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FORMULATION AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE TABLETS OF SITAGLIPTIN

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Abstract : In the present study, Gastro retentive mucoadhesive drug delivery systems of sitagliptin, an anti diabetic drug, have been designed to increase the therapeutic efficacy & gastric residence time and to reduce frequency of administration. Therefore a sustained release medication was advantageous so as to achieve the prolonged therapeutic effect and to reduce peak and valley effect in plasma concentration. This can be achieved by formulating modified gastro retentive sustained release dosage forms which resides in the stomach for long period to release the drug in vicinity of the absorption zone. The tablets were prepared by direct compression method, by employing polymers like Carbopol 934P, HPMC K4M and PVP K30 in various concentrations. The triturated mixture of all ingreidents were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner"s ratio and results obtained were satisfactory compressed formulations were further evaluated for thickness, friability, hardness, swelling index, mucoadhesive study and in-vitro dissolution studies. All the formulations showed good results which were compliance with pharmacopoeial standards. In vitro dissolution study was carried out in pH 1.2 buffers. From in vitro dissolution studies, F15 showed very good drug release for long period.

Key Words : GRDDS, Mucoadhesive, Antidiabetic, Carbopol, HPMC K4M

Introduction : High level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of the dosage form. A lot of advancements have been seen in oral sustained drug delivery system in the last few decades. But still oral sustained drug delivery system is complicated by limited gastric residence time. Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract like mucoadhesive drug dosage systems . Gastroretentive systems can remain in the gastric region for several hours and hence can significantly prolong the gastric residence time of drugs that offer numerous advantages; improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine.(Deshpande *et al.*, 1996)(Rajput *et al.*, 2010)

The main objective of the study is to formulate Gastroretentive dosage forms (GRDFs) of sitagliptin in order to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. Gastroretentive dosage form (GRDFs) are designed on the basis of various approaches like, formulating high density (sinking) system that is retain in the bottom of the stomach. mucoadhesive system that cause bioadhesion to stomach mucosa, expandable, unflodable or swellable system which limits the emptying of dosage form through the pyloric sphincter of stomach, super porous hydrogels magnetic systems etc.(Murphy *et al.*, 2009)(Ahuja, Khar and Ali, 1997)

The gastroretentive tablets results in release of the drug in to the more absorptive regions of the GIT, is in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. This is achieved by adjusting the time period of release for the drug so that it is about the same as or less than the retention time of the tablets at the site of absorption. Thus the system is not transported past the "absorption window" prior to releasing the entire drug, and the maximum bioavailability is attained.(Lopes *et al.*, 2016)

Materials:

Sitagliptin as gift sample from Teva Pharma,Mumbai, India, and all other polymers used were of analytical grade.

Methods:

Precompression Parameters:

The various Pre-compression parameters are Angle of repose, Bulk density, Tapped density, compressibility index, Hausner‟s ratio and Carr‟s index were studied.

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in G/CC and is given by

Db= Mass powder/Volume

Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in G/CC and is given by
Dt =M/Vt
Where, M - Mass of the powder V t – Tapped volume of the powder

Angleof Repose: The accurately weighed quantities of granules were taken in to funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the granules. The granules were allowed to flowfreely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the formula.
Tan (θ) = h/r
Where h and r are the height and radius of the powder cone.

Carr's index (I) & Hausner's ratio: Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula.

C.I =(Dt – Db)100/Dt
Where, Dt – Tapped density of the powder Db

Preparation of Sitagliptin Tablet by Direct Compression Method

All the ingredients were passed through sieves separately and weighed as per the formula given in Table 1. Weighed ingredients were transferred into polythene bag and mixed for 15 minutes. After mixing thoroughly the powder is subjected for compression. The powder was evaluated for

various pre-compression parameters like bulk volume, tapped volume, bulk density, tapped density and angle of repose. After compression they were evaluated for appearance, diameter, tablet weight, thickness, hardness, and friability, uniformity of dispersion, weight variation, content uniformity and mucoadhesive strenght. The in vitro dissolution profile and stability studies were also carried out.(Tablets, 2015)(Agarwal and Murthy, 2015)

Table.1 FORMULATIONS CONTAINING & VARIOUS CONCENTRATIONS OF EXCIPIENTS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
DRUG	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
CARBOPOL	75	50	62.5	75	62.5	62.5	62.5	75	50	50	62.5	62.5	50	75	62.98
HPMC	35	35	35	50	20	50	35	20	35	20	20	50	50	35	50
PVP K-30	15	15	23.5	23.5	15	32	23.5	23.5	32	23.5	32	15	23.5	32	15
MCC	46	71	50	46	73.5	26.5	50	52.5	54	97.5	56.5	43.5	47.5	64	43.02
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Evaluation of sitagliptin controlled release tablets: The matrix tablets prepared were evaluated for the following parameters(Schneider, Koziolek and Weitschies, 2019):

1. **Weight Variation Test**: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.
2. **Hardness and Friability**: For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India) respectively.

3. **Drug Content**: Five tablets were weighed and triturate, from that transfer an accurately weighed portion of the powder equivalent to about 100mg of sitagliptin in a 100ml volumetric flask containing buffer solution and then concentration is measured at λ max 267 nm(Press, 2017).
4. **In-Vitro Dissolution Studies**: The in-vitro dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900ml of phosphate buffer pH 6.8, maintained at 37±0.50C. An aliquot (5ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer at 271nm. The study was performed in triplicate(Brahmandam, 2014).

5. **Mucoadhesive Strenght**: Mucoadhesion strength of the tablet was measured by using sheep stomach mucosa as model mucosal membrane. Fresh sheep stomach mucosa was obtained from a local slaughter house and was used within 2-3 h of slaughtering. The mucosal membrane was washed with distilled water and then with pH 1.2. The mucoadhesive strength measurement apparatus was fabricated locally as shown in to the Figure no The mucoadhesive strength of the tablets was determined using this locally fabricated apparatus. The weight at which the tablet was detached was recorded. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with phosphate buffer and left for 5 minutes before placing a new tablet to get appropriate results for the formulation(Yadav, Gaikwad and Gaikwad, 2013).

6. **Swelling Index**: The swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle results to saturation of capillary spaces within the particles. The liquid enters the particles through pores and bind to large molecule breaking the hydrogen bond and resolution in the swelling of particle. One tablet from each batch was weighed and placed in a Petri plate containing 25 mL of pH 1.2 buffer solution. After each 2 hrs interval the tablet was removed from plate, removes excess of buffer by using filter paper and weighed again up to 24 hrs. The swelling index was calculated using following formula(Singh and Goswami, 2015).

$$\text{Swelling Index} = \frac{Wt - Wo}{Wo} \times 100$$

Where, Wt = Weight of tablet at time t

Result and Discussion

Pre-compression evaluation parameters: For each type of formulation the active pharmaceutical ingredients and excipients was formulated and evaluated for various pre- compression parameter as explained earlier. The Bulk density was found in the range of 0.44 to 0.47G/CC and the tapped density was found to be in the range of 0.47 to 0.53 G/CC. Using the above two density data, the Carr"s compressibility index were calculated, the compressibility index was found to be in the range of 10.41 to 16.98% the compressibility and flow ability data indicated good flow properties for all the blended formulation. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 19.92 to 25.37. Angle of repose below 30º indicates good flow property. In the present study all powder blends showed good flow property. The results are shown in the Table

Table 2. Pre-compression evaluation parameters

BATCHES	BULK DENSITY	TAPPED DENSITY	HUSNERS RATIO	ANGLE OFREPOSE (Θ)	CARRS INDEX
1	0.44	0.51	1.15	$19^0.98'$	13.72
2	0.44	0.51	1.15	$18^0.92'$	13.72
3	0.46	0.53	1.10	$25^0.37'$	13.20
4	0.44	0.53	1.15	24˚.47′	16.98
5	0.45	0.53	1.17	23˚.98′	15.09
6	0.42	0.49	1.16	22˚.83′	14.28
7	0.45	0.52	1.15	22˚.53′	13.46
8	0.43	0.48	1.11	$21^0.69'$	10.41
9	0.42	0.49	1.16	$21^0.31'$	14.28
10	0.46	0.53	1.15	$20^0.43'$	13.20
11	0.42	0.47	1.11	20˚.93′	10.63
12	0.43	0.48	1.11	20˚.13′	10.41
13	0.44	0.51	1.15	19˚.89′	13.72
14	0.47	0.53	1.12	$19^0.98'$	11.32
15	0.45	0.51	1.13	$18^0.93'$	11.76

Post-Compression Parameters

1. **Shape of the tablets:**

Visually inspection of prepared all tablets were done. The shapes of the tablets were found to be good.

2. **Friability (F)**

Friability determines the strength of the tablets. The values of friability test were given in the Table no 7.7. 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 0.67 to 0.92

3. **Hardness:**

The mean hardness values were measured for all the formulation using Monsanto hardness tester. The results were tabulated in Table no 3. The hardness value ranges from 4.97± 0.032 to 6.93± 0.133 kg/cm^2.

4. **Weight variation:**

Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was recorded and is shown in Table no 3. The obtained data were almost uniform. The values of tablets ranging from 197.9± 1.786 to 199.8± 1.259 mg. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia's limits of ±7.5% of the weight.

5. **Thickness**

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 (200 mg). The average weight of each formulation was recorded in shown in Table no 3. The value of thickness ranges between 2.839± 0.026 to 3.129± 0.043 mm.

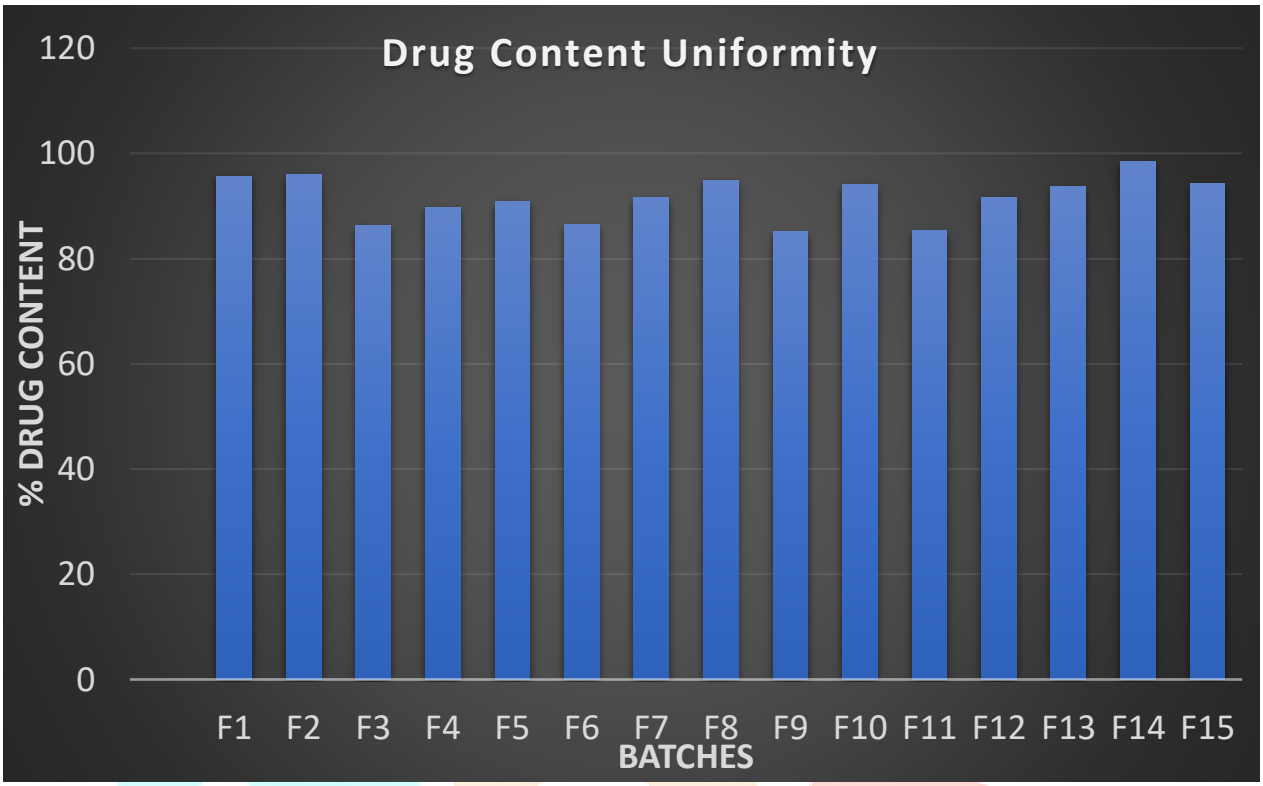
6. **Uniformity of drug content**

The % drug content of all the formulated tablets were found within the limit. % drug content value of Sitagliptin Phosphate was within 94.89± 0.886% to 97.89± 1.009%.The results within the range indicate uniform of mixing. The Table no 3. shows the % drug content in each formulation

Table 3. Pos-tcompressional parameters of formulations

Formulation Code	Friability (%)	Hardness Kg/cm^2	Weight Variation (mg) n = 20	Thickness (mm) (n=3) Mean±S.D	ug Content (%) (n=3) Mean±S.D
1	0.83	5.04	198.4	2.899± 0.083	95.66
2	0.74	4.97	198.7	2.879± 0.046	95.95
3	0.79	6.93	199.4	3.059± 0.019	86.25
4	0.88	6.42	199.5	2.969± 0.038	89.77
5	0.83	6.23	198.6	2.839± 0.026	90.86
6	0.87	6.29	198.9	2.929± 0.021	86.43
7	0.77	5.99	199	3.049± 0.039	91.72
8	0.88	5.85	198.9	2.969± 0.054	94.83
9	0.68	5.54	198.7	3.129± 0.043	85.11
10	0.87	5.35	197.9	2.919± 0.021	94.11
11	0.92	5.23	199.3	2.959± 0.047	85.35
12	0.67	5.14	198.6	2.999± 0.079	91.71
13	0.73	5.03	199.8	3.019± 0.033	93.66
14	0.83	5.04	198.4	2.899± 0.083	98.55
15	0.74	4.97	198.7	2.879± 0.046	94.23

Fig 1. Graph of Drug Content Uniformity



7. Swelling study

Swelling index was carried out for preliminary formulation. The swelling index of the tablets from each formulation (F1 to F15) was evaluated and the results are mentioned in Table no 4.

Table 4. % swelling index for polymer gum formulations

FORM. CODE	% Swelling index								
	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	1hr
1	54.54	60.78	64.91	67.21	68.25	69.23	68.25	69.69	54.54
2	53.48	62.96	66.10	68.75	68.75	69.69	70.14	70.14	53.48
3	50	64.25	65.51	67.21	68.25	68.75	69.23	69.23	50
4	52.38	64.28	65.51	67.21	68.75	69.69	70.14	71.12	52.38
5	58.33	64.28	64.21	66.66	67.21	68.25	68.75	68.75	58.33
6	53.48	64.28	67.24	70.58	71.42	71.83	72.60	72.60	53.48
7	54.69	60.78	63.69	66.66	68.75	69.23	69.23	70.58	54.69
8	51.21	56.52	62.96	68.25	67.21	67.74	67.74	70.23	51.21
9	54	62.96	66.10	68.25	69.23	69.69	70.14	72.10	54
10	52.38	60.78	62.96	64.28	66.66	67.21	69.74	70.25	52.38
11	53.48	60.78	69.36	64.9	65.51	67.21	67.74	70.11	53.48
12	54.54	62.96	66.66	68.25	69.39	70.14	71.58	72.59	54.54
13	60.78	62.96	66.10	68.75	69.23	70.14	70.58	70.58	60.78
14	47.36	55.55	58.33	62.96	63.63	64.28	68.91	71.83	47.36
15	53.48	60.78	66.10	68.72	70.64	71.12	72.55	73.14	53.48

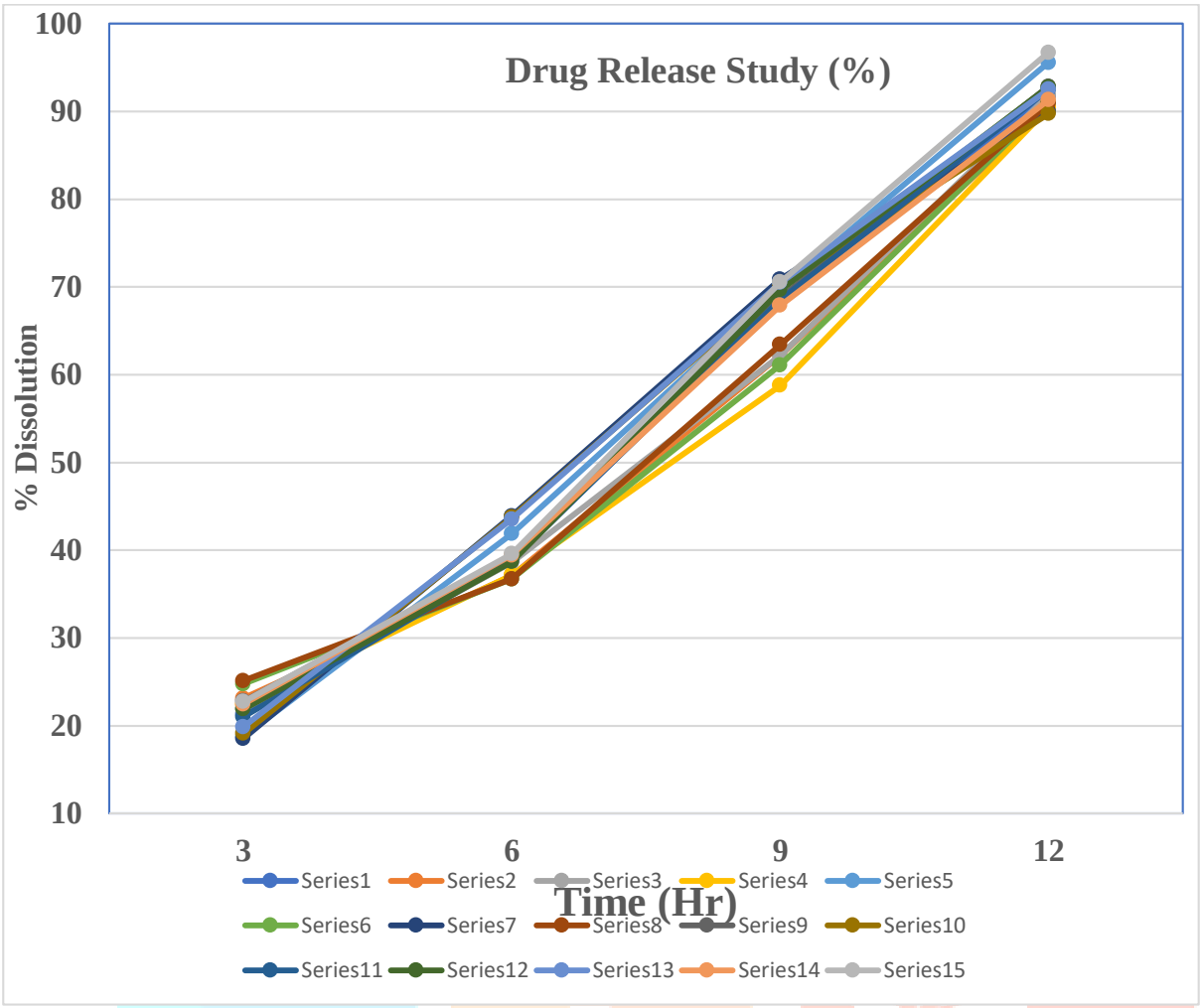
8. In Vitro Dissolution Study

In vitro drug release studies were performed by using USP XXIII dissolution test apparatus- II at 50rpm using 900 mL of 1.2 pH buffer maintained at 37±0.5ºC as the dissolution medium.The in vitro drug release profiles for the formulations were tabulated in Table no 5.

Table 5. % Cumulative drug release of Formulations (F1-F15)

Time(Hrs) / Sr.No	% DR – 3Hr	% DR- 6Hr	%DR-9Hr	%DR-12Hr
1	21.33	38.78	68.76	91.74
2	23.12	37.11	62.21	90.45
3	21.89	38.59	62.21	91.85
4	22.42	37.18	58.77	90.41
5	18.78	41.89	69.78	95.56
6	24.75	37.21	61.11	91.02
7	18.55	43.89	70.87	90.01
8	25.12	36.71	63.44	90.96
9	22.79	39.05	68.79	92.86
10	19.11	43.76	70.22	97.74
11	21.01	38.89	68.56	92.48
12	21.89	38.68	69.65	92.79
13	19.88	43.55	70.49	95.53
14	22.47	39.43	67.89	91.32
15	22.73	39.59	68.54	92.72

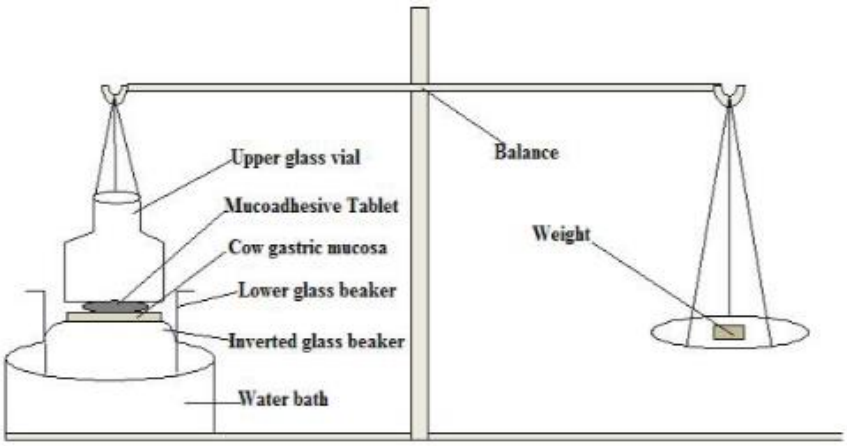
Fig 2. Dissolution Study Graph (F1-F15)



9. Mucoadhesive Study

In *vitro* mucoadhesive strength was carried out by using self-fabricated instrument. Results for *in vitro* mucoadhesive strength and force of adhesion were shown in Table no.6 (a) and 6(b).

Fig 3. Modified Physical Balance for calculating mucoadhesive strength



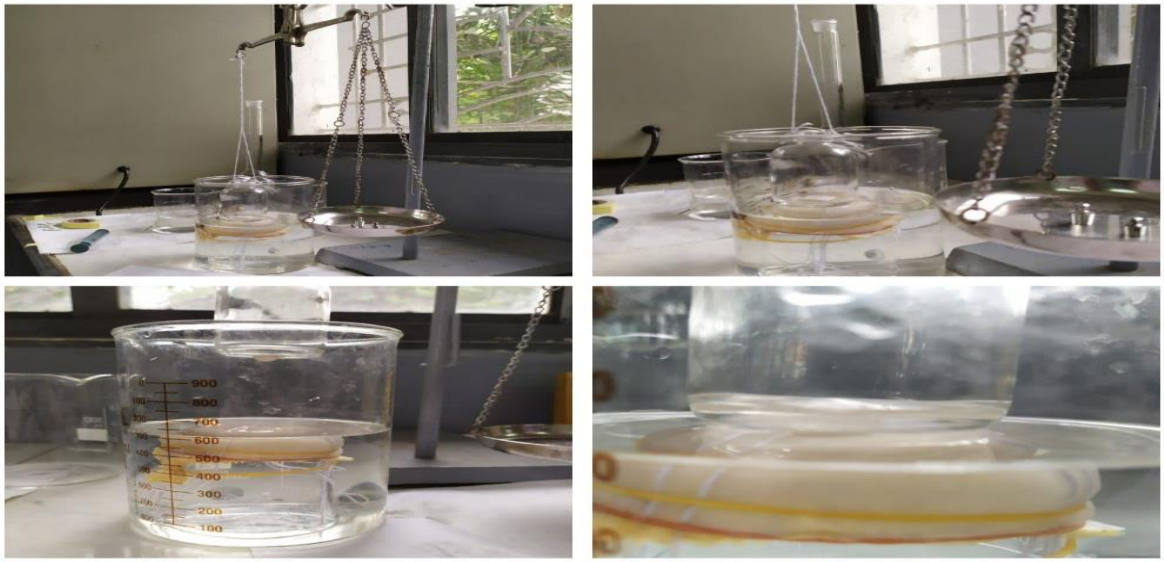


Table 6(a) : mucoadhesive strength of formulations(F1-F8)

Sr.No		F1	F2	F3	F4	F5	F6	F7	F8
Mucoadhesive strength	T-1	19.8	18.75	17.58	19.78	15.21	19.23	17.28	14.23
	T-2	18.9	18.66	17.54	19.35	15.45	19.01	17.53	14.66
	T-3	18.6	18.44	17.31	19.41	15.23	18.89	17.45	14.69

Table 6(b): mucoadhesive strength of formulations(F9-F15)

Sr.No		F9	F10	F11	F12	F13	F14	F15
Mucoadhesive strength	T-1	21.38	20.14	19.98	13.79	17.35	14.87	22.49
	T-2	21.10	19.68	19.56	14.22	17.98	14.44	22.86
	T-3	20.79	19.42	19.41	14.01	17.68	14.35	23.01

- **Conclusion** The formulations F1 to F14 batches were prepared using the mucoadhesive polymer for gastroretentive drug delivery to retain the dosage form in stomach. The results of in vitro evaluation subjected in to the Design Expert Software to obtain the optimized batch
- formulation F15 is obtained as the optimized batch and given better in vitro evaluation results. The dosage form showed the good mucoadhesive strength and drug release for longer time. The polymer Carbopol and HPMC in combination increased the mucoadhesive strength.

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