Formulation and evaluation of gastroretentive mucoadhesive tablets containing Repaglinide

Nilesh Kumar Upadhyay[1] , Dr Rakesh Kumar Meel[2]

Shridhar University
Chirawa-Pilani road, Jhunjhunu, Rajasthan

ABSTRACT

In this study, the antidiabetic drug repaglinide was formulated as a gastroretentive mucoadhesive tablet to increase its bioavailability. Hydroxypropyl methylcellulose K200M, carboxymethylcellulose sodium, carbomer 974P, karaya gum, chitosan and xanthan gum are used as mucoadhesive polymers in the tablet formulation. Various formulations have been prepared using different polymer concentrations. The angle repose, bulk density, tap density, Carr index and Hausner ratio of the pre-pressed mixture of repaglinide mucoadhesive tablets were characterized. The results showed that all formulations had a good swelling index. Flotation delay time and buoyancy studies showed that the formulation had good buoyancy. Drug release studies have shown that there is a controlled and improved drug release within 12 hours. In vivo studies have been conducted using well-known drugs. Based on in vitro drug release and related tests, the RT11 formulation with a drug:karaya gum ratio of 1:2 was optimized. The drug release of the RT11 formulation followed the Higuchi model with a regression value of 0.984.

Keywords: Repaglinide, Mucoadhesive tablets, gastroretentive, Mucoadhesive polymers.

DOI: 10.48047/ecb/2023.12.10.1011

INTRODUCTION:

The most satisfactory method of drug administration is oral route . At least 90% of the medication will be taken orally. In oral drug delivery, bioavailability is affected by the short duration of the drug within the absorption window. Oral medications represent the most popular mode of administration and sustained drug delivery, offering many advantages that minimize the

negative effects of conventional treatments. This type of drug delivery releases the drug at a fixed or variable release rates[1-3].

The digestion of the dosage form can be changed differently and the residence time of the dosage form is increased, ensuring that the dosage form remains in the stomach for a longer time than the normal drug form[4]. The most popular method of oral drug administration is the gastroretentive dosage form, which keeps the drug in the stomach for a long time and controls the residence time in the stomach [5]. GRDDS can be explained as a technological modification of how much information can be stored in the stomach for a long time by changing the digestive system and releasing the drug accordingly and subsequently metabolizing it[6]. In the current context, there are various ways in which GRDDS can improve GRT. The primary goal of developing GRDDS is to overcome problems associated with current oral and sustained-release formulations and develop effective drug delivery models for patients[7-9].

There are different parameters listed out which effects on the GRT affects the dosage form, the first being the "liquid level". Abdominal fluid is not constant. This creates a problem with the time it takes for GRDDS to float in the stomach and release the drug.[10] Gastroretentive drug delivery is effective for drugs that cause local effects in the stomach or are unstable due to lack of solubility and instability of alkaline pH. Narrow absorption window [11]. The size of GRDDS is smaller than fruit juice, so it can remain in the stomach for a long time without affecting the digestive system. Since it floats in the juice for a long time, the drug must be released slowly in the amount of form slowly[12]. Therefore, a new delivery system was developed together with flotation and mucoadhesion technology to overcome the problem of short-term gastric emptying. In this study, repaglinide, an anti-diabetic drug, was developed with different types of controlled release and different sizes of mucoadhesive polymers to improve the structure to help overcome the above problems.

MATERIAL AND METHODS:

Repaglinide was obtained from the supplier Triveni Chemicals. Polymers such as HPMC K200M13, sodium carboxymethylcellulose (NaCMC), Carbopol 974P, karaya gum, chitosan, xanthan gum and other pore expanding excipients such as sodium bicarbonate, magnesium stearate, talc, Lactose were also purchased from S.D Fine Chemicals. All excipients used are of laboratory quality.

Pre compression evaluation:[14,15]

Solubility Studies:

The solubility of repaglinide in 0.1 N HCl solution pH1.2 was examined by the phase equilibrium method. Add 10 mL of 0.1 N HCl (pH 1.2) in a 20 mL flask and remove excess solution. The vial was capped with a rubber cap and shaken using vacuum for 24 hours at room temperature. After 24 h, the solution was filtered through 0.2 μm Whatmann filter paper. The value of the solution is then determined using a UV spectrophotometer to obtain the absorbance at 281 nm. Prepare the repaglinide formula in 0.1 N HCl and estimate the solubility of repaglinide based on the slope of the calibration curve. This study was repeated three times (n = 3) and the average value was calculated.

Drug-excipient compatibility studies:
Fourier transform infra red spectroscopic studies:

Fourier Transform-Infrared Spectrophotometry was carried out to check drug-excipient compatibility by non-thermal analysis (binary mixture of drug:excipients in 1: 1 ratio). Spectra of the samples were recorded in the range of 450-4000 cm-1.

Pre-compression Evaluation:

Pre-formulation studies are a group of studies that include the physical and chemical properties of the drug and also support formulation and distribution guidelines for the selection of additives or excipients.

Compressibility index:

It is an important parameter that determines the tablet production method. It is determined by the apparent density of the particles. The compressibility index (compression ratio percentage) of the API is calculated by the following formula.

$I = (D_T - D_b / D_T)100$

Where, I = Compressibility index Dt= Tapped density of the powder D_b= Bulk density of the powder.

Hausner's ratio:

It takes into account the flow of the powder and is measured by the ratio of tap to density

$H = D_t / D_b$

Where, H =Hausner's ratio
D_t= tapped density of the powder D_b= bulk density of the powder.

Angle of repose:

It is the maximum angle between the center of the mass or powder and the horizontal plane. The tangent of the angle of repose is equal to the coefficient of friction of the object. It is expressed as

$\theta = \tan^{-1} (h / r)$

Where, θ= angle of repose; h = height in cm; r = radius in cm.

Preparation of Gastroretentive mucoadhesive tablets:[16]

Use of the direct compression method for the preparation of gastroretentive mucoadhesive tablets containing repaglinide. Various batches were created from different concentrations of HPMC K200M, Na CMC, Carbopol 974P, karaya gum, chitosan and xanthan gum. Sodium bicarbonate is used to improve the gastroretentive behavior of tablets. Talc and magnesium stearate are used as lubricants and lubricants. Lactose is used as a filler to control the volume of the preparation. Mix the drug, polymer, sodium bicarbonate and lactose evenly in a glass mortar for 15 minutes. This mixture is lubricated with talc and magnesium stearate. Mix the final powder thoroughly using a polyethylene bag. The mixture is then compressed using a 6 mm diameter die in a 9-station field press (Lab Press, India).

Table No. 1: The Composition of gastroretentive Mucoadhesive Tablets of Repaglinide

Ingredients	RT1	RT2	RT3	RT4	RT5	RT6	RT7	RT8	RT9	RT10	RT11	RT12	RT13	RT14	RT15	RT16	RT17	RT18
Repaglinide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K200 M	0.5	1	1.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Na CMC	-	-	-	0.5	1	1.5	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 974P	-	-	-	-	-	-	0.5	1	1.5	-	-	-	-	-	-	-	-	-
Karaya gum	-	-	-	-	-	-	-	-	-	0.5	1	1.5	-	-	-	-	-	-
Chitosan	-	-	-	-	-	-	-	-	-	-	-	-	0.5	1	1.5	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.5	1	1.5
NaHCO3	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Lactose	82.5	81.5	81	82.5	81.5	81	82.5	81.5	81	82.5	81.5	81	82.5	81.5	81	82.5	81.5	81
Total Weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Post- compression Evaluation:[17-19]

Physicochemical characterization of tablets:

Physical and chemical properties of the prepared repaglinide gastroretentive mucoadhesive tablets such as weight change, hardness, thickness, friability and chemical content were examined.

A. Weight variation:

A. Weight change:This test was done by selecting 20 tablets and measuring accuracy. Average tablet weight is obtained by dividing the total weight by 20. The weight of the tablets (maximum two tablets) should not differ from the average weight by ± 7.5%, and no tablet should differ by more than two percent.

% Deviation = (Individual weight – Average weight / Average weight) X 100

The average weight of tablets in each formulation was calculated and represented with standard deviation.

Table No. 2: Pharmacopoeia standards for the weight variation of tablet

Average weight of tablets(mg)	Maximum % of differenceallowed
80 or less	± 10
More than 80 but less than 250	± 7.5
250 or more	± 5

B. Tablet Thickness:

The thickness and diameter of the tablet are carefully controlled during the production process. The density of the packaging machine can be changed without changing the weight, as the density varies such as dense, dense, dense, dense, dense, dense, dense dense, dense, dense, dense, dense, dense, dense. Therefore, this measure is very important in terms of customer satisfaction, tablet uniformity and packaging.. The Digital Vernier caliper[20] was used to examine the thickness and diameter of the tablets. The tablets (10 tablets for each formulation) were randomly selected and the average values were calculated. The average thickness for tablet is calculated and presented with standard deviation.

C. Tablet Hardness:

Tablet hardness is defined as the force required to break a tablet in a diameter compression test. Tablets require a certain level of strength and resistance to brittleness to withstand any impact during handling, manufacturing, packaging and shipping. From every formulation tablets were taken (6 tablets) and hardness was determined using Monsanto hardness tester[21] and the average was calculated. It is expressed in Kg/cm^2.

D. Friability:

The hardness of a tablet is not a clear indication of firmness, as some formulations will loosen the plastic position during compression of the tablet drug. Therefore, an additional measure of the tablet, friability, was proposed to analyze the strength of the tablet. Decide to use the Roche friability tester. Tablets selected for testing are exposed to a combination of electronic devices (interference and damage) by placing the tablet 6 inches apart using a Roche crusher with a plastic chamber rotating at 25 rpm for 4 minutes. [22.] Place the pre-weighed tablets into a Roche brittle crusher and run at 25 rpm for 4 minutes. The tablets are then dusted and recycled.

$$\text{Friability (\%)} = \frac{\text{Initial weight of 10 tablets} - \text{final weight of 10 tablets (W)}}{\text{Initial weight of 10 tablets(Wo)}} \times 100$$

Where,
Wo is the initial weight of the tablets (Preweighed) W is the final weight of the tablets (Reweighed)

E. Assay[23]:

Tablets (6 per sample) were selected and the drug content in each tablet was determined. Take the powder equal to the weight of one tablet and dissolve it in 100 ml of 0.1N HCl by stirring for 10 minutes. Filter the above solution with a membrane filter (0.45μ) and measure the absorbance

of 281 nm of 0.1N HCl with a UV-visible spectrophotometer after appropriate dilution.

In vitro Buoyancy studies:

External buoyancy is determined by two parameters, namely swim time delay and total swim time. These were measured by placing the tablet in a 100 ml beaker containing 0.1 N HCl. Flotation lag time (FLT) is evaluated by measuring the time it takes for the tablet to float to the surface, and total floatation time (TFT) is determined by writing the tablet as it continues to float on the dissolution medium[11]

In vitro release studies:[24,25]

USP Type II dissolution tester is used to measure drug release from gastroretentive mucoadhesive tablets. In gastroretentive mucoadhesive tablets the drug needs to be released from one side, so to check in vitro digestion the non-adhesive film is placed on the other side of the tablet and then advanced onto a 2x2cm glass slide. cyano based. Acrylate Adhesive. It is then placed in the melting device. The separation medium was 900 ml pH 1.2 HCl buffer, paddle speed 50 rpm, and temperature 37 ± 0.5 °C. 5 ml samples are taken at different time intervals up to 12 hours, diluted appropriately and analyzed using UV. Spectrophotometer at 281 nm..

In vitro bioadhesion strength:

Measurement of bioadhesion of tablets using a mechanical strength testing device (Ultra Test Tensile Strength Tester, Mecmesin, West Sussex, United Kingdom) based on a microprocessor equipped with the highest dynamometer Adhesion strength. Adjust the 25 kg load cell. The pork membrane was firmly placed in the circular stainless steel adapter, and the gastroretentive mucoadhesive tablet (tablet model) was attached to another cylindrical stainless steel adapter in diameter using cyanoacrylate bioadhesive. Apply 100 µl of 1% w/v mucin solution to the mucosal surface and contact the tablet with the mucosa. After a while, the upper stent is removed at a speed of 0.5 mm/second until the tablet is completely separated from the mucosa. The area under the force distance curve helps determine the work of adhesion. Peak peel force is the highest force required to peel a tablet from the mucosa.

$$\text{Forec of adhesion} = \frac{\text{Bioadhesion strength}}{1000} \times 9.8 \text{ Force of adhesion}$$

$$\text{Bond strength} = \frac{\text{Force of adhesion}}{\ldots\ldots\ldots\ldots}$$

Surface area

Moisture absorption[26]:

Dissolve the agar (5% m/v) in hot water. Transfer it to the Petri dish and wait for it to freeze. Before study, gastroretentive mucoadhesive sheets (6 per design) were placed in a vacuum oven overnight to remove any moisture and then immediately laminated with non-recoverable film. Place the above tablet on the surface of the agar medium and incubate at 37°C for one hour. After an hour, take out the tablet and weigh it and calculate the percentage of moisture absorbed according to the following formula:

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} 100$$

Kinetic analysis of dissolution data[27,28,29]:

To analyze release data in vitro, zero-order model (drug released as a percentage of time), first-order model (drug released as a percentage of time function of time), Higuchi model – data % accumulation logarithm of drug release versus time.

In vivo studies - Pharmacokinetic studies:

The In vivo studies were carried out on male Wistar rats weighing range from 250-300gm. They were housed in polypropylene cages and had free access to food and water. The formulation for the test was formulated according to the doses of anti-diabetic drugs whichwere calculated as per the body weight of animals. The protocol for the animal study was approved by the Institutional Animal Ethical Committee (IEAC), which is recognized by Committee for the Purpose of Control and Supervision of Experiments on Animal (CPCSEA). The optimized Gastroretentive mucoadhesive matrix tablets were administered orally. Blood samples were collected within 24 hours of the scheduled sample collection time. Various pharmacokinetic parameters such as Cmax, Tmax, AUC determined[30,31].

RESULT AND DICSUSSION:

The solubility studies indicated that the drug is having less solubility in water as compared to methanol and 0.1N HCl.

Drug –Polymer Compatibility Studies by FTIR

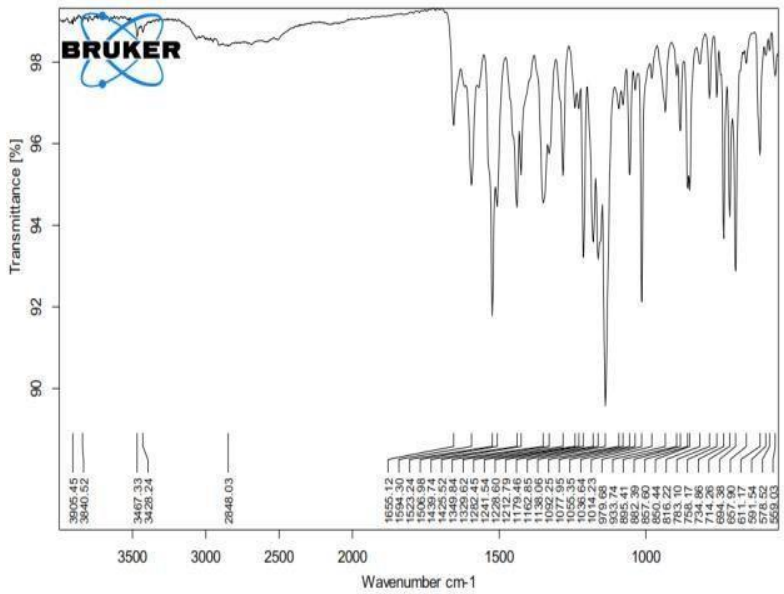

Figure No.1: FTIR of Repaglinide pure drug.

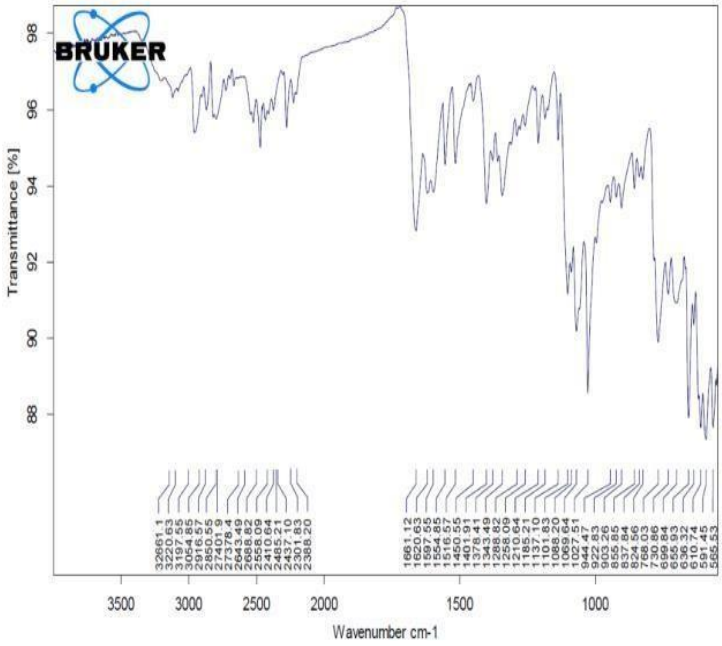

Figure No. 2: FTIR Spectra of Drug+Polymer Physical Mixture.

Pre-compression Evaluation:

Table No :3

FormulationCode	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
RT1	0.521± 0.003	0.501± 0.010	25.11± 1.63	9.32± 0.58	1.21± 0.25
RT2	0.56± 0.008	0.53± 0.009	26.25± 1.17	10.12± 0.47	1.06± 0.18
RT3	0.58± 0.006	0.63± 0.005	25.12± 1.68	10.18± 0.38	1.15± 0.22
RT4	0.53 ± 0.011	0.68 ± 0.016	26.13 ± 1.14	9.96 ± 0.57	1.10± 0.29
RT5	0.52 ± 0.002	0.62 ± 0.013	26.10± 0.99	10.5 ± 0.37	1.16± 0.17
RT6	0.736± 0.010	0.899± 0.008	22.29 ± 1.34	18.13± 0.64	1.20± 0.19
RT7	0.721± 0.06	0.910± 0.007	26.06± 1.48	20.77± 0.55	1.22± 0.25
RT8	0.701± 0.005	0.905± 0.015	31.09± 1.29	22.54± 0.48	1.21± 0.21
RT9	0.694± 0.009	0.852± 0.014	30.07± 1.57	18.54± 0.36	1.05± 0.18
RT10	0.664± 0.015	0.823± 0.013	27.08± 1.38	19.32± 0.34	1.07± 0.14
RT11	0.652± 0.009	0.807± 0.018	32.15± 0.88	19.21± 0.30	0.98± 0.16
RT12	0.662± 0.017	0.901± 0.009	37.39± 1.18	26.53± 0.42	0.95± 0.17
RT13	0.667± 0.012	0.907± 0.014	31.47± 1.47	26.46± 0.57	0.99± 0.21
RT14	0.624± 0.006	0.801± 0.019	31.09± 1.51	22.10± 0.34	1.10± 0.24
RT15	0.648± 0.001	0.862± 0.013	28.12± 1.42	24.82± 0.67	0.91± 0.26
RT16	0.681± 0.008	0.887± 0.012	26.89± 0.98	23.22± 0.49	0.98± 0.19
RT17	0.651± 0.003	0.817± 0.017	25.9± 1.15	20.32± 0.39	1.13± 0.31
RT18	0.672± 0.007	0.826± 0.011	24.70± 1.37	18.64± 0.47	1.18± 0.28
Note: Each worth speaks to the mean ± SD (n=3)					

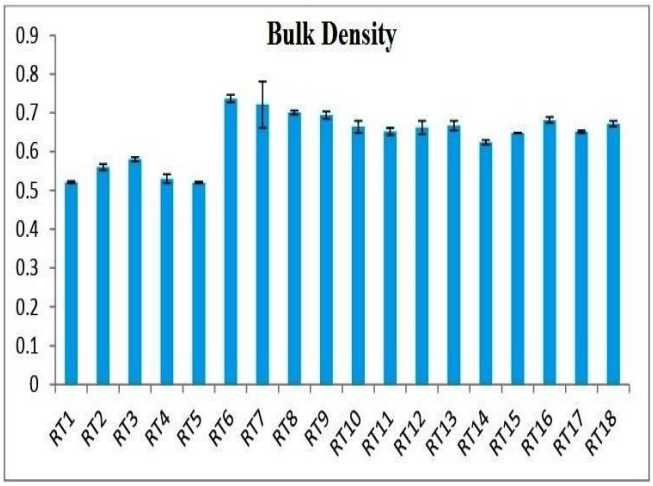

Figure No.3: Bulk Density for obtained formulation

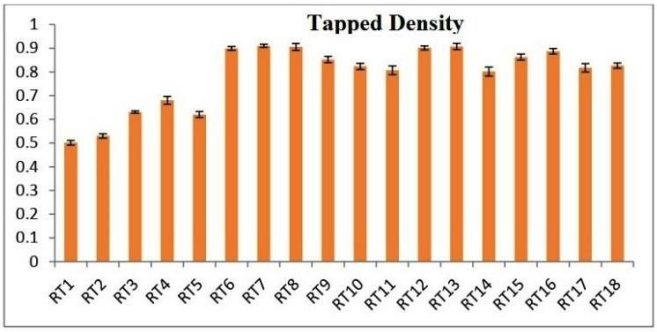

Figure No.4: Tapped Density for obtained formulation

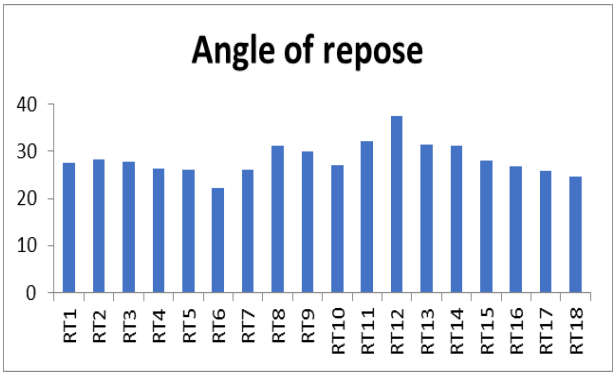

Figure No.5: Angle of repose for obtained formulation

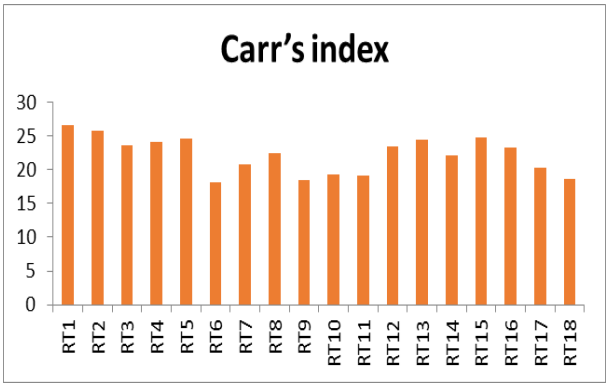

Figure No.6: Carr's Index for obtained formulation

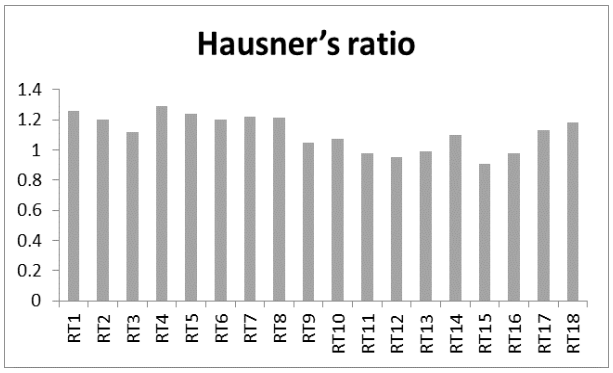

Figure No.7: Hausner's Ratio for obtained formulation

The angle of repose for all formulations was in the rangeof 22.29 to 37.39. This suggested that the powder blend has

excellent to moderate flow property. The results of Carr's Index and Hausner's ratio showed that the powder has a good compressibility index. This is anindication that the tablets can be prepared by direct compression method.

The thickness of the prepared tablets was in range between 3.01mm to 3.92mm. The weight variation was in the limit as specified in I.P. The maximum and minimum hardness of tablets was 4.9Kg/cm^2 and4Kg/cm^2 respectively. This is an optimum hardness for gastroretentive mucoadhesive tablet. The friability study depicted that all formulations have tendency to withstand handling and packing. The maximum gastroretentive lag time was 2.17min

Post-compression Evaluation:

Table No.4: Evaluation of gastroretentive mucoadhesive tablets of Repaglinide

Formulation Code	Thickness (mm)	Average Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)	Total Gastroretentive Time (h)	Gastroretentive lagtime (Min-s)
RT1	3.15±0.29	98.21±0.11	4.1±0.08	0.15±0.09	98.30±0.35	16±0.48	1:06±0..5
RT2	3.56±0.21	95.13±0.18	4.3±0.07	0.36±0.04	99.16±0.31	17.5±0.73	2:17±0.04
RT3	3.48±0.22	99.45±0.17	4.9±0.03	0.14±0.06	97.91±0.24	14±0.85	2:16±0.06
RT4	3.92±0.19	98.26±0.09	4.2±0.05	0.24±0.04	99.38±0.31	20±0.92	1:19±0.05
RT5	3.68±0.34	99.12±0.12	4.8±0.04	0.61±0.06	96.63±0.27	23±0.69	1:02±0.07
RT6	3.17±0.27	100.0±0.19	4.0±0.09	0.39±0.07	99.12±0.26	19±0.74	1:18±0.01
RT7	3.86±0.28	98.75±0.14	4.8±0.11	0.18±0.09	99.10±0.24	20±0.62	1:15±0.09
RT8	3.92±0.27	99.86±0.17	4.9±0.07	0.45±0.04	98.34±0.22	18±0.71	1:20±0.05
RT9	3.67±0.21	99.48±0.14	4.6±0.02	0.98±0.06	95.61±0.24	21±0.66	1:40±0.03
RT10	3.29±0.19	96.38±0.04	4.3±0.06	0.14±0.08	98.74±0.29	20±0.59	1:53±0.09
RT11	3.48±0.31	97.49±0.15	4.7±0.05	0.61±0.12	97.62±0.24	21±0.82	1:01±0.10
RT12	3.26±0.25	98.29±0.21	4.0±0.09	0.75±0.05	100.2±0.24	19±0.76	1:06±0.08
RT13	3.54±0.29	97.90±0.14	4.1±0.05	0.31±0.06	95.26±0.28	16±0.46	2:12±0.04
RT14	3.24±0.33	99.67±0.09	4.9±0.13	0.62±0.04	99.12±0.29	18±1.03	1:19±0.11
RT15	3.48±0.28	98.64±0.10	4.2±0.08	0.34±0.06	98.61±0.21	14.5±0.67	1:41±0.06
RT16	3.10±0.21	100.1±0.18	4.4±0.15	0.42±0.03	97.31±0.29	17±0.46	1:15±0.02
RT17	3.01±0.24	98.78±0.14	4.3±0.04	0.11±0.04	98.85±0.23	15.5±0.68	1:09±0.13
RT18	3.65±0.28	99.73±0.13	4.5±0.06	0.52±0.05	99.69±0.36	18±0.93	1:24±0.04

Each value represents the mean±SD (n=3)

In vitro release studies:

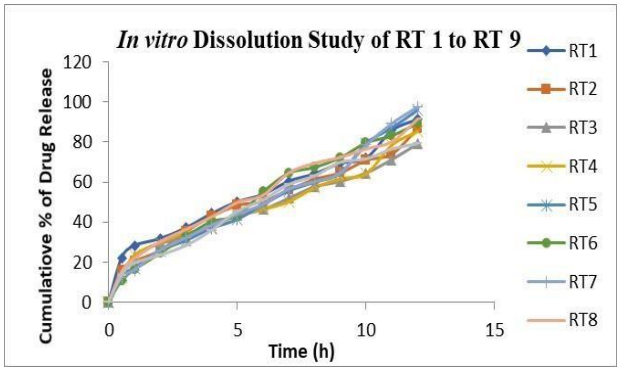

Figure No.8: In vitro Dissolution study of RT 1 to RT 9

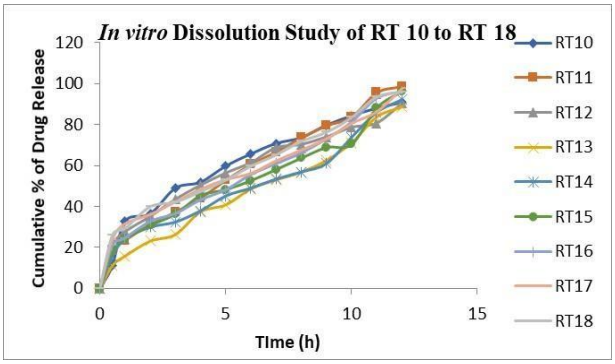

Figure No.9: In vitro Dissolution study of RT 10 to RT 18

The minimum drug release was observed for formulation RT3 which contains drug: carbopol 974P in ratio of 1:3. This may be due to the high concentration of rate controlling polymer. The maximum drug release is found in formulation RT7 which contains drug: carbopol 974P in ratio 1:1. This shows that the drug: carbopol 974P in ratio 1:1 is optimum to achieve a mucoadhesive and gastroretentive tablet.

Table No. 5: Moisture absorption, bioadhesion strength values of selected formulations.

FormulationCode	Moisture absorption	Bioadhesion strength	
		Peak detachment force (N)	Work of adhesion (mJ)
RT11	37±0.23	3.2±0.28	12.75±4.21

Each value represents the mean±SD (n=3)

Release kinetics:

Data from in vitro release studies on models demonstrating improved drug release were incorporated into various equations to describe the release kinetics of repaglinide from mucoadhesive tablets. The data were fitted to various kinetic models such as zero, first-order kinetics, higuchi and korsmeyerpepas mechanisms, and the results are shown in the table below.

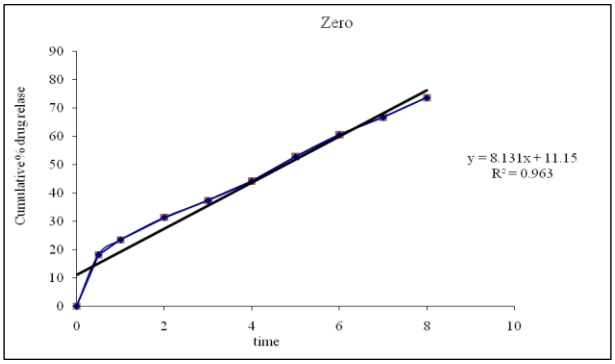

Figure No.10: Zero order plot of optimized formulation

Table No 6: Table of release kinetics and correlation factors

Cumulative (%) releaseq	Time (t)	Root(t)	Log (%) release	Log (t)	Log (%) remain	Release rate (cumulative % release / t)	1/Cum% release	Peppas log q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2				100	4.642	4.642	0
18.17	0.5	0.707	1.26	-0.301	1.913	36.38	0.055	-0.74	81.81	4.642	4.341	0.3
23.45	1	1	1.37	0	1.884	23.46	0.0426	-0.63	76.54	4.642	4.246	0.396
31.35	2	1.414	1.497	0.301	1.837	15.685	0.0319	-0.503	68.63	4.642	4.094	0.547
37.31	3	1.732	1.572	0.477	1.797	12.437	0.0268	-0.428	62.69	4.642	3.973	0.669
44.13	4	2	1.645	0.602	1.747	11.048	0.0226	-0.355	55.81	4.642	3.822	0.82
52.82	5	2.236	1.723	0.699	1.674	10.568	0.0189	-0.277	47.16	4.642	3.613	1.029
60.53	6	2.449	1.782	0.778	1.596	10.095	0.0165	-0.218	39.43	4.642	3.404	1.238
66.72	7	2.646	1.824	0.845	1.522	9.531	0.015	-0.176	33.28	4.642	3.217	1.425
73.61	8	2.828	1.867	0.903	1.421	9.205	0.0136	-0.133	26.36	4.642	2.976	1.665
79.52	9	3	1.9	0.954	1.311	8.836	0.0126	-0.1	20.48	4.642	2.736	1.906
83.72	10	3.162	1.923	1	1.211	8.375	0.0119	-0.077	16.25	4.642	2.533	2.109
95.62	11	3.317	1.981	1.041	0.636	8.697	0.0105	-0.019	4.33	4.642	1.63	3.012
98.64	12	3.464	1.994	1.079	0.134	8.22	0.0101	-0.006	1.36	4.642	1.108	3.534

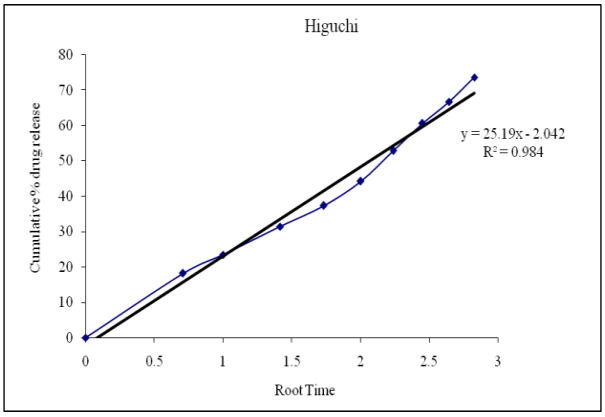

Figure No.11: Higuchi plot of optimized formulation

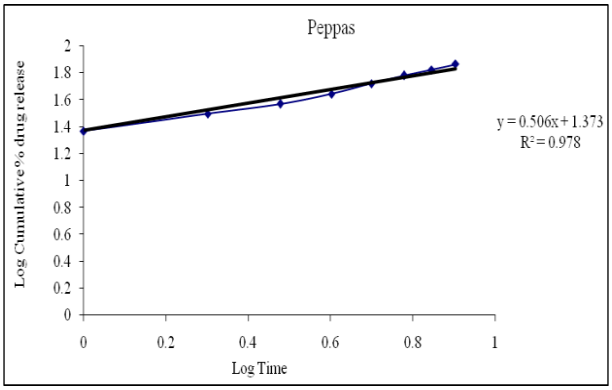

Figure No.12: Koresmeyer-peppas plot of optimized formulation

Based on the all studies RT11 formulation was found to be better when compared with all other formulations. This formulation was following Higuchi mechanism with regression value of 0.984.

***In vivo* Studies - Pharmacokinetic Studies:**

All the pharmacokinetics parameters displayed in Table. 6 Mean time to reach peak drug concentration (Tmax) was 0.8 hours, while mean maximum drug concentration (Cmax) was 30.24µg/ml. The values for Cmax, Tmax, AUC were found to be comparable indicating that their sustained release patterns were similar.

Table No 7: Pharmacokinetic parameters of optimized formulation

S. No	Parameter	Repaglinide
1	C_{max}	30.24µg/ml(±0.67)
2	T_{max} (hr)	0.8 hours(±0.27)
3	AUC	40.54µg.h/ml (±2.94)

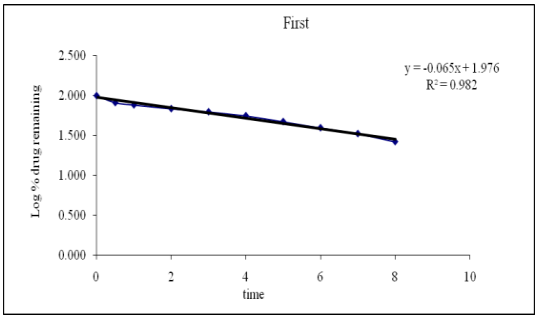

Figure No.13: First order plot of optimized formulation

CONCLUSION:

Repaglinide is formulated as a gastroretentive mucoadhesive tablet to increase its bioavailability. HPMC K200 M, Na CMC, Carbopol 974P, karaya gum, chitosan and xanthan gum were selected as polymers. Various parameters (stand angle, bulk density, tap density, Carr index and Hausner ratio) of the pre-compressed mixture of repaglinide gastroretentive muco-adhesive tablets were characterized and the results showed good liquidity and better liquidity of the product. Maximum separation force (N) and adhesion work were calculated and found to be good. Repaglinide RT11 formulation, good drug release in 12 hours (98.64%), moisture absorption (37 ± 0.23), peak peel force (N) (3.2 ± 0.28) It is considered an optimized formulation due to). N), adhesion activity (12.75± 4.21mJ). The RT11 formula follows the Higuchi mechanism with a regression value of 0.984. In vivo pharmacokinetic studies have shown that the drug reaches its

maximum at 0.8 hours. Cmax and AUC data predict oral bioavailability of the drug. Different drugs can be used to combine data for further research.

ACKNOWLEDGEMENT:

The authors would like to express sincere gratitude to Dr Rakesh meel Principal Shridhar University Pilani for their esteemed support towards this work.

AUTHORS CONTRIBUTION:

All the authors have equal contribution in making this research a success.

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