore, et al. Formulation and In-vitro Evaluation of Risedronate Effervescent Floating Tablets, W. J. Pharm. Biotech., 2019, 6(2): 62-67.

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1. Introduction

Gastroretentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Such retention systems are important for those drug that are degraded in the intestine like antacids or certain antibiotics, enzymes that act locally in the stomach. This systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract, 1,2 thus ensuring optimal bioavailability.

2. Materials and Methods

Materials: Risedronate, Methocel K15M, Sodium CMC, MCC pH 102, Magnesium stearate, Talc, Sodium bicarbonate all the chemicals used were laboratory grade.

Formulation (Or) Preparation of Floating Tablets of Risedronate:

Optimization of Sodium bicarbonate concentration:

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed.

Based on that the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Table 1: Optimization sodium bicarbonate concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Risedronate	75	75	75
2	Methocel K15 M	50	50	50
4	$NaHCO_3$	30	60	90
5	Mg.Stearate	5	5	5
5	Talc	5	5	5
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	300	300	300

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimized.

Method of Preparation:

Risedronate and all other ingredients were individually passed through sieve no ≠ 60.All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Evaluation of post compression parameters for prepared Tablets: The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

3. Results and Discussion

Analytical Method: Graphs of Risedronate was taken in Simulated Gastric fluid (pH 1.2) at 266 nm.

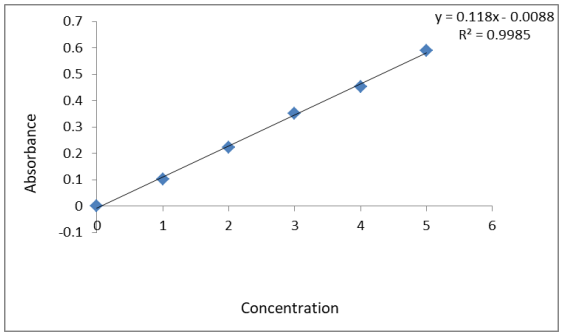

Fig 1: Standard graph of Risedronate in 0.1N HCl

Pre formulation parameters of powder blend:

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43 to 0.58 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 30 mg concentration showed less floating lag time of 3 min and the tablet was in floating condition for more than 12 hours.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

***In-Vitro* Drug Release Studies:**

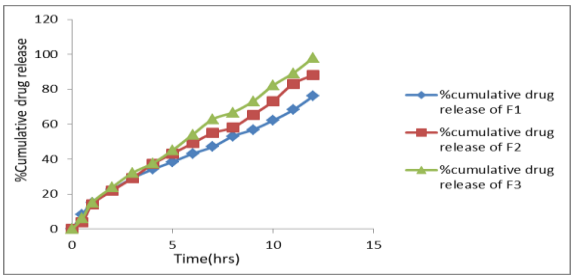

Fig 2: Dissolution profile of Risedronate floating tablets (F1, F2, F3 formulations)

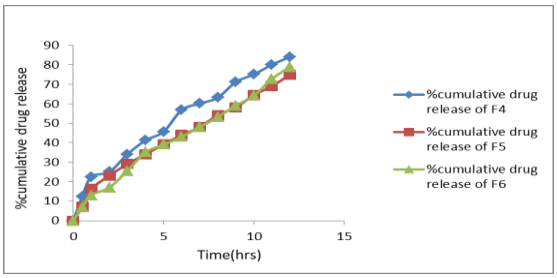

Fig 3: Dissolution profile of Risedronate floating tablets (F4, F5, F6 formulations)

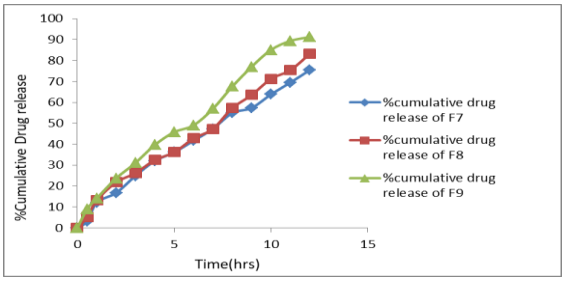

Fig 4: Dissolution profile of Risedronate floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Methocel K15M retarded the drug release in the concentration of 75 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.12 % in 12 hours (Formulation F3) with good floating lag time and floating buoyancy time.The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

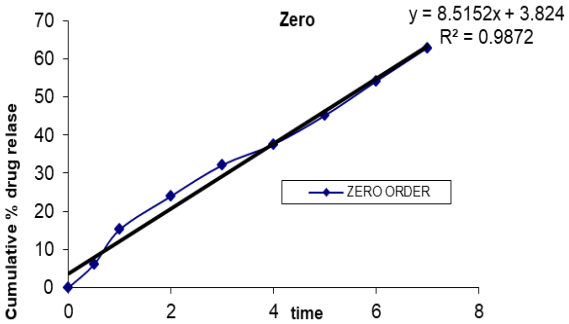

Fig 5: Zero order release kinetics graph

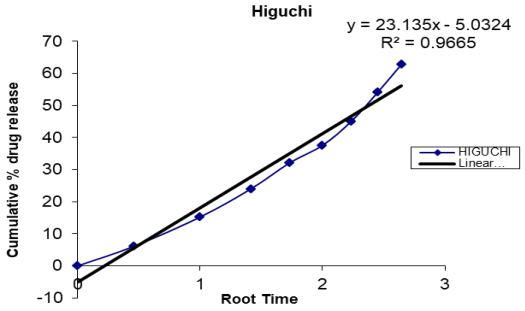

Fig 6: Higuchi release kinetics graph

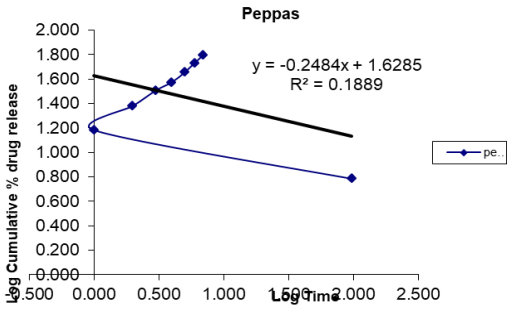

Fig 7: Kars mayer peppas graph

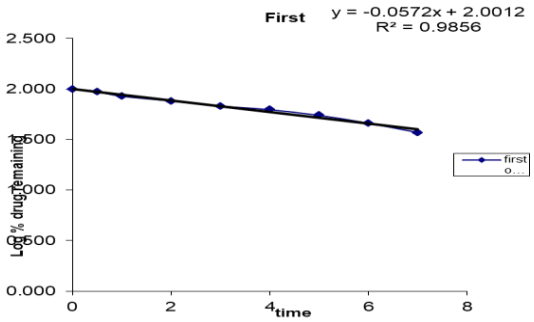

Fig 8: First order release kinetics graph

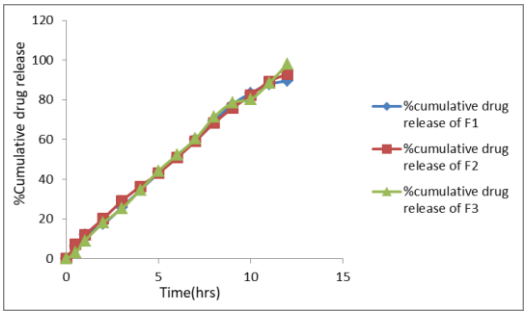

Fig 3: Dissolution graphs for the formulations F1,F2,F3

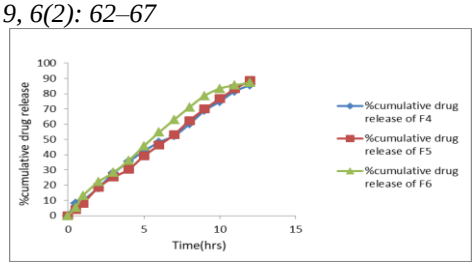

Fig 4: Dissolution graphs for the formulations F4,F5,F6

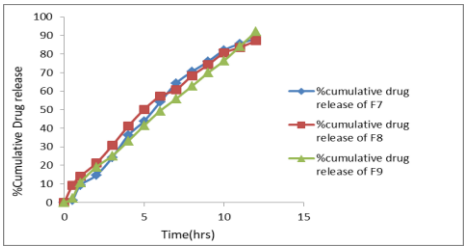

Fig 5: Dissolution graphs for the formulations F7,F8,F9

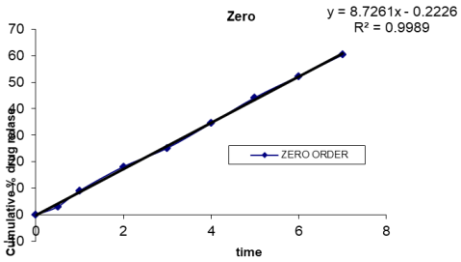

Fig 6: Zero order release kinetics graph

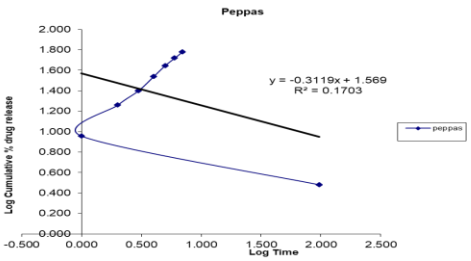

Fig 7: Higuchi release kinetics graph

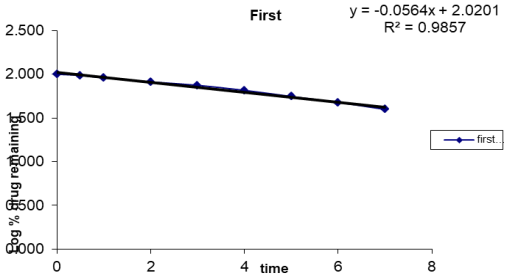

Fig 8: Kars mayer peppas graph

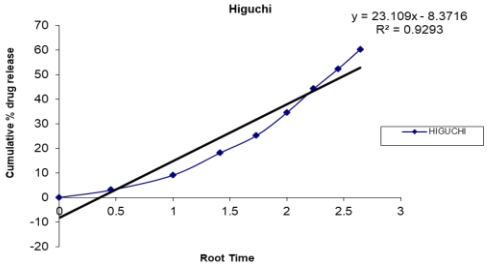

Fig 9: First order release kinetics graph

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

4. Conclusion

In the present research work effervescent floating matrix formulation of Risedronate by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared with Methocel K4 M retarded the drug release up to 12 hours in the concentration of 75 mg (F3). The formulations prepared by using Methocel K15M were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Locust bean gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order mechanism of drug release.

Table 2: Formulation composition for floating tablets

Formulation No.	Risedronate	Methocel K15M	Methocel K100M	Sodium CMC	$NaHCO_3$	Mag. Stearate	Talc	MCC pH 102
F1	75	25	-----	-----	30	5	5	QS
F2	75	50	-----	-----	30	5	5	QS
F3	75	75	-----	-----	30	5	5	QS
F4	75	-----	25	-----	30	5	5	QS
F5	75	-----	50	-----	30	5	5	QS
F6	75	-----	75	-----	30	5	5	QS
F7	75	-----	-----	25	30	5	5	QS
F8	75	-----	-----	50	30	5	5	QS
F9	75	-----	-----	75	30	5	5	QS

All the quantities were in mg, Total weight is 300 mg.

Table 3: Observations for graph of Risedronate in 0.1N HCl (266 nm)

Conc [µg/l]	Abs
1	0.101
2	0.223
3	0.351
4	0.453
5	0.589

Table 4: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	24.21	0.45	0.57	17.34	0.87
F2	23.28	0.56	0.69	16.98	0.99
F3	21.22	0.53	0.65	17.45	0.57
F4	24.09	0.56	0.58	16.98	1.19
F5	25.11	0.51	0.59	17.43	1.20
F6	24.11	0.47	0.63	16.56	1.15
F7	23.12	0.58	0.66	17.24	0.78
F8	24.11	0.48	0.59	16.45	1.17
F9	25.45	0.50	0.65	16.25	1.18

Table 5:: *In vitro* quality control parameters for tablets

Formulation code	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time(sec)
F1	302.7	3.6	0.56	4.5	99.76	90
F2	307.5	3.4	0.57	4.1	99.45	112

F3	299.3	3.2	0.58	3.8	99.34	121
F4	301.8	3.1	0.54	3.6	99.87	87
F5	303.2	3.5	0.52	4.4	99.14	110
F6	309.4	3.3	0.49	4.1	98.56	106
F7	302.1	3.2	0.51	3.9	98.42	118
F8	297.3	3.5	0.50	3.8	99.65	101
F9	295.9	3.2	0.54	3.6	99.12	121

Table 6: Dissolution Data of Risedronate Tablets Prepared With Methocel K 15M In Different Concentrations

TIME **(hr)**	**CUMULATIVE PERCENT DRUG RELEASED**		
	F1	**F2**	**F3**
0.5	8.09	3.65	6.09
1	14.98	14.19	15.23
2	22.41	21.98	23.98
3	29.13	29.12	32.13
4	34.09	37.12	37.58
5	38.42	43.19	45.12
6	43.12	49.14	54.09
7	47.05	54.98	62.88
8	53.09	58.12	66.79
9	56.87	65.41	73.09
10	62.13	73.12	82.23
11	68.19	83.18	89.23
12	76.08	88.01	98.12

Table 7: Dissolution Data of Risedronate Tablets Prepared With Methocel K100M In Different Concentrations

TIME **(hr)**	**CUMULATIVE PERCENT DRUG RELEASED**		
	F4	**F5**	**F6**
0.5	12.45	7.11	6.98
1	22.51	16.19	13.12
2	25.09	23.19	17.08
3	34.12	29.12	25.61
4	41.23	34.09	35.11
5	45.71	39.21	39.07
6	56.81	43.98	43.08
7	60.12	48.03	48.11
8	63.19	54.27	53.19
9	71.23	58.12	59.14
10	75.12	64.51	64.18
11	80.09	69.12	72.81
12	84.12	75.04	79.01

Table 8: Dissolution Data of Risedronate Tablets Prepared With Sodium CMC in Different Concentrations

TIME **(hr)**	**Cumulative percent drug released**		
	F7	**F8**	**F9**
0.5	3.19	5.09	8.98
1	12.15	13.22	14.09
2	16.72	21.76	23.67
3	24.88	26.21	31.07
4	32.01	32.43	39.66
5	36.12	36.12	45.76
6	41.65	42.76	49.01
7	47.34	47.32	56.91
8	54.87	57.21	67.54
9	57.32	63.48	76.99
10	63.78	71.23	85.06

11	69.44	75.33	89.34
12	75.39	83.19	91.18

Table 9: Release kinetics data for optimized formulation

Cumulative (%) Release Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
6.09	0.5	0.458	0.785	1.987	1.973
15.23	1	1.000	1.183	0.000	1.928
23.98	2	1.414	1.380	0.301	1.881
32.13	3	1.732	1.507	0.477	1.832
37.58	4	2.000	1.575	0.602	1.795
45.12	5	2.236	1.654	0.699	1.739
54.09	6	2.449	1.733	0.778	1.662
62.88	7	2.646	1.799	0.845	1.570
66.79	8	2.828	1.825	0.903	1.521
73.09	9	3.000	1.864	0.954	1.430
82.23	10	3.162	1.915	1.000	1.250
89.23	11	3.317	1.951	1.041	1.032
98.12	12	3.464	1.992	1.079	0.274

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