CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.14523419

https://www.iajps.com/volumes/volume11-december-2024/49-issue-12-december-24/

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF ANTI-DIABETIC DRUG

N.Manogna[1], D. Raj kumar[2]

Mother Teresa College of Pharmacy, N.F.C Nagar, Ghatkesar, Medchal, Telangana.

Article Received: October 2024 Accepted: November 2024 Published: December 2024

Abstract:

The objective is to develop and assess Repaglinide floating tablets. Based on FTIR tests, the medication is proven to be compatible with the excipients. The findings indicated that the drug release rates of the preparations were influenced by the drug-polymer ratio. The concentration of sodium bicarbonate has to be at least 10% to achieve buoyancy. The repaglinide formulations remained floating for more than 12 hours, whereas all of the other formulations (RP1–RP9) floated for more than 24 hours. The optimized formulation RP6 showed first-order release instead of zero-order release, indicating that the medication was released from RP1–RP9 by fickian diffusion.

Keywords: *Repaglinide, floating tablets, drug-polymer, buoyancy, optimized formulation.*

Corresponding author:

Devara Raj kumar,

Mother Teresa College of Pharmacy,

N.F.C Nagar, Ghatkesar, Medchal, Telangana.

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Please cite this article in press **Devara Raj kumar** *et al.,* ***Formulation And Evaluation Of Gastroretentive Floating Tablets Of Anti-Diabetic Drug.,****Indo Am. J. P. Sci, 2024; 11 (12).*

INTRODUCTION:

Oral dosage forms capable of having prolonged retention in the stomach to extend drug delivery for a longer time have been receiving much attention nowadays [1]. Gastric residence time (GRT) is one of the important factors affecting the bioavailability of drugs in pharmaceutical dosage forms. Variable and short gastric emptying time can result in incomplete drug release from the delivery system above the absorption zone (stomach and upper part of small intestine), thereby, abolishing the effectiveness of the administered dose [2]. Drug bioavailability can be sufficiently increased by prolonging GRT through gastroretentive dosage form such as a floating drug delivery system (FDDS). Floating drug delivery remains buoyant over gastric and intestinal fluid owing to their lower density than aqueous medium [3]. In floating dosage form both single and multiple systems have been developed. Multiple unit dosage forms can be an attractive alternative to single unit form as they have been shown to reduce inter and intra variabilities in drug absorption as well as to lower the probability of accumulation of dose.

Gastrointestinal tract targeting dosage forms are prepared to release the drug at the gastrointestinal site[4]. A floating drug delivery system is useful for several categories of drugs that act locally in the stomach, are poorly soluble in alkaline pH, have a narrow window of absorption, are unstable in the intestine or colonic environment, and are primarily absorbed in the stomach. Drugs having solubility in an acidic medium and higher absorption in the upper part of the intestine can be used to deliver through a floating system [5]. Repaglinide is an oral hypoglycemic agent and the first member of the meglitinide class, used to treat type-2 diabetes mellitus. It blocks the ATP-dependent potassium channel to stimulate the release of insulin by binding to specific sites on pancreatic β-cells. Repaglinide requires frequent dosing before meals due to its short half-life and thereby imposing side effects such as skeletal muscle pain, headache, and GIT effects. Microspheres encapsulated with anti-diabetic drugs, increase the effectiveness and release of the drug in a controlled manner from the polymeric membrane and thereby, maintain its concentration for a longer duration [6]. Due to short-lasting action, fast clearance, enzymatic stability, and absorption throughout git make repaglinide a suitable target for developing gastroretentive dosage form.

MATERIALS & METHODS:

Repaglinide was obtained as a gift sample from Lupin Limited, Pune. HPMC K15M, HPMC K100M, and HPMC K4M were purchased from Danmed Pharmaceuticals, Hyd. Microcrystalline cellulose, Sodium bicarbonate, Magnesium Stearate were purchased from S.D. Fine Chemicals Pvt Ltd, Mumbai.

Experimental Work:

Drug-Excipient Compatibility Studies

Fourier transform infrared spectroscopy

One of the most effective analytical methods for determining a drug's functional groups is infrared spectroscopy. By passing infrared light through a material, infrared spectroscopy can be performed [7]. The sample either absorbs or transmits a portion of the infrared energy. A molecular fingerprint of the sample is formed by the resultant spectrum, which represents the absorption and transmission of molecules. No two molecules with the same molecular structure will have the same infrared spectrum, just as fingerprints.

Preparation of repaglinide Floating Tablets:

Tablets with 10 mg of repaglinide were made by direct compression by the design shown in the table. Separately, the powders of repaglinide, a gas-generating agent (NaHCO3), and a release- retarding polymer (MCC) were passed through sieve no. 60. After 10 minutes of grinding in a mortar and pestle, the remaining ingredients—citric acid and microcrystalline cellulose—were added in geometric proportions; the mixture was then ground to a homogeneous consistency. Finally, the mixture was lubricated with the weighed and sieved magnesium stearate and talc in a polybag for 5 to 10 minutes to create the compression blend [8]. The final step in making the required tablets was to compress each mixture using a sixteen-station rotary tablet punching machine.

Table 1: Design formulation of repaglinide floating tablets

Formulation	drug	HPMCK15M	HPMCK100M	HPMCK4M	MCC	NaHCO3	Talc	Magnesium stearate
RP1	10	50	--	--	20	60	5	5
RP2	10	70	--	--	20	40	5	5
RP3	10	90	--	--	20	20	5	5
RP4	10	--	50	--	20	60	5	5
RP5	10	--	70	--	20	40	5	5
RP6	10	--	90	--	20	20	5	5
RP7	10	--	--	50	20	60	5	5
RP8	10	--	--	70	20	40	5	5
RP9	10	--	--	90	20	20	5	5

Post-Compression parameters:

General appearance:

Every single one of the tablets, regardless of its composition, were visually examined for things like size, shape, color, smell, surface roughness, physical imperfections, and consistency [9].

Thickness:

Using a vernier caliper, we measured the thickness of the tablets from every batch. The tablet's thickness shouldn't deviate more than ± 5% from the reference value [10].

Hardness test:

To determine the tablets ' hardness, a device known as the "Monsanto Hardness Tester" was used. Six tablets from each batch were tested using a tablet hardness tester made by Monsanto [12].

Friability test:

The tablets' friability was tested using a Roche friabilator, which spins a plastic container at 25 rpm, lowering the tablets six inches with each rotation, and subjecting them to abrasion and shock. For tablets weighing 650 mg or less, it is recommended to take a full tablet sample that is as close to 6.5 g as possible for examination [13]. The friabilator was turned on for 100 revolutions after dusting the weighed sample of entire tablets. The tablets were powdered again and weighed every rotation.

$$\text{Percentage loss} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

$$SI = \frac{\text{Final weight of tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

Weight variation test:

To guarantee that each pill has the correct dosage of medication, their weight was assessed. For each batch, twenty pills were chosen at random, and their average mass was determined. Then, each tablet was weighed separately and the difference between the two was represented as a percentage deviation from the average weight [14].

Uniformity of drug content:

Twenty randomly crushed tablets' worth of powder were combined with 100 milliliters of simulated gastric fluid (SGF) that had a pH of 1.2. After diluting the solution to the proper concentration and filtering it through Whatman filter paper no.41, each repaglinide was measured separately using spectrophotometry at 207 and 258 nm, using SGF pH

1.2 as a blank [15]. The results for the floating tablet of repaglinide are shown in each table according to the consistency of the medicine content.

Swelling index:

The measurement was taken at room temperature in a pH 1.2 simulated stomach fluid. The tablet's inflated weight was measured over 24 hours [16]. The following equation was used to determine the swelling index (SI), which was given as a percentage.

In vitro buoyancy studies:

For this experiment, we used a beaker with 100 ml of pH 1.2 simulated stomach fluid as a testing medium and kept it at 37 ºC. We then randomly placed a tablet from each formulation into the beaker [17]. When the tablet finally reached the surface, the amount of time it took for it to float there was recorded as the floating lag time (FLT).

In vitro dissolution studies:

We used the USP Dissolution Testing Apparatus II (Paddle type) to see how fast repaglinide was released from the floating tablets. At 37 ± 0.5 ºC and 50 rpm, the dissolution test was carried out with 900 ml of pH 1.2 simulated stomach fluid [18]. Every hour for 10 hours, a small portion of the sample was taken out of the dissolving equipment and replaced with a new dissolving medium at predetermined intervals. Whatman filter paper no. 41 was used to filter the samples. The solutions were tested for absorbance at a wavelength of 234 nm.

In vitro drug release kinetics:

The dissolution of solid dosage forms of drugs was previously characterized by a kinetic model, where the amount of drug dissolved is a function of test time [19].

Zero-order kinetics:

The following equation represents that the area remains constant and no equilibrium conditions are achieved 20].

$$Q_t = Q_0 + K_0 t$$

Qt is the drug concentration at time t, Q0 is the drug concentration at the beginning of the solution, and K0 is the zero-order release constant.

First-order kinetics:

The following equation was used to fit the release rate data to understand the kinetics of first order release rates:

Here, Qt is the drug release at time t, Q0 is the drug concentration at the beginning of the solution, and K1 is the first-order release constant.

Higuchi model:

To examine the release of pharmaceuticals that are

$$Q_t = K_H . t^{1/2}$$

water-soluble or have low solubility when mixed with semisolids or solid matrices.

$$Mt / M_\infty = K \cdot t^n$$

In this context, Qt represents the drug release at time t while KH stands for the Higuchi dissolution constant.

Korsmeyer and Peppas release model:

The following equation is used to fit the release rate data to examine this model:

In this context, Mt / M∞ represents the fraction of drug release, K stands for the release constant, t for the release period, and n for the diffusional coefficient.

Stability Studies

Stability testing is done to show how the medication formulation's quality changes over time in response to several environmental factors like light, humidity, and temperature. The study's findings provide light on the drug's ideal storage conditions, re-test intervals, and potential shelf life [21].

RESULTS & DISCUSSION:

Fourier Transformation Infra-Red Spectroscopy (FTIR)

The well-known peaks of repaglinide can be attributed to various processes: O-H stretching at 3310 cm-1, Ar-H stretching at 3080 cm-1, C-H stretching at 2880 cm-1, C-N stretching at 1600 cm-1, N-H bending at 1597 cm-1, C-H bending at 1340 cm-1, C-C stretching at 1070 cm-1, -C-O-C group at 1030 cm-1, and substituted benzene ring at 791 cm-1.

$$\text{Log } Q_t = \log Q_0 + + K_1 t/2$$

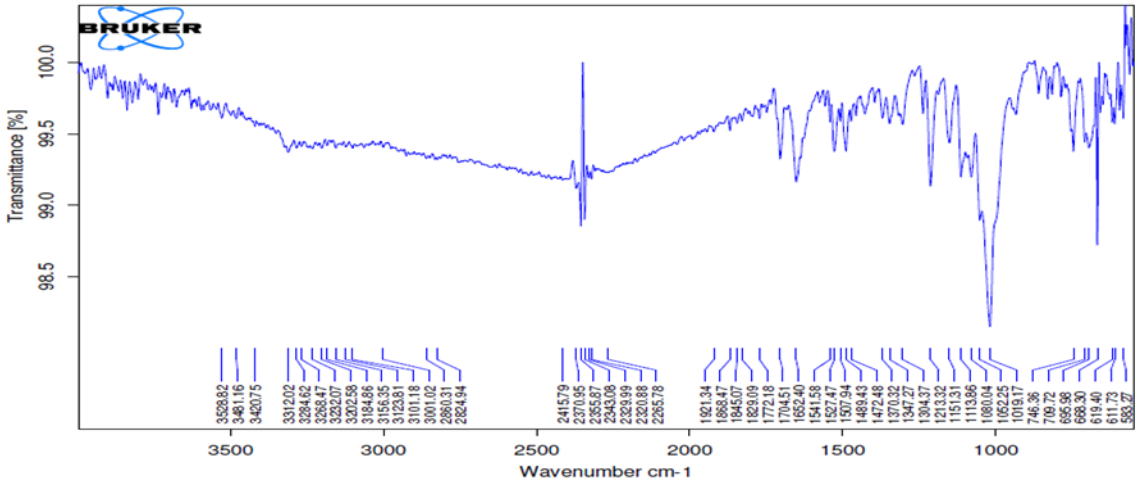

Figure 1: FTIR of Repaglinide pure drug

Evaluation of Pre-Compression Parameters of Repaglinide

The table displays the values of the angle of repose for each formulation. A range of 22.59˚ to 31.24˚ was determined for the values. This shows that the powder has an excellent flow quality. All of the formulations' compressibility index values are listed in the table. According to the compressibility index, which can be anywhere from 10.52 to 20.22%, the powder possesses the necessary flow quality for compression. The Hausner's Ratio values fall within the range of 1.11 to 1.25 %.

Table 2: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped densit (gm/ml)	Carr's index (%)	Hausner's Ratio
RP1	22.59	0.56	0.68	17.647	1.21
RP2	31.24	0.69	0.81	14.814	1.17
RP3	30.46	0.67	0.79	15.189	1.17
RP4	28.95	0.59	0.72	18.05	1.22
RP5	34.57	0.65	0.78	16.66	1.2
RP6	36.51	0.71	0.89	20.22	1.25
RP7	28.94	0.68	0.76	10.52	1.11
RP8	26.73	0.64	0.74	13.51	1.15
RP9	24.15	0.52	0.65	20.00	1.25

Several requests led to the pre-formulation of a tablet powder mixture. The statistics on the angle of repose show that the powder blend has great flow properties. All of the formulations' bulk densities ranged from 0.52 to 0.72 (gm/cm3), suggesting that the powder has adequate flow characteristics. All of the formulations' tapped densities fell within the range of 0.65 to 0.89, which means the powder had adequate flow characteristics. Compressibility indices ranging from 10.52 to 21.21 across all formulations suggest that the powder has outstanding flow properties. The powder has great flow properties, as shown by the Hausner's ratio, which falls between 1.11 and 1.26. This is correct regardless of the formulation.

Evaluation of Post Compression Parameters of repaglinide floating Tablets

The range of tablet mean thicknesses was 4.20 mm to 4.65 mm, which was nearly constant across all formulations. Low standard deviation values were observed for the tablet weights, which were determined to be uniform. The average weight of the tablets was not significantly different from the weight of the individual tablets. Each batch's measured hardness of tablets ranged from 4.50 to 5.60 kg/cm2, as shown in the table. All the formulations were consistent in terms of tablet hardness. To ensure that the tablets were mechanically stable, the percentage

of friability was NMT 1% throughout all formulations, as shown in the table for repaglinide. The permissible range for the percentage of drug content in repaglinide floating tablets was determined to be between 97.38±0.35 and 102.58±0.76.

Table No 3: Post-compression parameters.

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
RP1	499.56	4.54	0.19	4.29	96.53
RP2	475.86	4.82	0.24	4.31	97.02
RP3	486.31	4.69	0.35	4.36	96.85
RP4	501.23	5.09	0.42	4.45	98.46
RP5	497.52	5.18	0.56	4.51	97.86
RP6	492.16	5.23	0.48	4.32	99.02
RP7	485.63	5.46	0.39	4.58	98.67
RP8	489.13	4.75	0.27	4.31	99.01
RP9	490.65	4.68	0.31	4.22	98.46

Floating lag time (FLT) and Total floating time (TFT)

The table displays the FLT and TFT. Results showed that the shortest FLT was 9 seconds and the longest FLT was 74 seconds.

Floating lag time & Total floating time

Sodium bicarbonate and citric acid were used as gas-developing salts in a swellable hydrophilic matrix to provide buoyancy in repaglinide tablets. This specific matrix is entirely made of hydrophilic polymers that can swell. The process begins when the dissolving medium is absorbed into the tablet matrix. This interaction between the fluid and the effervescent base creates a swelling gel and traps carbon dioxide gas. As a result, the matrix expands, causing the density to decrease and the buoyancy to increase. The floating lag time decreased as the percentage of sodium bicarbonate increased in the case of repaglinide, which is a gas-generating effervescent base.

Swelling index

We found that the swelling index of repaglinide-containing formulations increased as the concentration of the polymer, TD, rose and that changes in the sodium bicarbonate content had minimal impact on tablet swelling.

In vitro buoyancy studies

The low-density polypropylene foam powder produced excellent buoyancy in vitro and eliminated floating lag time (Zero) in all of the formulations. To achieve their stomach retention capabilities, the pills stayed buoyant for over 12 hours. Table 5.04 displays the results, while figure 5.03 displays the images captured at various time intervals.

Figure 2: A) At zero-time D) At 12th h

Table 4: Design formulation of repaglinide floating tablets

Formulation	Swelling Index (%)	In vitro buoyancy	In vitro drug release
RP1	142	268	65.29
RP2	189	385	80.41
RP3	124	215	55.43
RP4	210	564	85.79
RP5	159	296	70.42
RP6	225	639	97.51
RP7	113	219	67.42
RP8	169	346	76.94
RP9	148	285	70.58

In-vitro drug release:

For the in-vitro release investigation, two distinct dissolving media were used: first, 0.1N HCl (an acidic buffer with a pH of 1.2) for two hours, and second, simulated intestinal fluid (a phosphate buffer with a pH of 6.8 over the following twenty-four hours). After 2 hours in 0.1N HCl, the amounts of drug released by the pure drug solution, optimized tablet, and commercial formulation were 89.35%, 15.36%, and 24.59%, respectively. Due to the lack of retardant TG in the pure drug solution formulation, nearly all of the drug was released after 2 hours. Optimal sustained-release tablets released 39% of the drug after 12 hours, whereas the commercial formulation released 62.59% after 12 hours. The results demonstrated that when the concentration of polymer increased in each formulation, the drug release from the formulations reduced. The optimized formulation table reveals that the medication release is slower than any other formulations. Formulation AF4, which releases 92.35% of the drug after 24 hours, was deemed the optimal formulation according to the drug release profile. You may see all of the formulations' in-vitro drug release statistics in the table and graph.

Table 5: In-vitro drug release profile of formulations

Time (h)	Pure drug Solution	Optimized Formulation (RP4)	Marketed Formulation
0	0	0	0
1	37.68	5.96	7.59
2	75.94	14.75	18.69
3	98.26	36.98	43.26
4	--	43.28	62.59
6	--	55.47	78.34
8	--	64.03	80.76
10	--	72.47	90.34
12	--	83.16	103.28
14	--	93.51	

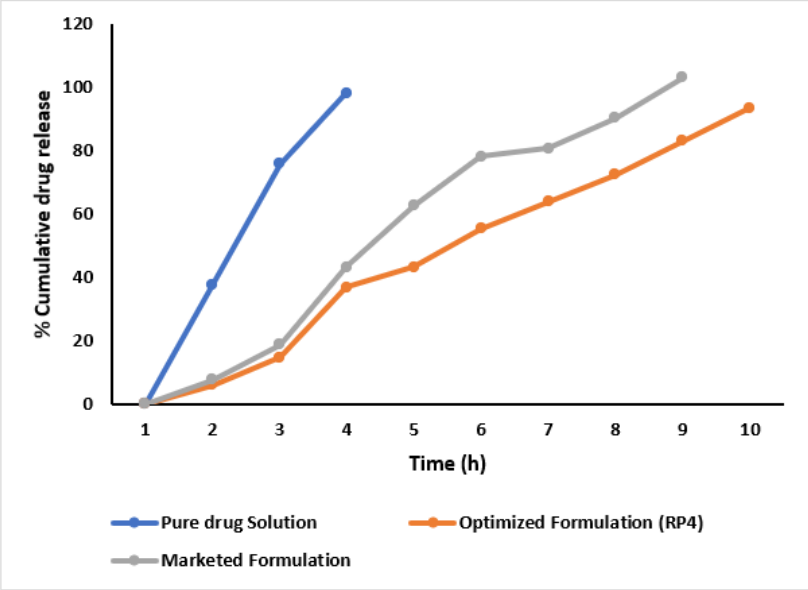

Figure 2: Invitro drug release studies

Release kinetics:

By comparing the values in the table for the kinetic model and the drug equation, we can see that the optimized formulations (RP4) follow the release kinetics model proposed by Higuchi with regression values of 0.9884. This conclusion was reached after fitting the release rate data to various models.

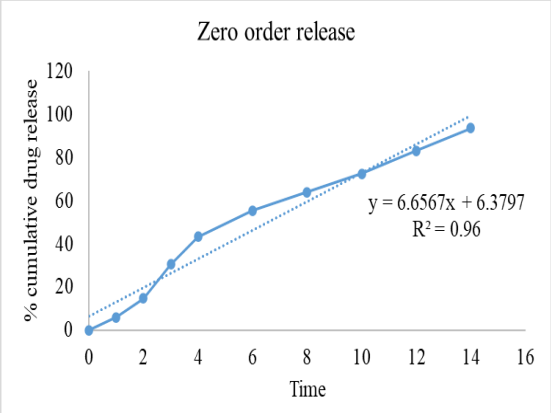

Figure 3: Zero order reaction

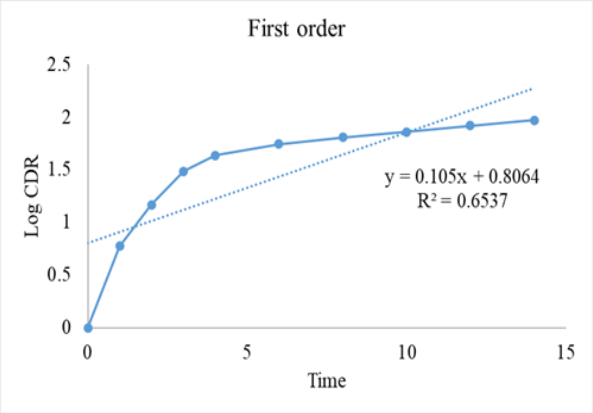

Figure 4: First order reaction

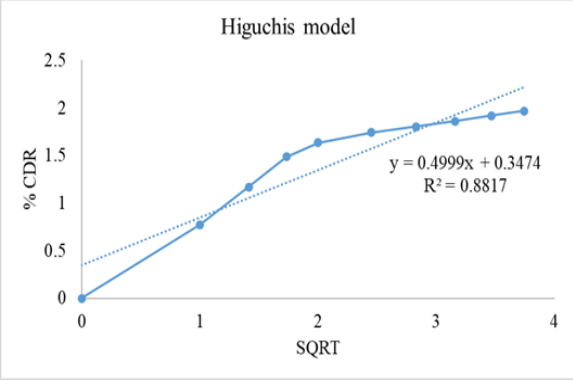

Figure 5: Higuchis Model

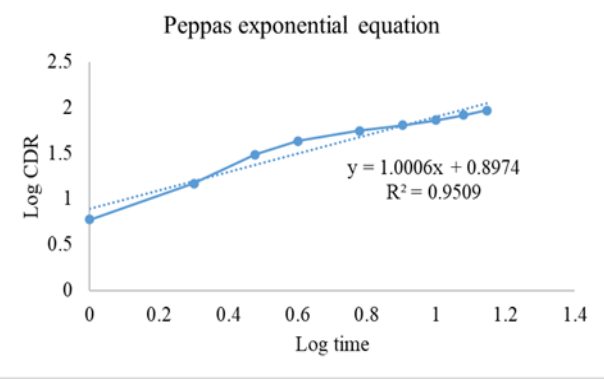

Figure 6: Peppas exponential equation

The in-vitro release of sustained-release tablets was studied using many models, including zero-order, first-order, Higuchi's equation, and Korsmeyer-Peppas equation. Formulations' zero-order plots were supposed to be linear, with high regression values indicating this. to validate the precise method of medication release from the polymer films. The hydrophilic nature of the polymers employed in the dissolution study had a significant impact on the amount of polymer that changed, and the study provided numerous factors to regulate in future batches. The release of the medication decreased as the concentration of the polymer increased.

FTIR

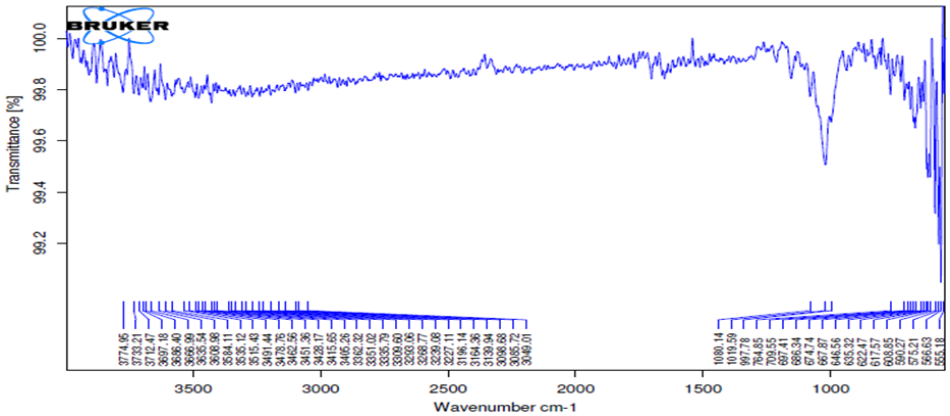

Figure 7: FTIR of Optimized formula

The FTIR spectra of the medicine and its improved formulation were captured in the 4000-400 cm-1 region. The secondary alcohol's O-H bond's stretching vibrations produced one peak at 3305 cm-1, whereas another peak at 1120 cm-1. Potentially associated with asymmetric C-H stretching in the CH3 group, symmetric C-H stretching in the CH2 group, and C=N stretching are peaks at 2967, 2856, and 1707 cm-1, correspondingly. Every one of the drug signature peaks is present in the optimized formulation, which means the excipients and medicine did not interact in any way.

SUMMARY AND CONCLUSION:

All of the tablet formulations were identical concerning the medication content. The medication appears to be distributed uniformly throughout the matrices, as indicated by the low standard deviation values. The medicine is found to be compatible with the excipients conferring to DSC and FTIR testing. Results showed that the drug-polymer ratio affected the formulations' drug release rates. Research has shown that medication release rates decrease with increasing polymer levels. To achieve buoyancy, a concentration of at least 10% sodium bicarbonate was determined. While the repaglinide formulations stayed afloat for over 12 hours, all of the other formulations (RP1–RP9) floated for over 24 hours. It was discovered that the drug was released from RP1–RP9 through fickian diffusion in the optimized formulation RP6, which exhibited first-order release rather than zero-order release in the optimized formulation. The RP6 optimized formulation including repaglinide features a zero-order drug release profile and a fickian diffusion for drug release.

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