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FORMULATION, DEVELOPMENT AND EVALUATION OF SUSTAIN RELEASE GASTRORETENTIVE TABLETS USING NOVEL NATURAL POLYMER

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Abstract:
Different formulations of floating gastroretentive tablets were prepared by using Xanthan gum, Gellan gum, Chitosan and Carbopol 940 P, Sodium bicarbonate, Citric acid and evaluated for pre compression and post compression parameters. The average weight of each formulation was recorded. The obtained data were almost uniform. The values of tablets average weight ranging from 245±5 to 258±1 mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight. The % drug content of all the formulated tablets were found within the limit. % drug content value of Rosiglitazone was within 98.12±0.45% to 99.45±0.32%.The results within the range indicate uniform of mixing. When the regression coefficient values of were compared, it was observed that 'r^2' values of Peppas was maximum i.e. 0.956 hence indicating drug release from formulations was found to follow Peppas release kinetics.

Key words: *Rosiglitazone, floating gastroretentive tablets, Sustain release, Natural polymers*

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INTRODUCTION

The major objective of oral controlled drug delivery system is to deliver drugs for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine. An Ideal drug delivery system should possess two main properties:

(1) It should be a single dose for the whole duration of the treatment.

(2) It should deliver the active drug directly at the site of action [1].

Gastroretentive drug delivery system (GRDDS) is one of the novel approaches in this area. Oral controlled release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems [2].Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT [3].

Poor absorption of many drugs in the lower GIT necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly the stomach and upper small intestine [4]. These drug delivery systems suffer from mainly two adversities: the short gastric retention time(GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine)leading to diminished efficacy of administered dose [5].To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery.

GRDDS are thus beneficial for such drugs by improving their bioavailability, therapeutics efficacy and possible reduction of the dose and improves the drug solubility that is less soluble in a high pH environment [6]. Apart of these advantages, these systems offer various pharmacokinetics advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels [7].

Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also prolonged gastric retention time in the stomach could be advantageous for local action in the upper part of the small intestine.

Diabetes mellitus Type-II (formerly called non-insulin-dependent diabetes mellitus (NIDDM) or adult - onset diabetes) is a metabolic disorder which is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Rosiglitazone maleate (±)-5-[[4-[2 (methyl-2-pyridinylamino) ethoxy]-phenyl] methyl]-2, 4-thiazolidinedione, (Z)- 2-butenedioate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. It is effective only in the presence of insulin. It decreases insulin resistance at peripheral sites and in the liver. This results in insulin-dependent glucose disposal and reduced hepatic glucose output. The half-life of Rosiglitazone maleate is 3-4 h and it reaches a peak plasma concentration after 1 h. It is highly soluble in 0.1 mol/l HCl (11.803 mg/ml) and its solubility decreases with increasing pH over the Physiological range.

Natural polymers and their derivatives are routinely used for the production of newer dosage forms due to their compatibility with other materials, biodegradability, and chemical modification ability. Synthetic excipients induce undesired side effects in humans, hence natural polymers are favored. Herbal remedies are becoming increasingly safer to use, thus patients and researchers are looking for natural ingredients rather than synthetic or semi-synthetic polymers. The main objective of present investigation is to formulate the sustained release tablet of Rosiglitazone Maleate natural polymers like Xanthan Gum, Guar Gum, Chitosan or sodium alginate.

MATERIAL AND METHODS

Formulation of sustain release gastroretentive tablets of Rosiglitazone

Direct compression was taken after to manufacture the gastroretentive tablets of Rosiglitazone[8]. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in table no. 1 and all the

definition were utilized for encourage assessments parameters.

Optimization of sustain release gastroretentive tablets of Rosiglitazone

Optimization of formulation carried out on the basis of OVAT (One variable at time) using amount of excipient used like Excipients like Xanthan gum, Gellan gum, Chitosan and Carbopol 940 P.

Table 1: Formulations of Rosiglitazonesustain release gastroretentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosiglitazone	4	4	4	4	4	4	4	4	4
Xanthan gum	80	100	120	-	-	-	40	50	60
Gellan gum	-	-	-	80	100	120	40	50	60
Carbopol 940 P	-	-	-	-	-	-	20	20	20
Chitosan	30	30	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Lactose	96	76	56	96	76	56	76	56	36
Total Weight	250	250	250	250	250	250	250	250	250

Xanthan gum, Gellan gum, Chitosan and Carbopol 940 P, Sodium bicarbonate, Citric acid, Magnesium Stearate were selected for the examination. Sodium bicarbonate and Citric acid were utilized as gas generating agent. Drug and different excipients selected were gone through 40 mesh sieve. Required amount of drug and polymer were weighed and transfer into polyethylene pack and the mix was blended 15 min. In the mix add magnesium stearate and talc and again blended for another 5min.

Evaluation of Precompression Parameter [9-10]

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

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

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\text{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

Hausner's ratio value <1.25 shows better flow properties

Evaluation of sustain release gastroretentive tablets

All the tablets were evaluated for following various parameters which includes;

General appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated [11].

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined [12]. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at $\lambda_{max}$of 260 nm using of 0.1 N HCl as blank.

Hardness

For each formulation, the hardness of five tablets was resolved utilizing the Monsanto hardness tester [13].

Friability

The friability of a sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated [14].

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

***Invitro*buoyancy studies:**

*Invitro*buoyancywasdeterminedbyfloating lag timeasperthemethod describedby Rosa*etal*.Thetabletswere separately ina100 mlglassbeakercontaining simulated gastricfluid,pH1.2asperUSP.Thetime necessaryforthetablettoincreasetothe outside and float was determined as floatinglagtime [14].

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37±0.5$^{°C}$ and rpm of 75. One prepared Rosiglitazone tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37$^{°}$C) was supplanted each time with a similar amount of the sample and takes the absorbance at 260nm using UV/Visible spectroscopy.

RESULTS AND DISCUSSION:

Different formulations of floating gastroretentive tablets were praepared and evaluated for pre compression and post compression parameters.

The thickness of the tablets was reported in the micrometer (mm). The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (250mg). The value of thickness ranges between 3.1±0.2 to 3.3±0.2mm.

Friability determines the strength of the tablets. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friability test indicate that the tablet possesses good mechanical strength. The friability value ranges from 0.658±0.005 to 0.985±0.006.

The mean hardness values were measured for all the formulation using Monsanto hardness tester. The hardness value ranges from 7.1±0.2 to 7.4 ±0.2kg/cm^2.

Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was recorded. The obtained data were almost uniform. The values of tablets average weight ranging from 245±5 to 258±1 mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight.

The % drug content of all the formulated tablets were found within the limit. % drug content value of Rosiglitazone was within 98.12±0.45% to 99.45±0.32%.The results within the range indicate uniform of mixing.

Table 2: Result of pre-compression properties

Formulation Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.345	0.452	23.67	1.310
F2	0.352	0.461	23.64	1.310
F3	0.347	0.452	23.23	1.303
F4	0.352	0.453	22.30	1.287
F5	0.348	0.458	24.02	1.316
F6	0.365	0.478	23.64	1.310
F7	0.345	0.456	24.34	1.322
F8	0.365	0.472	22.67	1.293
F9	0.347	0.458	24.24	1.320

Table 3: Results of post compression properties of Rosiglitazone tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.1±0.1	7.2±0.1	256±4	0.708±0.007	99.05±0.15	>12
F2	3.2±0.2	7.1±0.2	245±5	0.658±0.005	98.85±0.25	>12
F3	3.2±0.2	7.0±0.1	248±2	0.745±0.003	98.78±0.31	>12
F4	3.1±0.1	7.3±0.2	258±1	0.712±0.005	97.95±0.15	>12
F5	3.2±0.1	7.2±0.2	256±7	0.698±0.004	98.12±0.21	>12
F6	3.3±0.2	7.2±0.1	253±4	0.985±0.006	99.03±0.17	>12
F7	3.2±0.1	7.4±0.2	257±1	0.674±0.004	98.65±0.15	>12
F8	3.2±0.2	7.3±0.1	256±2	0.854±0.003	99.85±0.016	>12
F9	3.1±0.2	7.2±0.1	255±2	0.712±0.002	98.14±0.25	>12

Table 4: Results of *in-vitro* buoyancy study of Rosiglitazone tablets floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	56±4
2.	F2	53±6
3.	F3	57±5
4.	F4	65±2
5.	F5	62±4
6.	F6	52±2
7.	F7	42±3
8.	F8	35±4
9.	F9	41±2

Table 5: *In-vitro* drug release study of sustain release gastroretentive tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	38.85	35.65	32.56	36.65	33.65	30.25	28.85	25.65	23.32
1	65.56	45.65	42.25	48.85	45.52	43.32	35.85	30.25	36.65
1.5	75.65	65.52	56.65	59.98	55.36	51.14	46.65	43.32	43.32
2	86.65	78.85	65.85	73.32	70.23	65.85	63.32	55.65	46.65
3	99.12	86.65	75.65	88.85	83.32	75.45	72.25	63.32	53.32
4	-	98.89	85.65	98.78	97.78	89.98	89.98	78.85	65.56
6	-	-	98.85	-	99.12	92.23	93.32	86.65	78.85
8	-	-	-	-	-	99.05	99.15	96.65	86.65
12	-	-	-	-	-	-	99.25	99.45	91.15

Table 6: *In-vitro* drug release data for optimized formulation F7

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	25.65	1.409	74.35	1.871
1	1	0	30.25	1.481	69.75	1.844
1.5	1.225	0.176	43.32	1.637	56.68	1.753
2	1.414	0.301	55.65	1.745	44.35	1.647
3	1.732	0.477	63.32	1.802	36.68	1.564
4	2	0.602	78.85	1.897	21.15	1.325
6	2.449	0.778	86.65	1.938	13.35	1.125
8	2.828	0.903	96.65	1.985	3.35	0.525
12	3.464	1.079	99.45	1.998	0.55	-0.260

Table 7: Regression analysis data of sustain release gastroretentive tablets

Batch	Zero Order	First Order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F8	0.814	0.985	0.930	0.956

CONCLUSION

Different formulations of floating gastroretentive tablets were praepared and evaluated for pre compression and post compression parameters,The*in vitro* drug release was carried out for formulation (F1, F2, F3, F4, F5, and F6 Formulation and release kinetics was calculated for optimized formulation F8. When the regression coefficient values of were compared, it was observed that 'r^2' values of Peppas was maximum i.e. 0.956 hence indicating drug release from formulations was found to follow Peppas release kinetics.

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