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FORMULATION AND EVALUATION OF FLOATING TABLET OF RISEDRONATE

[1]K.Nagamani, [2]D.Rajkumar

[1]Mother Teresa College of Pharmacy

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Abstract:

Single and multi-unit skimming systems of risedronate sodium were readied utilizing Gelucire 43/01 by lessen cementing and separate granulation framework, solely. The controlled delivery drifting systems were assessed for in vitro and in vivo skimming limit and in vitro quiet delivery. Impact of creating on Gelucire 43/01 was overviewed by hot stage microscopy (HSM), isolating electron microscopy (SEM), differential taking a gander at calorimetry (DSC), in vitro skimming limit, and in vitro fix discharge. Multi-unit framework got has shown starting affected delivery, which was covered in single unit structure. Both single-and besides multi-unit structures displayed expansion in pace of medication discharge on creating because of changes in the properties of the Gelucire 43/01. Multi-unit structures picked up by separate granulation were adequately less mentioning for scale up and valuable if the essential burst discharge doesn't make any indispensable clinical misery.

Keywords: *Formulation, Evaluation, Floating Tablet, Risedronate*

Corresponding author:

K.Nagamani,

M. Pharmacy, Department of Pharmaceutics

Mother Teresa College of Pharmacy, Ghatkesar, NFC Nagar

Hyderabad, Telangana, India.

E-mail: nagamanikamminana88@gmail.com

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INTRODUCTION:

The major challenge in the development of an oral sustained release drug delivery system is not just to sustain the release of drug but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [1]. Gastro-retentive drug delivery systems have gained significant interest in the past few decades. Most of the conventional oral delivery systems have shown some limitations related to fast gastric-emptying time [2]. Garg and Gupta [3] classified the gastro-retentive dosage forms into four main classes: (A) floating systems [4], (B) expandable systems [5], (C) bioadhesive systems [6] and (D) high density systems [7]. Floating systems are of two types: (i) effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids, and (ii) non-effervescent systems. The latter systems can be further divided into four sub-types, including hydrodynamically balanced systems [8], microporous compartment systems [9], alginate beads [10] and hollow microspheres or microballons [11]. In addition, super-porous hydrogels [12] and magnetic systems [13]. In floating dosage forms (FDs), the dosage form remains buoyant on the gastric fluid when the stomach is full. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be due to passage of the dosage form through the pylorus into the small intestine. Thus, the buoyancy of floating dosage form in the stomach may be limited to only 3–4 h. Furthermore, FDs do not always release the drug at the intended site. In a bioadhesive drug delivery system, the mucous secreted by the mucosa lining of stomach wall may detach the drug from stomach wall due to high mucous turnover. Then the detached tablet may emptyed from the stomach along with its contents [14]. A floating-bioadhesive drug delivery system (FBDDS) would overcome these drawbacks of floating and bioadhesive systems and would have a significant effect on improving the therapeutic effect of the drug involved [15].

Risedronate sodium (RS) is a potent pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. In preclinical studies, risedronate demonstrated potent anti-osteoclast and anti-resorptive activity, increasing bone mass and biomechanical strength. It is a third generation bisphosphonate and is relatively rapidly absorbed from the upper gastrointestinal (GI) tract with a short biological half-life of 1.5 h [16]. Due to these characters it is considered as a potential candidate for development of floating-bioadhesive drug delivery system.

MATERIALS:

Table 1: Materials used

S.NO	MATERIALS USED
1	Residronate sodium
2	NaCMC
3	Guargum
4	Sodium bicarbonate
5	MCC
6	Magnesium stearate
7	Talc

METHODOLOGY:

Preformulation Studies

It is one of the critical essential being developed of any medication conveyance framework. Preformulation ponders were performed on the medication, which included dissolving point assurance, solvency and similarity contemplates

A) Determination of liquefying point

Softening purpose of Residronate sodium was dictated by fine technique.

B) Solubility

Solvency of Residronate sodium was resolved in water, 0.1N HCl, essentially insoluble in water dissolvable in warm water and solvent in liquor.

C) Compatibility Studies

One of the prerequisite for the choice of appropriate excipients or transporter for pharmaceutical definition is its similarity. Thusly in the present work an examination was done by utilizing FTIR spectrometer to see whether, any conceivable substance connection of Residronate sodium with NaCMC and GUARGUM.Compatibility with excipients was acclimated via completed FTIR considers.

Fourier change infrared spectrometry (FTIR):

Compatibility investigation of medication with the excipients was controlled by I.R. Spectroscopy (FTIR) utilizing Perkin Elmer range RX1 FT-IR spectrometer show. The pellets were set up at high compaction weight by utilizing KBr and the proportion of test to KBr is 1:100.The pellets subsequently get ready were inspected and the spectra of medication and different fixings in the plans were contrasted and that of the first spectra.

Planning of Standard Calibration Curve of Residronate sodium

Stock Solution:

100 mg of Residronate sodium was broken down in 100 ml of 0.1 N HCL, in order to get a stock arrangement of 1000 µg/ml fixation.

Standard Solution

5 ml of stock arrangement was made to 100 ml with 0.1N HCl, along these lines giving a centralization of 50 g/ml. Aliquot of standard medication arrangement running from 1 to 10ml were moved in to 10 ml volumetric carafe and were weakened sufficient with 0.1N HCl. Along these lines the last fixation ranges from 10-50 g/ml. Absorbance of every arrangement was estimated at 262.0 nm against 0.1N HCl as a clear. A plot of centralizations of medication versus absorbance was plotted.

Schematic Representation

100 mg of unadulterated 0.1 N HCL 100 ml (1 mg/ml)

Residronate sodium with 0.1 N HCL

5 ml 100 ml (50 µg/ml)

2ml,4ml,6ml,8ml.10ml was exchanged to 10ml volumetric jar and make up upto 10ml with 0.1 N HCL to give 10 µg/ml,20 µg/ml,30 µg/ml,40 µg/ml,50 µg/ml.

Detailing Of Floating Tablets:

Gliding lattice tablets containing Residronate sodium was set up by Direct pressure strategy utilizing variable groupings of NaCMC and GUARGUM with sodium bicarbonate.

Every one of the fixings were mixed in glass mortar consistently. Blended every one of the fixings and the granules were straightforwardly packed into tablets utilizing 13mm punch in a Mega rotating punching machine.

Sythesis of drifting tablet of Residronate sodium (in mgs)

Table 2:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Residronate sodium	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Guar gum	40mg								25mg	25mg
xanthane gum			25mg	13mg	35mg	35mg	35mg	35mg		
colacassia		2mg					5mg			5mg
Fenugreek					5mg				5mg	
Rumex						5mg				
cocsinia								5mg		
HPMC4M		30mg		25mg						
Citric acid	10mg	8mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
NaHCO3	10mg	8mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg	15mg
Ethylcellulose	28mg	40mg	38mg	25mg	23mg	23mg	23mg	23mg	33mg	33mg
Talc	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg

RESULTS AND DISCUSSION:

In order to achieve the improvement of antagonistic to rheumatoid estimation shapes Residronate sodium was used as a model drug. Floating tablets were characterized by direct weight procedure using guargum and sodium carboxy methyl cellulose and microcrystalline cellulose in different extents for upheld the appearance of medicine, and Magnesium stearate and Talc as oil and glidant.

In the current assessment definitions (F1-F8) were set up by using NaCMC,GUARGUM with different assessments and microcrystalline cellulose.To know the segment of drug release from these subtleties, the data were fitted in various engine models like zero solicitation plot, first-mastermind plot, Higuchi's plot, and Korsmeyer condition/Peppa's model et al's conditions.

The results related to physicochemical and invitro appraisal of oral bolstered Preformulation Studies:

I) Melting point confirmation

Relaxing motivation behind Residronate sodium was seen to be in the range 252-262°C which assented to I. P. rules, demonstrating flawlessness of the medicine test.

ii) Solubility

Residronate sodium is really dissolvable in warm water .It is dissolvable to the degree of one segment in to three areas of water and one a major part in ethanol.

iii) Compatibility Study

(a) FTIR consider

The FT-IR Spectrum of Residronate sodium unadulterated drug was differentiated and the FT-IR scope of physical mix of Residronate sodium (Residronate sodium, NaCMC, GUARGUM and MCC). There was no appearance or disappearing of any characteristics tops. This exhibits there is no substance cooperation between the prescription and the polymers used in the tablets. The proximity of peaks at the ordinary range confirms that the materials taken for the examination are genuine.The brand name absorbition apexes of Residronate sodium were procured at cm-1 and cm-1

The apexes gained in the spectra of each itemizing compares with the zeniths of prescription range. This shows the drug was acceptable with the definition parts.

SPECTRUM OF RESIDRONATE SODIUM:

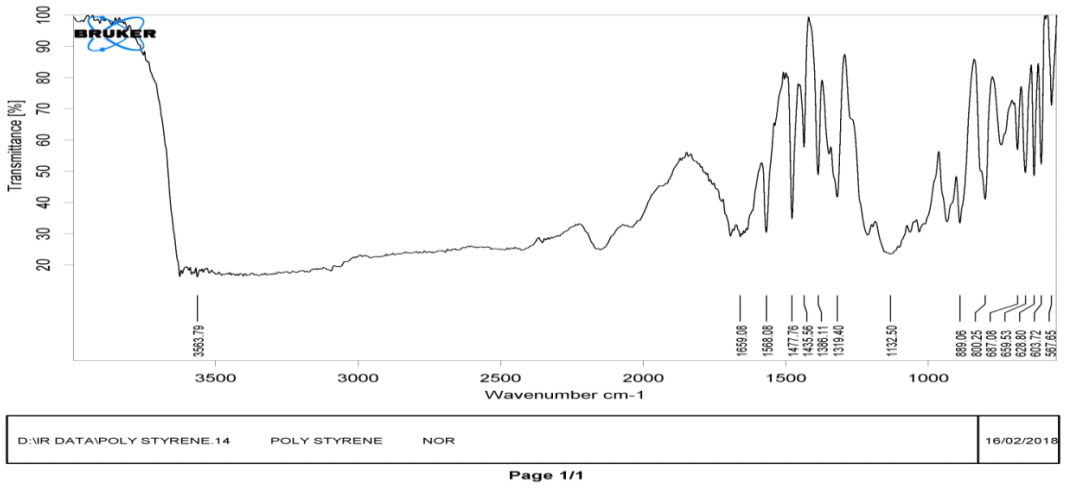


Fig:1 FTIR(KBr) SPECTRUM OF GUARGUM POLYMER

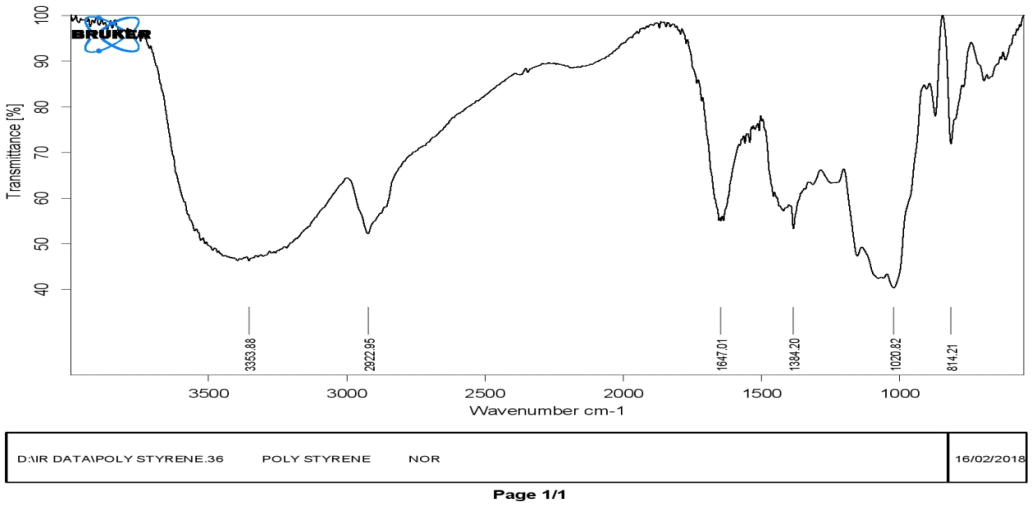


Fig:2 FTIR(KBr) SPECTRUM OF NACMC POLYMER

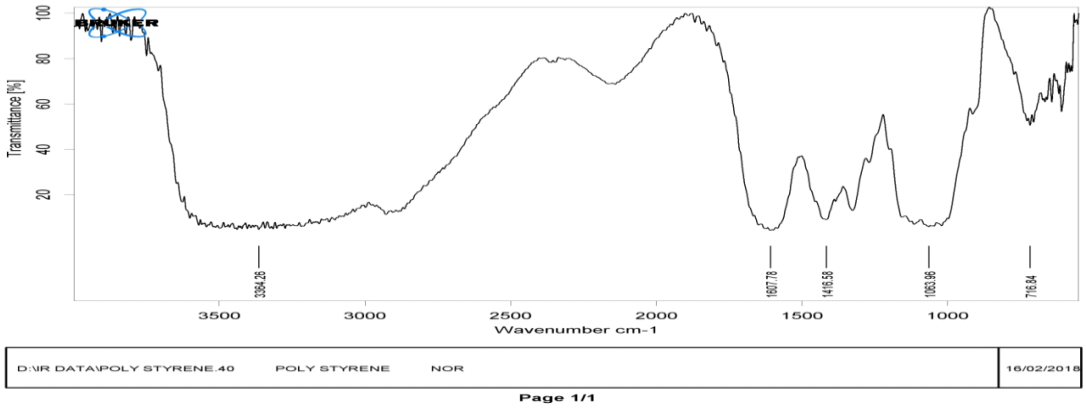


Fig:3 FTIR(KBr) SPECTRUM OF RESIDRONATE SODIUM+NACMC

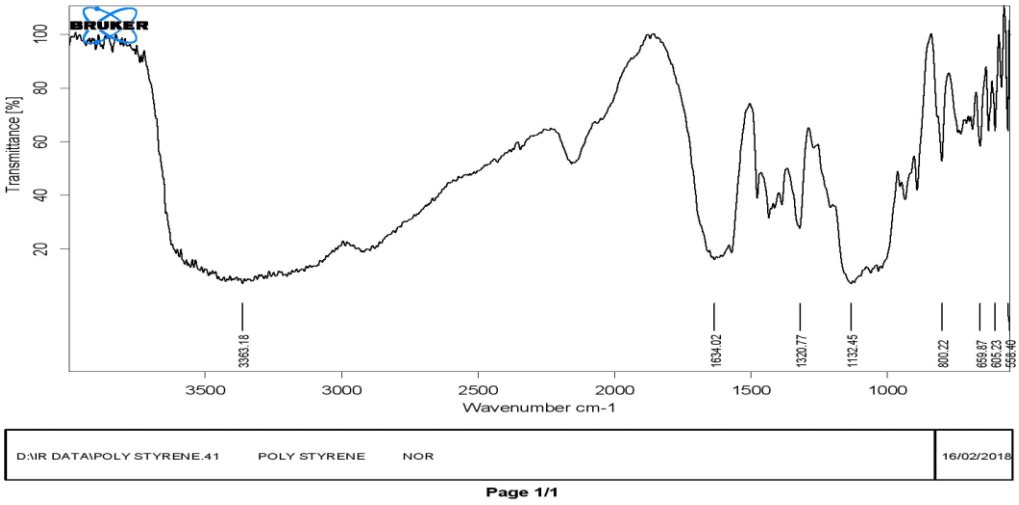


Fig:4 FTIR(KBr) SPECTRUM OF RESIDRONATE SODIUM+GUARGUM

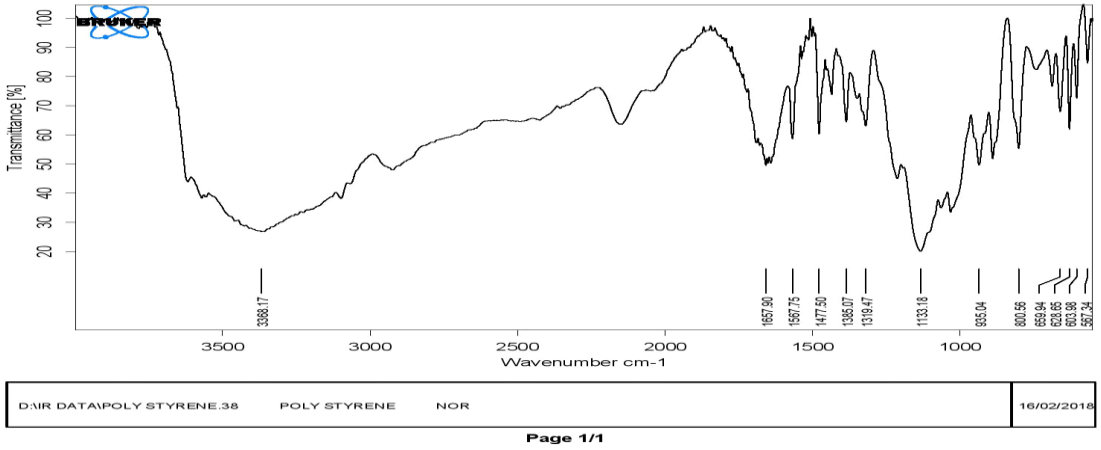
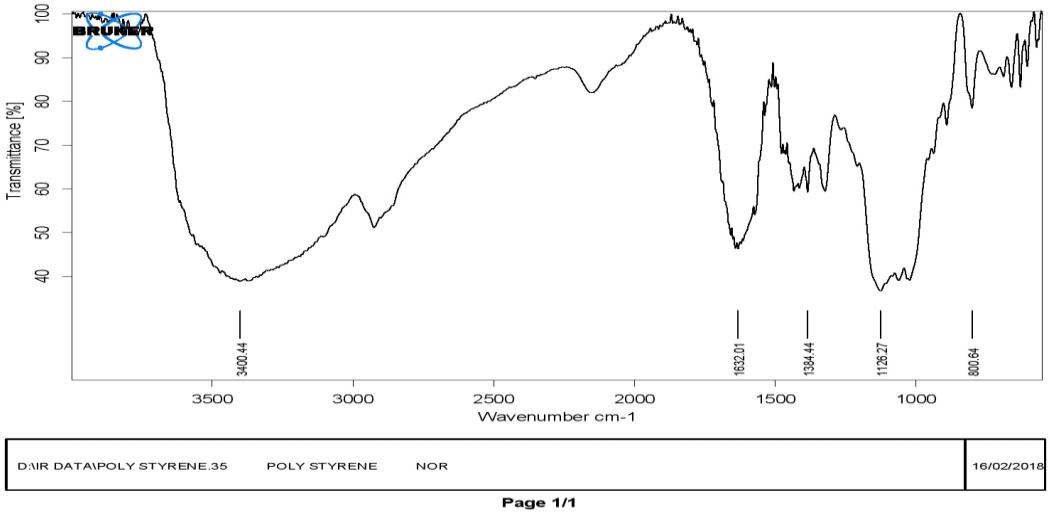


Fig:5 FTIR(KBr) SPECTRUM OF RESIDRONATE SODIUM+GUARGUM+NACMC



Standard calibration curve of Residronate sodium:

Standard Curve of Residronate sodium was determined by plotting absorbance (nm) versus concentration /at 262 nm and it was found to follow the Beer's law in the range 10 – 50 . The results obtained are as follows: -

Table No.3

S. No.	Concentration	Absorbance (262 nm)
	0	0
	10	0.219
	20	0.353
	30	0.479
	40	0.591
	50	0.695
Slope		0.119
Regression		0.9972

The linear regression analysis was done on absorbance data points. A straight-line equation was generated to facilitate the calculation of amount of drug. The equation is as follows.
(Y = mx+c)
where Y = Absorbance, m = slope, x = Concentration, c = Intercept.

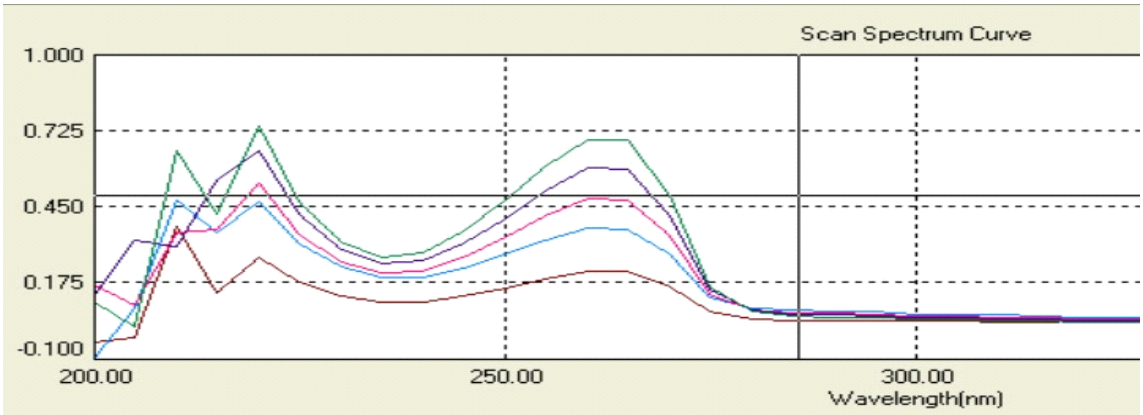


Fig:6: Evaluation of floating tablet formulations

1. Pre-compression parameters
The granules of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, and Hausner's ratio. The results of these evaluations are as follows

a) Angle of Repose *()*
The angle of repose for the formulated blend was carried out and the results were shown in the table. It concludes the entire formulation blend was found to be in the range 23° 8" to 27°8"The values are in table no .12.

b) Bulk density and tapped density
Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.322±0.039 to 0.388±0.042 and 0.38 ± 0.24 to 0.45 ± 0.032 respectively. (Table No.12).

c)Compressibility Index
Compressibility index was carried out, it found between 15.26±0.6 to 13.77±0.39 indicating the powder blend have the required flow property for compression. The values are mentioned in table no .12.

d) Hausner's Ratio
The Hauser ratio ranged from 1.12to 1.55 (Table No.12). The result indicates the free flowing properties of the granules.

Table no:4

Formulation	Bulk density(g/cc)	Tapped dencity(g/cc)	Carr'sindex(%)	Hausner ratio	Angle of repose(θ)
F1	0.598	0.706	15.29745042	1.180602007	25.64
F2	0.601	0.71	15.35211268	1.181364393	26.61
F3	0.624	0.678	7.96460177	1.086538462	24.7
F4	0.612	0.731	16.27906977	1.194444444	28.22
F5	0.598	0.698	14.32664756	1.16722408	26.56
F6	0.614	0.71	13.52112676	1.156351792	28.22
F7	0.616	0.72	14.44444444	1.168831169	27.51
F8	0.602	0.731	17.64705882	1.214285714	25.45
F9	0.623	0.701	11.12696148	1.125200642	26.56
F10	0.624	0.701	10.98430813	1.123397436	25.55

Physical Evaluation of tablets:
The results of the uniformity of weight, hardness, thickness and friability, the tablets are given in Table .All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied with in the limits.The hardness of the tablets ranged from 5.3- 5.24kg/cm^3 and the friability values were less than 0.43% indicating that the floating tablets were compact and hard. The thickness of the tablets ranged from 5.2-5.4mm.Thus all the physical attributes of the prepared tablets were found be practically within control.

Drug content determination:
The results of the drug content of the tablets are given in table.All the tablets of different batches complied with the official requirements.All the formulations satisfied the content of the drug as they contained 97.2%-101.1%Residronate sodium and good uniformity in drug content was observed.

Table no:5 Drug content determination

Formultn	%drug content
F1	73.54771784
F2	83.92116183
F3	94.29460581
F4	91.70124481
F5	78.73443983
F6	89.10788382
F7	99.4813278
F8	85.47717842
F9	89.10788382
F10	79.25311203

Fig 20 Drug content determination

Invitro buoyancy studies

Table no: 6

FORMULATION	floating time sec	Total floating time(hr)
F1	40	>16
F2	45	>16
F3	70	>24
F4	60	>20
F5	52	>20
F6	31	>18
F7	11	>8
F8	17	>12
F9	65	>24
F10	16	>12

Swelling index:
Swelling study was performed on all the batches(F1 to F8) for 5hr.From the results it was concluded that Swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer.The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface.As the gelatinous layer progressively dissolves/dispersed, the hydration swelling release process is continuostowards now exposed surfaces,thus maintaining the integrity of the dosage form.In the present study,the higher swelling index was found for tablets of batch F1containing combination of guargum and sodiumcarboxy methyl

cellulose (1:1).Thus the viscosity of the polymer had major influence on swelling process,matrixintegrity,as well as floating capability,hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

Swelling studies
Table no 7:

TIME(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	185	226	134	189	198	172	180	150	166	174
2	231	264	233	223	252	193	199	193	205	225
3	257	313	241	268	292	225	236	260	250	265
4	291	325	273	263	300	267	280	299	289	290
5	331	326	294	270	332	290	320	310	301	296
6	335	356	325	279	356	320	333	324	312	302

Formulation code	**Initial weight(Gm)**	**Final weight(gm)**	**F-I/I**	**SWELLING INDEX**
F1	0.080	0.402	4.125	412.5
F2	0.1	0.300	2.001	200.1
F3	0.095	0.230	1.4210526	142.10526
F4	0.2	0.277	3.85	385
F5	0.2	0.275	3.75	375
F6	0.2	0.245	2.25	225
F7	0.097	0.355	2.659793	265.9793
F8	0.098	0.420	3.2857142	328.57142

Swelling index = (final weight-initial weight /initial weight)*100
In vitro drug release data for Residronate sodium floating tablet

Formulation (F1-F8) Table no:15

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	4.04±1.15	6.50±1.0	1.78±1.09	4.02± 1.03	1.78±1.15	5.58± 1.09	7.40±1.03	4.52± 1.07
2	11.65± 1.06	9.15±1.04	6.05±1.08	9.85±1.14	7.40±1.05	12.02±1.05	14.05±1.03	6.86± 1.05
3	16.47± 1.09	20.7±1.1	11.67± 1.02	17.36±1.18	18.26±1.03	21.02±103	19.25±1.02	10.03±1.09
4	30.26± 1.07	31.3±1.15	19.2±1.03	21.12±1.04	22.19±1.12	21.96±1.07	29.22±1.06	19.34±1.04
5	30.87± 1.36	41.61± 1.01	22.2±1.08	35.68±1.01	30.18±1.1	31.81±1.06	31.43±1.01	20.21±1.06
6	41.03± 1.14	51.2±1.09	35.1±1.06	41.81±1.06	41.08±1.06	42.73±1.08	45.06±1.02	31.88±1.04
7	51.1±1.08	60.3±1.03	41.8±1.05	51.85±1.05	42.21±1.09	51.14±1.07	51.5± 1.05	50.56±1.01
8	60.34± 1.03	61.6±1.13	51.17± 1.04	62.97±1.02	51.26±1.07	60.37±1.03	60.84±1.03	61.03±1.03
9	70.86± 1.05	71.06± 0.89	54.24± 1.02	72.52±1.09	61.37±1.05	67.03±1.05	62.47±1.04	77.73±1.02
10	81.28± 1.36	81.8±1.06	80.66± 1.03	81.99±1.01	70.89±1.02	71.73±1.02	68.64±1.06	71.31±1.06
11	90.47± 1.14	89.6±1.12	85.65± 1.09	87.15±1.06	71.1±1.01	82.01±1.03	79.88±1.02	92.16±1.09
12	95.01± 1.09	94.04± 1.02	88.1±1.14	98.04±1.02	88.85±1.05	99.05±1.02	95.27±1.01	97.31±1.09

Drug release profile:

- The data obtained from in vitro dissolution studies of all 8 formulations
- The optimized formulation F6 containing maximum concentration of NaCMC,medium concentration of Guargum powder shows the better sustained release effect and cumulative percentage drug release 96.05% at the end of 12hrs.

- The formulation were prepared mainly with NaCMC and Guargumpolymers.Both polymers were chosen as they are well established in the similar studies and have good swelling and sustained release properties respectively.
- Sodium bi carbonate is added to the formulation has gas generating agent.
- The formulation up on contact with HCL liberates CO2 and expels from the dosage from creating pores through which water can penetrate into dosage from and the rate of wetting of polymer increases.

Table -9

Time	AMT in 1ml	AMT in 900ml	loss to be added	Total	%drug release
1	0.004573	4.115353	0.009602	4.124954	41.24954
2	0.003079	2.770954	0.008855	2.779809	27.79809
3	0.003784	3.405809	0.008232	3.414041	34.14041
4	0.005402	4.862241	0.014041	4.876282	48.76282
5	0.006896	6.206639	0.01429	6.220929	62.20929
6	0.009635	8.671369	0.009635	8.681004	86.81004
7	0.00312	2.808299	0.009394	2.817693	28.17693
8	0.009054	8.148548	0.009054	8.157602	81.57602
9	0.008639	7.775104	0.008639	7.783743	77.83743
10	0.008639	7.775104	0.008639	7.783743	77.83743

Invitro Kinetic plots for Formulation 6:
Table -10

Time (hrs)	**Root T**	**Log time**	**Cum % of drug release**	**Log cum % of drug release**	**Cum % of drug retained**	**Log cum % of drug retained**
0	0	0	0	0	100	2
1	1	0	5.88	0.769377	94.12	1.973682
2	1.4	0.151	11.8	1.071882	88.2	1.945469
3	1.7	0.239	22.02	1.342817	77.98	1.891983
4	2	0.301	28.96	1.461799	71.04	1.851503
5	2.2	0.349	36.81	1.565966	63.19	1.800648
6	2.4	0.389	44.7	1.650308	55.3	1.742725
7	2.6	0.423	56.94	1.755417	43.06	1.634074
8	2.8	0.452	63.37	1.801884	36.63	1.563837
9	3	0.477	69.03	1.839038	30.97	1.490941
10	3.2	0.5	74.73	1.873495	25.27	1.402605
11	3.317	0.521	83.01	1.91913	16.99	1.230193
12	3.5	0.54	93.05	1.968716	6.95	0.841985

The kinetic data showed that the release of drug followed dissolution-controlled mechanism for theformulations.In vitro release profiles could be best expressed by Zero order release kinetics as all formulations showed good linearity.

Table 11:

Release Pattern	R^2 value	n value
Zero order release	0.964	-
First order release	0.877	-
Higuchi model	0.920	-
Korsmeyer'speppas	0.895	2.85

SUMMAY AND CONCLUSION:

Supported release bubbly and non bubbly skimming tablets of Residronate sodium were set up by using different gathering of low thickness polymers.

- The powders blends of all plans were depicted concerning purpose of rest ,mass thickness, tapped thickness ,Carr's rundown and Hausner'sratio.Thus all the physical properties of the prepared powder blend were found be in every practical sense with in control.
- The masterminded tablets were depicted by consistency of weight, hardness, thickness,friability and medicine substance of all the tablets.Thus,all the physical properties of the prepared tablets were found be in every practical sense with in control.
- The in-vitro softness consider was finished in 0.1N HCL using USP gadget 2.The definition F6 showed 96.05% release in 12hrs and saw to be sensible to use in skimming tablets.
- The invitro delicacy contemplate was accomplished for the prepared tablets.Sodiumbicarbonate,microcrystalline cellulose powder offered gentility to extend the upkeep of the oral estimation shape in the stomach.
- The sedate release vitality was dismembered through the various numerical models and it was found that zero solicitation release vitality was fit to these upheld release floating tablets.
- Drug-excipient similitude considers were finished by FIIR spectroscopy. No prescription polymer affiliation was found in the FT-IR spectra of the powder mix of cutting edge plan.

Inferable from its phenomenal hydrophobicity and low thickness, Gelucire 43/01 may be seen as a reasonable carrier for organizing upheld release drifting medication transport structures of risedronate sodium. SEM, HSM, DSC showed that developing of Gelucire 43/01 is accountable for an extension in prescription release. Further undertakings are required to adjust Gelucire 43/01 in the midst of developing.

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