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Original Research

Formulation, evaluation, and optimisation of bilayer floating tablet that contained repaglinide and glipizide

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Abstract
Effective glycemic control is crucial in managing type 2 diabetes. This study aimed to develop a novel bilayer tablet formulation to provide both rapid onset and sustained release of antidiabetic agents. The Immediate-Release (IR) layer contained repaglinide for quick blood sugar lowering, while the floating bio adhesive Sustained-Release (SR) layer housed glipizide for prolonged therapeutic effect. This design aimed to improve patient compliance and optimize glycemic control. This study investigated the development and *in-vivo* evaluation of a novel floating tablet formulation for extended drug delivery. Barium sulfate tablets with varying concentrations were prepared and evaluated for their floating properties *in vitro*. Tablets containing 30% barium sulfate demonstrated optimal buoyancy and structural integrity. These (batch A6 and C2) were chosen for further *in-vivo* evaluation using X-ray imaging in Albino rabbits. The X-ray results confirmed successful floating of both batches (A6 and C2) in the rabbit stomach for over 8 hours. Additionally, batch C2 exhibited minimal positional change, suggesting potential mucoadhesive properties. This research highlights the potential of gastroprotective tablets for prolonged drug delivery via the oral route. By extending gastric residence time, these formulations can potentially improve drug bioavailability and overcome challenges associated with variable gastric emptying rates. Further investigation is required to optimize the formulation and fully understand its *in-vivo* performance.

Keywords: Bilayer tablet, repaglinide, glipizide, floating Bio-adhesive, sustained release, type 2 diabetes

Introduction
Type 2 diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia (high blood sugar). Maintaining optimal blood sugar levels is essential to prevent long-term complications. Repaglinide and glipizide are widely used oral hypoglycemic agents with distinct release profiles. Repaglinide offers a rapid onset of action but a short duration, necessitating frequent dosing [1]. Glipizide provides a longer duration of action but has a slower onset [2].

Limitations of Conventional Therapy [1-4]
Frequent Dosing: Frequent dosing regimens with both repaglinide and glipizide can lead to non-compliance and potential side effects like hypoglycemia.

Variable Gastric Residence Time: Conventional oral formulations may be affected by gastric emptying variability, impacting drug release.

Proposed Bilayer Tablet Design: This study proposes a novel bilayer tablet formulation to address these limitations:

Immediate-Release (IR) Layer: This layer will contain repaglinide for a rapid initial dose, promoting quick blood sugar control.

Floating Bioadhesive Sustained-Release (SR) Layer: This layer will contain glipizide incorporated within a floating bioadhesive matrix. The floating mechanism ensures prolonged gastric residence time, enabling sustained release of glipizide over an extended period [2]. The bioadhesive properties will further enhance gastrointestinal retention, optimizing drug delivery.

Benefits of the Bilayer Design [4-11]

Improved Compliance: By combining rapid and sustained release mechanisms in a single dosage form, this design can potentially reduce dosing frequency, enhancing patient adherence.

Enhanced Glycemic Control: The rapid onset of action from repaglinide followed by sustained release of glipizide can offer better overall glycemic control throughout the day.

Reduced Gastric Variability: The floating mechanism can potentially overcome variability in gastric emptying time, leading to more consistent drug delivery [4, 5].

Materials and Methods [1-4, 12]

The following materials are used in the formulation of a bilayer floating tablet for diabetes mellitus.

Drug: Repaglinide, Glipizide

Polymers and Excipients: Hydroxypropyl Methylcellulose K4M, Sodium Carboxymethyl Cellulose, Microcrystalline Cellulose, Polyvinyl Pyrilidone (PVP K30), Sodium Lauryl Sulphate, Sodium Bicarbonate, Magnesium Stearate, Citric cid, and Sodium Starch Glycolate

Other chemicals: hydrochloric acid, potassium chloride, methylene chloride, sodium hydroxide, methanol, acetone, and potassium dihydrogen phosphate.

Procurement of drugs or chemicals

Repaglinide was obtained as a gift sample from Sun Pharma, Ahmedabad.
Glipizide was obtained as a gift sample from Torrent Pharmaceuticals Ltd., Mumbai.
Other materials used were of AR grade and were purchased from Space Chemicals, Nasik**.**

Instruments used for study

The following laboratory equipment was used during the development of Bilayer floating tablets.
Monsanto hardness tester (Cad Mach, Ahmadabad, India).
Roche friabilator (Remi Electronics, Mumbai, India).
Digital Balance (PGB-100, Wensar, India).
Vernier calliper (Mitutoyo absolute digimatic).
UV-visible spectrophotometer (UV-3000+, Labindia, Mumbai).
Infrared Spectrophotometer (Shimadzu, 8400S, Kyoto, Japan).

Differential Scanning Colorimeter

Mechanical Shaker (CIS-24, Remi Lab, Mumbai).
Tap Density Tester USP II, Electrolab ETD, 1020, Mumbai,
Minipress-I tablet compression machine (Rimek, Karnavati Engineering Pvt. Ltd., Ahmedabad).
Disintegration Tester (Omega Industries, India).
Dissolution test apparatus USP (TDL-08L, Electrolab, Banglore).
X-ray (Meditronics MFG Com Pvt. Ltd., PDY-3010-D)
Design Expert Software (Version DX-8)
Stability Chamber (372LAG, Remi Lab)

Pre-formulation study

While developing a pharmaceutical dosage form, it is very important to determine the physico-chemical properties of the drug molecule and other derived properties of the drug powder. This first phase of study is known as pre-formulation studies. The following pre-formulation studies were conducted on the active pharmaceutical ingredient.

Confirmation of Drug

Confirmation of drugs was carried out using UV spectroscopy, infrared spectroscopy, differential scanning calorimetry (DSC), and simple melting points [1, 6].

UV Spectrophotometer: The UV spectrum of Repaglinide and Glipizide in 1.2 pH buffer was scanned from 400 nm to 200 nm. 72, 73

Infrared Spectroscopy: The IR spectrum of drugs was measured in the solid state as potassium bromide dispersion. The bands (cm^{-1}) have been assigned.74,75

DSC Study: In DSC analysis, 5 mg of Repaglinide and Glipizide were taken in hermatically sealed flat-bottom aluminium pans, which were subjected to DSC study, and the thermograms of both drugs were studied [7, 6, 12].

Melting Point Determination The melting point of both drugs was determined using the capillary method.

Drug Excipients Compatibility Studies

The drug-excipient interaction study was carried out using FTIR and DSC.

A study of FTIR spectroscopy IR spectroscopy was used to determine the molecular interaction between polymers and drugs. All physical mixtures and drug samples were mixed with dried KBR in a ratio 1:1. Then a small fraction of the mixtures was compressed on an automatic IR press at a pressure 10 tonnes to form a transparent pellet. Then the IR spectrum of pellets was taken on a FTIR spectrophotometer [1-5]r.

DSC study

We filled the prewashed, dried ampoules with physical mixtures of drugs and polymers and sealed them. The sealed ampoules were stored at 37±0.5 °C for 28 days in the stability chamber. At the end of 28 days, ampoules were removed from the stability chamber and subjected to an interaction study. A drug-polymer interaction study was carried out using DSC. In this study, a thermogram of mixtures of repaglinide, sodium starch glycolate, microcrystaline cellulose, and glipizide, HPMC K4M, and NaCMC, along with an effervescent system, was taken. Heating was done at a scan rate of 10 °C/min [1, 7-12].

Result and Discussion

Reformulation Study Confirmation of drug

Confirmation or identification of drugs was carried out by following methods.

UV spectroscopy

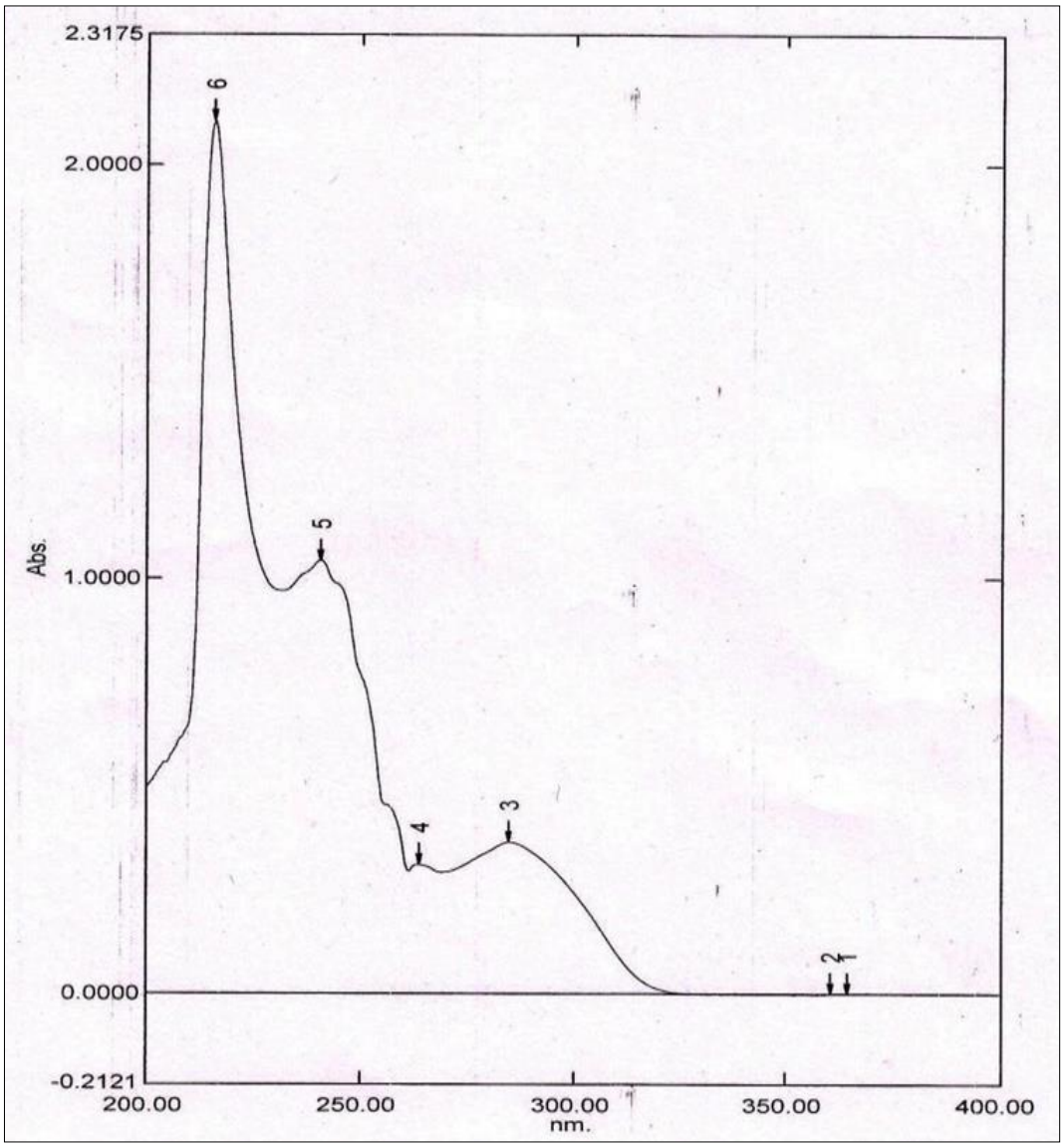


Fig 1: UV spectrum of Repaglinide in 1.2 pH buffer

Table 1: Wavelength of Repaglinide in 1.2 pH

No.	Wavelength	Absorbance
1	364.80	0.0007
2	360.40	0.0002
3	285.00	0.3640
4	263.60	0.3104
5	240.60	1.0442
6	215.60	2.1067

Repaglinide solution was scanned at 400 nm to 200 nm, maximum absorption was observed at 241 nm as shown in Fig. 1 was confirmed with reported UV spectrum of Repaglinide.

Table 2: Wavelength of Glipizide in 1.2 pH

No.	Wavelength	Absorbance
1	372.80	-0.0118
2	359.80	-0.0120
3	318.00	0.0113
4	275.20	0.3169
5	229.60	0.6834
6	220.00	0.2626
7	210.40	0.2229

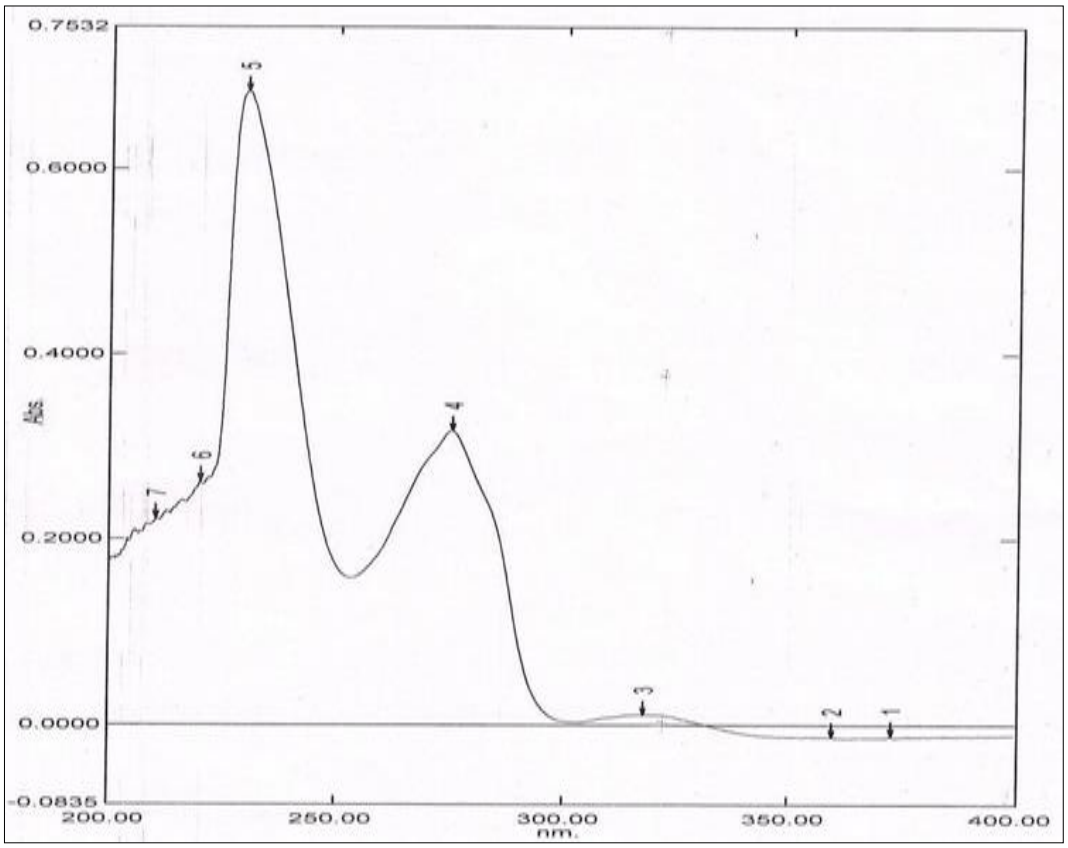


Fig 2: UV spectrum of Glipizide in 1.2 pH buffer

Glipizide solution was scanned at 400 nm to 200 nm, maximum absorption was observed at 276 nm as shown in Fig 2 this was confirmed with reported UV spectrum of Glipizide.

IR spectrum

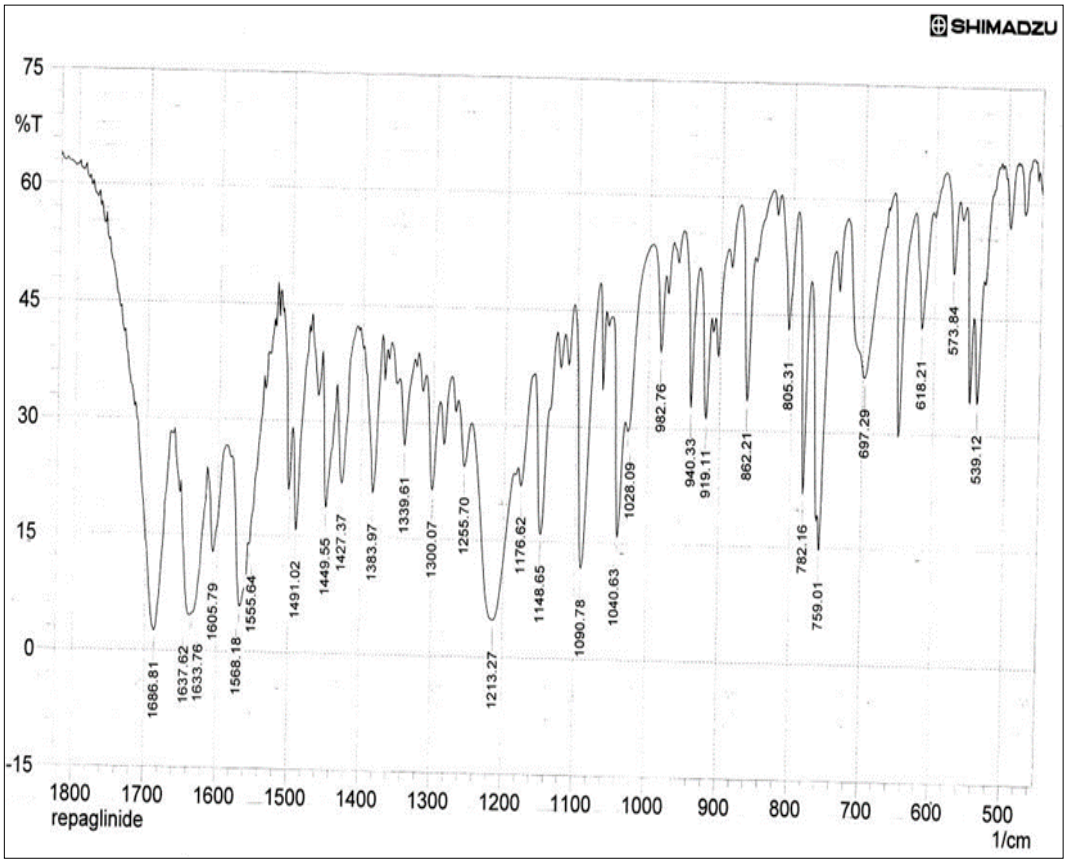


Fig 3: IR spectrum of Repaglinide

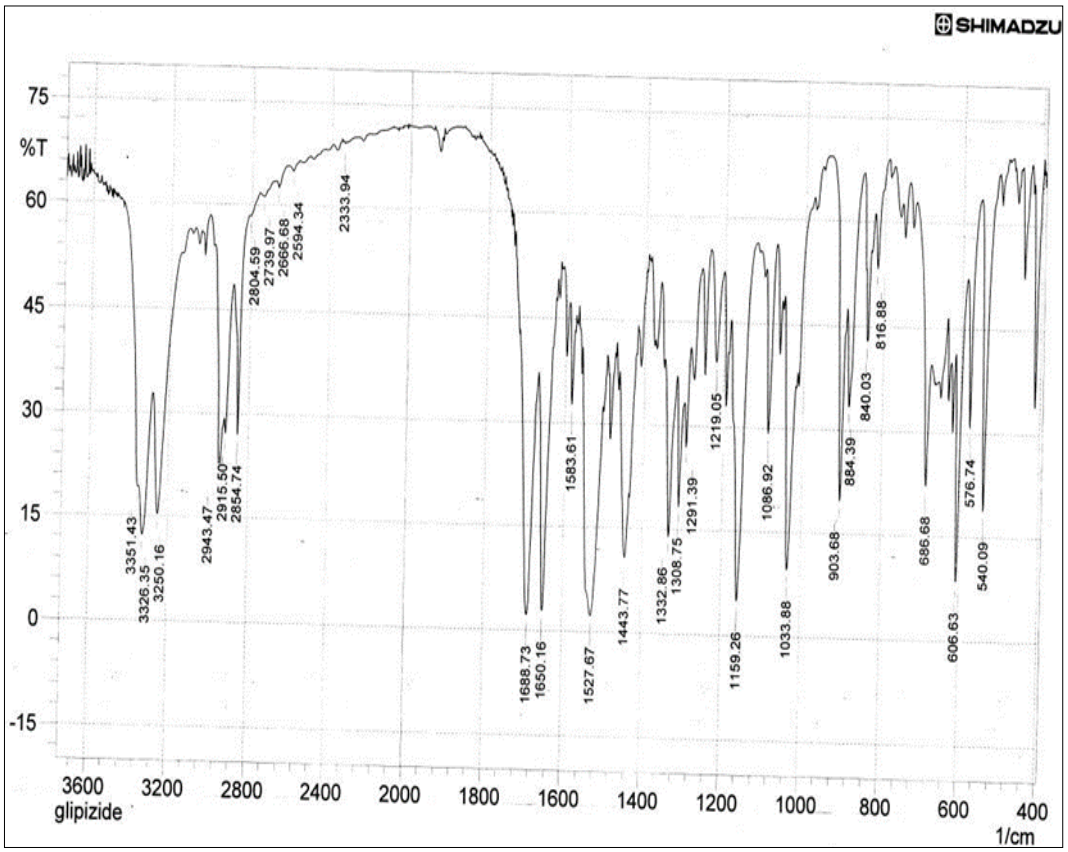


Fig 4: IR spectrum of Glipizide

The IR spectrum was measured in the solid state as potassium bromide dispersion.

The IR spectrum of Repaglinide is represented in Fig. 3 and Glipizide is represented in Fig. 4 Observed peaksare shown in Table 3 for Repaglinide and Glipizide these peaks are similar to reported peaks of Repaglinide and Glipizide.

DSC study

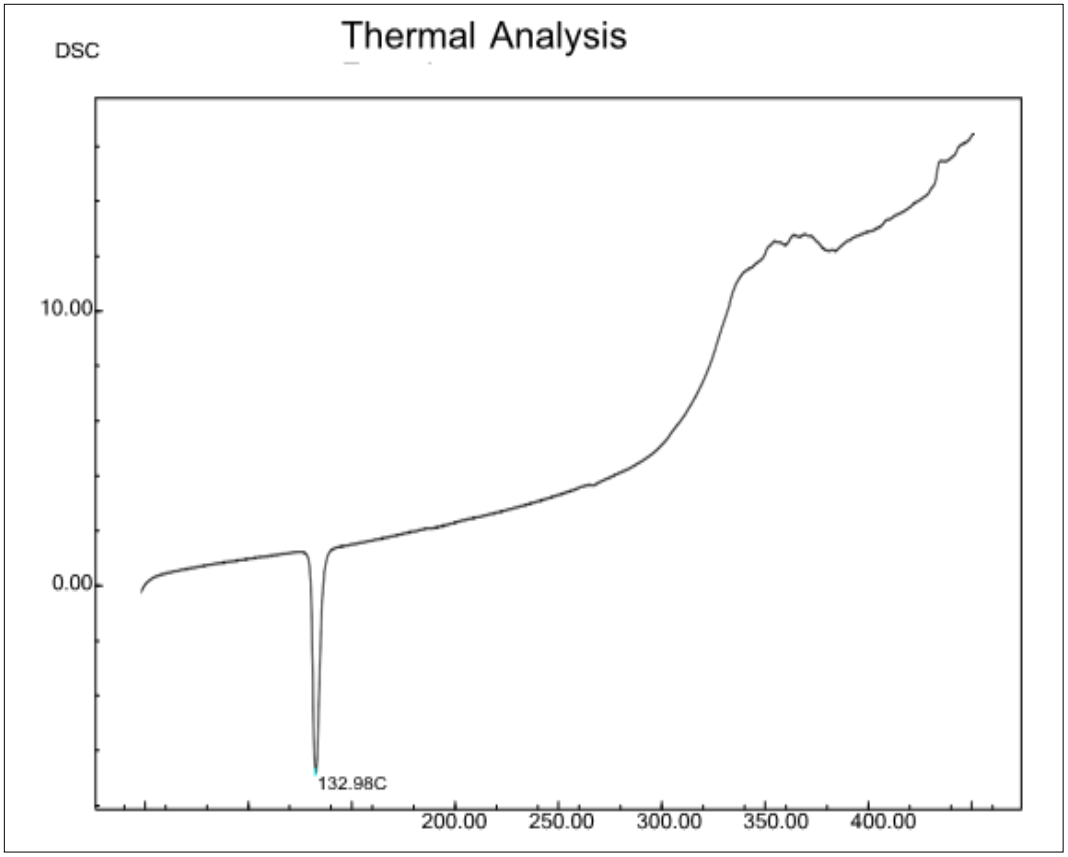


Fig 5: DSC thermogram of pure Repaglinide

Repaglinide was confirmed by differential scanning calorimetry (DSC) at scan rate of 10oC/min. It exhibits a sharp melting endotherm with onset temperature 129.5oC and peak temperature 132.9oC as shown in Fig5. It was confirmed with the reported melting point of Repaglinide i.e. 131oC – 134oC.

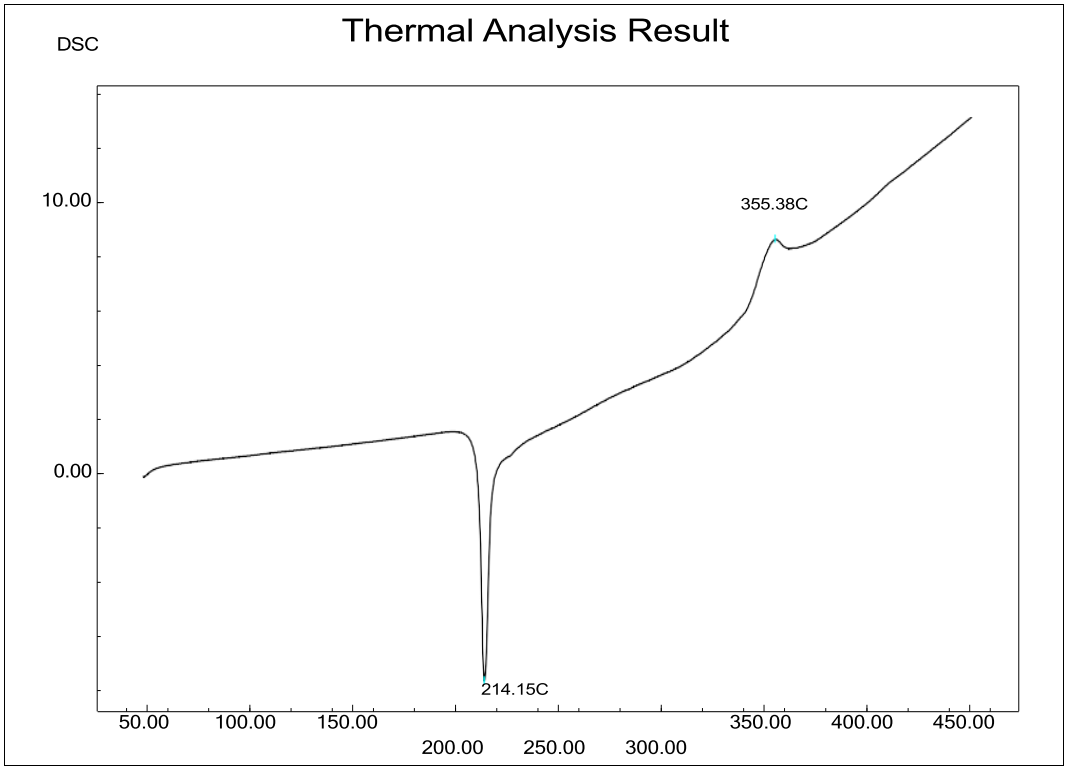


Fig 6: DSC thermogram of pure Glipizide

Glipizide was confirmed by differential scanning calorimetry (DSC) atscan rate of 10oC/min. It exhibits a sharp melting endotherm with onset temperature 209.34oC and peak temperature 214.15oC as shown in Fig.6. It was confirmed with the reported melting pointof Glipizide i.e. 209oC – 214oC.

Melting Point Determination

Melting point of Repaglinide was also measured in laboratory and found to be in the range of 1320C –1340C. It was confirmed with the reported melting point of Repaglinide i.e. 1300C – 1340C.

Melting point of Glipizide was also measured in laboratory and foundto be in the range of 2100C –2120C. It was confirmed with the reported melting point of Glipizide i.e. 2100C – 2140C.

Drug polymers interaction study

Drug Polymer interaction study by FTIR spectroscopy

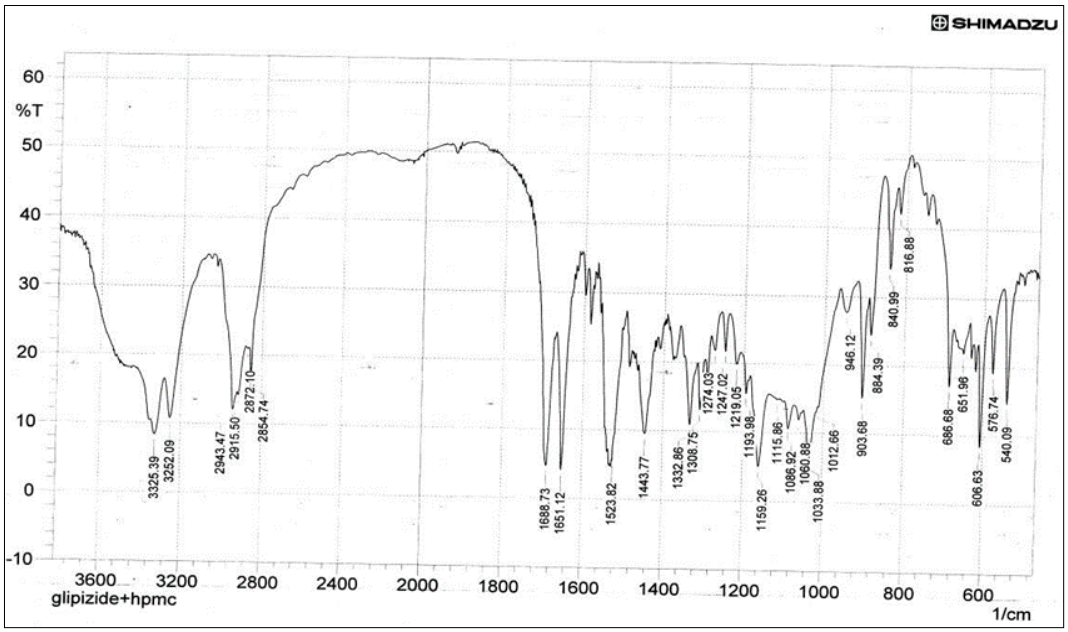


Fig 7: FTIR spectra of physical mixture of Glipizide andHPMC K4M

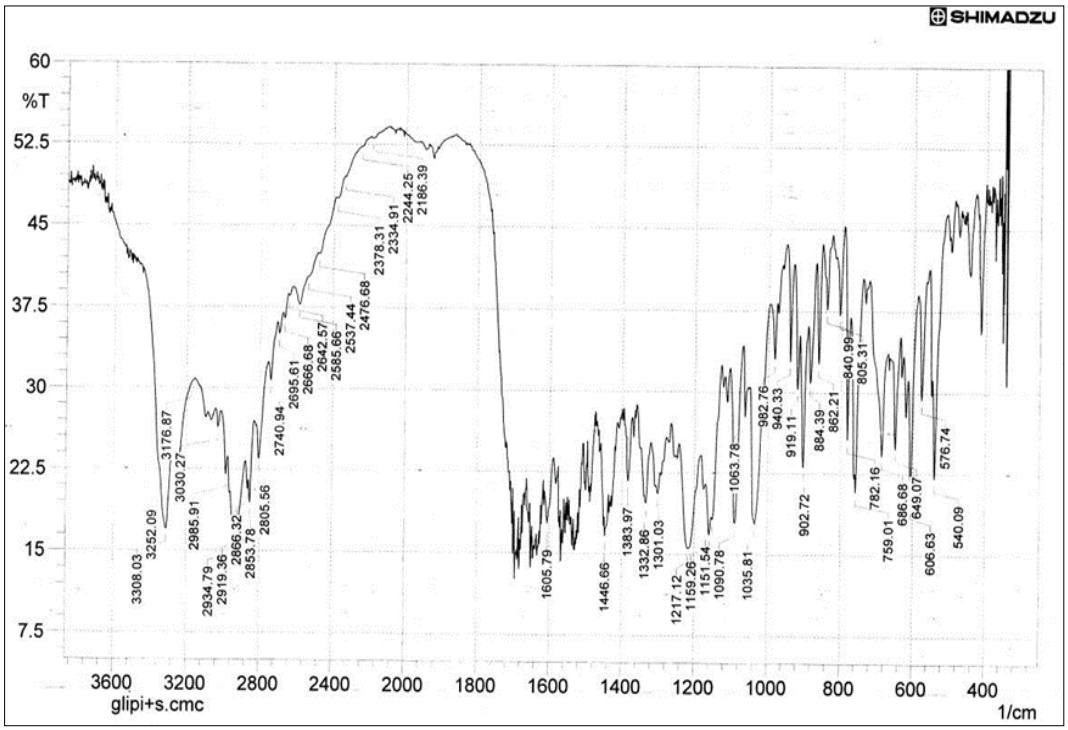


Fig 8: FTIR spectra of physical mixture of Glipizide and Na CMC

Table 4: Interaction study between drug, polymer through IR spectroscopy

Polymers	Drug peak (Glipizide) cm^{-1}	lymerspeak cm^{-1}	Drug+ polymers peaks cm^{-1}	Observation
HPMCK4M	540, 576, 840, 903, 1033, 1159, 1219, 1332, 1443, 1527, 1650, 2854, 2943, 3250,3351	670, 946, 1056, 1370, 2838, 2932, 3177, 3336	540, 576, 840, 903, 946, 1033, 1058, 1193, 1247, 1159, 1219, 1332, 1443, 1523, 1651, 2854, 2943,3252, 3325	No Interaction
Na CMC	686, 840, 884, 903, 1033, 1159, 1219, 1332, 1443, 2333, 2594, 2666, 2739, 2804, 2915, 3250, 3351	606, 946, 1058, 1370, 2312, 2608, 2838, 2932, 3336	686, 840, 884, 902, 940, 1035, 1159, 1217, 1332, 1446, 2334, 2585, 2666, 2740, 2805, 2919, 3252, 3308	No Interaction

Physical mixtures of drug and polymers were characterized by FTIR spectral analysis for any physical as well chemical alteration of the drug characteristics. By comparing Fig 8, Fig. 7 it can be concluded that there was no interference in the functional group of the principle peaks of the Glipizide, as they were found to be unaltered in the Fig. 7 and 8 drug polymers physical mixtures, indicating that they were chemically compatible.

Drug-Drug interaction study.

Table 5: Interaction study between two drugs through IRspectroscopy

Epaglinide Peak cm^{-1}	Glipizide Peak cm^{-1}	Repaglinide + zide peaks cm^{-1}	Observation
539, 618, 782, 805, 862, 982, 1176, 1213, 1300, 1383, 1491, 1555, 1686	540, 576, 840, 903, 1033, 1159, 1219, 1332, 1443, 1527, 1650, 2854, 2943, 3250, 3326	540, 619, 576, 782, 805, 840, 862, 982, 1035, 1159, 1217, 1300, 1332, 1383, 1448, 1491, 1528, 1567, 1690, 2852, 2943, 3251, 3309	No Interaction

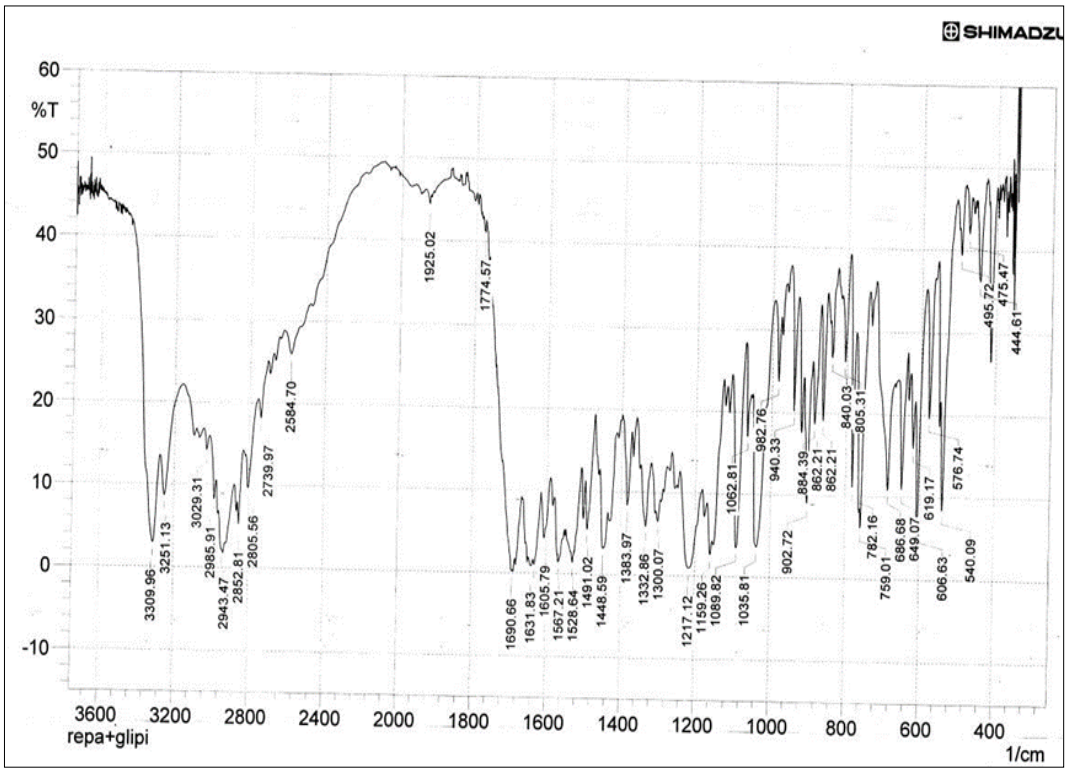


Fig 9: FTIR spectra of physical mixture of Repaglinide and Glipizide

Physical mixtures of two drugs (Repaglinide + Glipizide) were characterized by FTIR. By comparing Fig. 7 and Fig. 8 with Fig.9 it can be concluded that there was no interference between two drugs and indicating that they were compatible chemically.

DSC study

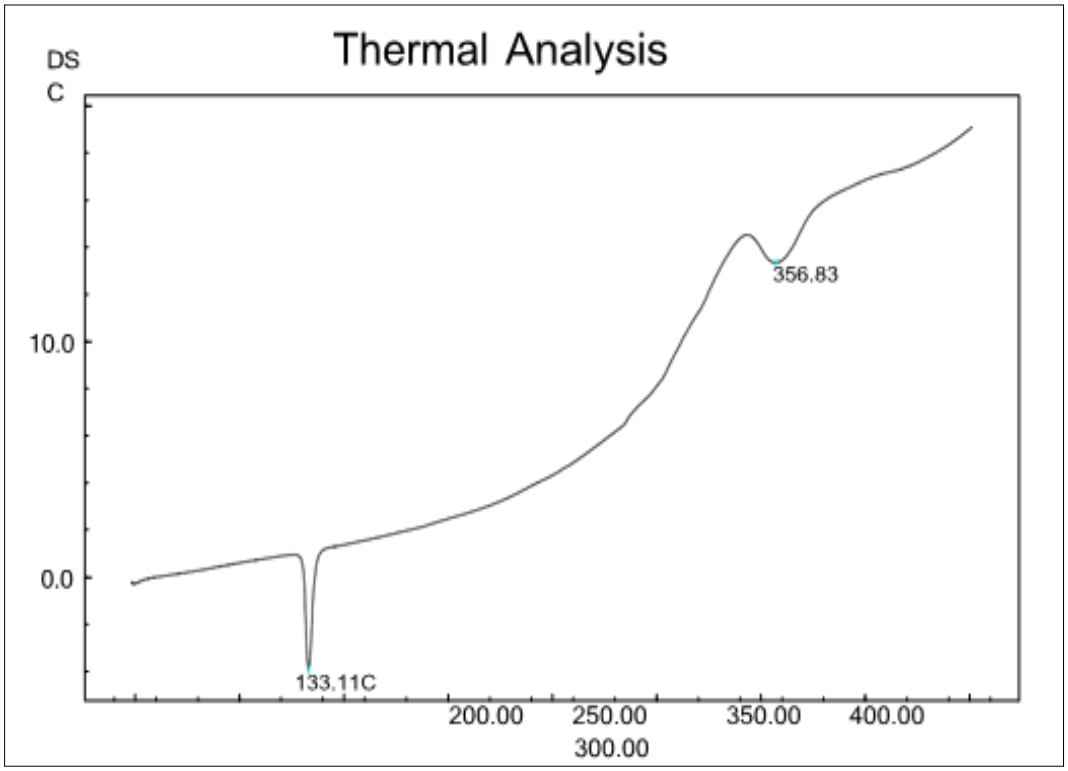


Fig 10: DSC thermogram of physical mixture of immediate release layer

DSC thermogram (Fig. 10) of pure drug Repaglinide powder showed a sharp endothermic peak near to 132.90C which indicating of its melting temperature. In Fig. 8.8 a melting endotherm of Repaglinide was observed 133.110C. DSC thermogram showed that there was no much more difference in onset temperature and peak temperature, when compared with pure drug's thermogram (Fig. 10). So no interaction was found between drug and polymers used.

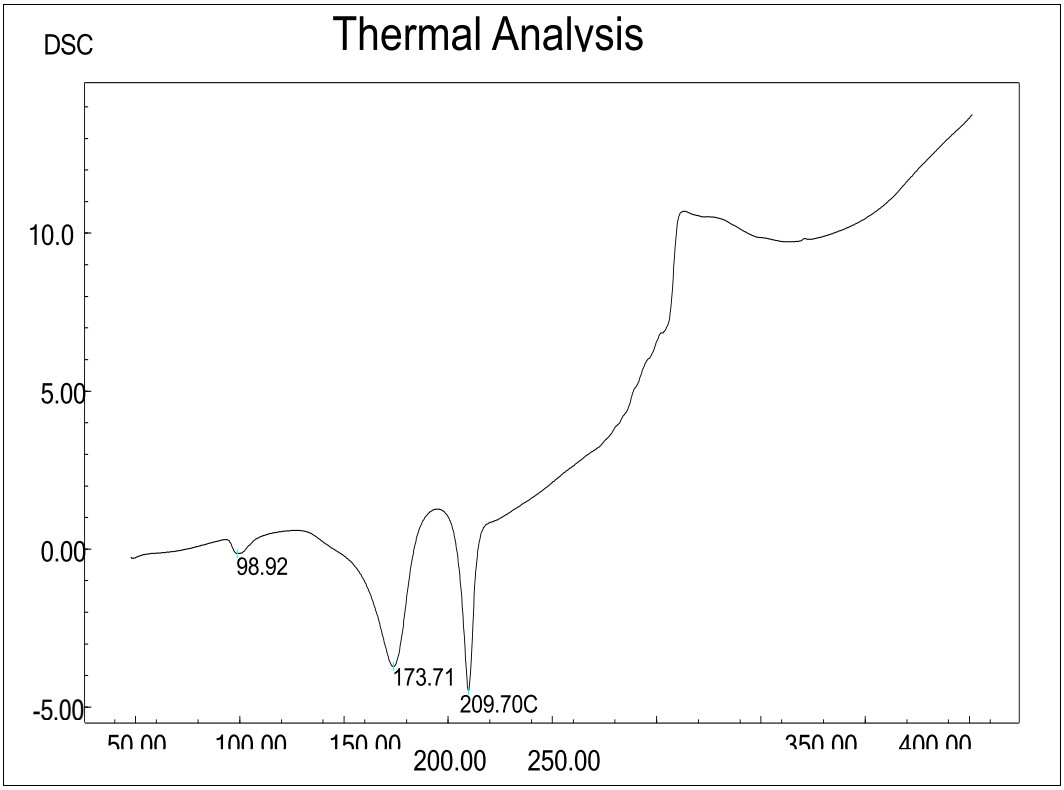


Fig 11: DSC thermogram of mixture of Glipizide, HPMC K4M, Na CMC and Effervescent system

DSC thermogram (Fig. 11) of pure drug Glipizide powder showed a sharp endothermic peak near to 214.150C which indicating of its melting temperature. In Fig. 12melting endotherm of Glipizide was observed to 209.700C. DSC thermogram showed that there was no much more difference in onset temperature and peak temperature, when compared with pure drug's thermogram (Fig. 8.4 b). So no interaction was found between drug and polymers used.

Standard calibration curve of Repaglinide in 1.2 pH buffer

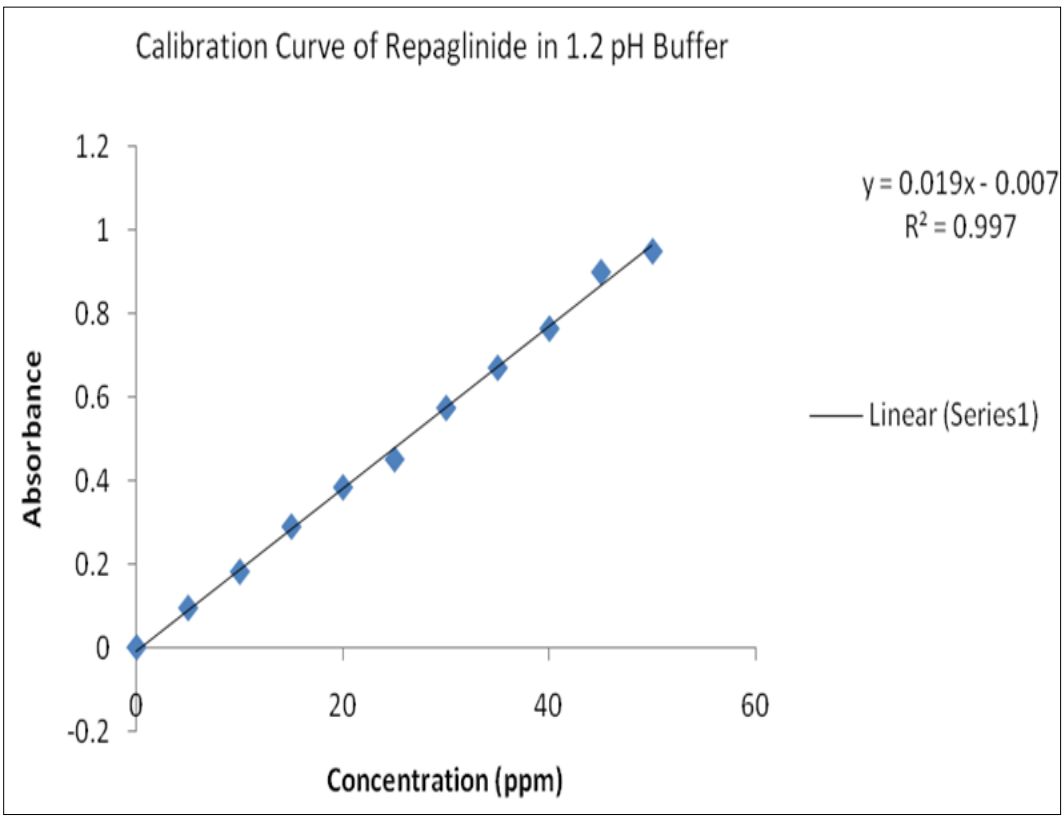


Fig 12: Standard calibration curve of repaglinide in 1.2 pH

Table 6: Standard calibration curve of Repaglinide in 1.2 pH Buffer

Sr. No.	Concentration (mcg/ml)	Absorbance
1	0	0
2	5	0.094
3	10	0.181
4	15	0.289
5	20	0.383
6	25	0.450
7	30	0.573
8	35	0.669
9	40	0.763
10	45	0.898
11	50	0.948

Buffer

Wetting study

Fig 13: Wetting Study of immediate release tablet

Varying concentration of sodium starch glycolate in formulation F1, F2, and F3 shows that F1 having faster wetting ability as compare to F2 and F3. The reason attributed to the higher wetting of F1 is due to more concentration of sodium starch glycolate as compared to F2 and F3. This wetting was occurs because of capillary and swelling mechanism of sodium starch glycolate.

***In vitro* dissolution study of immediate release layer tablet**

Table 7: Dissolution data of immediate release layer tablets

Time (min)	F1	F2	F3
0	0	0	0
5	81.14±1.1	75.90±1.6	73.67±1.3
10	85.27±1.3	82.27±1.3	79.84±1.5
15	91.87±1.2	85.73±1.5	83.89±1.3
20	92.85±1.3	90.93±1.2	88.94±1.4
25	93.25±1.2	92.95±1.3	89.45±1.6
30	94.89±1.6	93.38±1.4	90.34±1.4
35	95.34±1.3	94.11±1.9	91.89±1.7
40	95.99±1.8	94.67±1.7	92.56±1.3
45	96.28±1.4	95.09±1.5	92.97±1.4
50	96.96±1.5	95.77±1.8	93.34±1.3
55	97.54±1.2	96.25±1.2	93.76±1.1
60	98.63±1.2	97.23±1.7	94.47±1.6

All values are mean ± SD, (n=3)

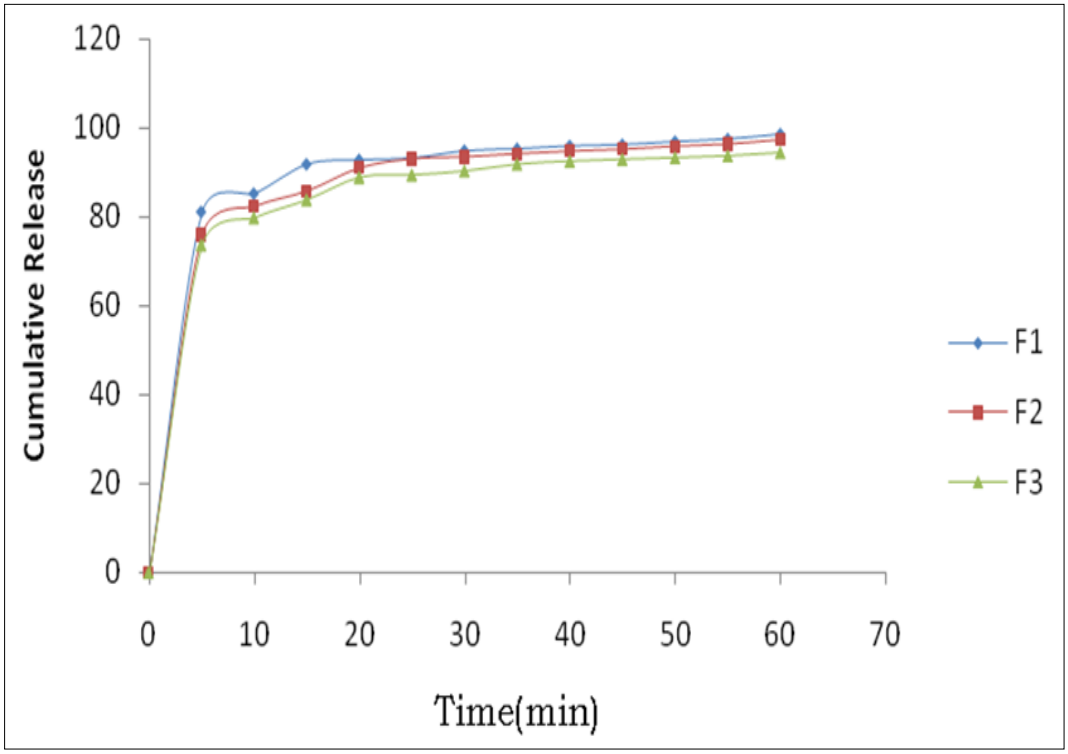


Fig 14: Dissolution profile of immediate release layer tablet in 1.2 pH buffer

***In vitro* drug release data is reported in Table8.13 and shown in Fig.14**

Formulation F1 showing *In vitro* drug release 98.63% within a period of 1 hr was further selected as optimized formulation for bilayer tablet. Floating bio-adhesive sustained release tablets Precompression parameters of floating bio-adhesive sustained release layer powder blend Results are shown in.

Table 8: Precompression parameters of floating bio adhesive sustained release layer powder blend

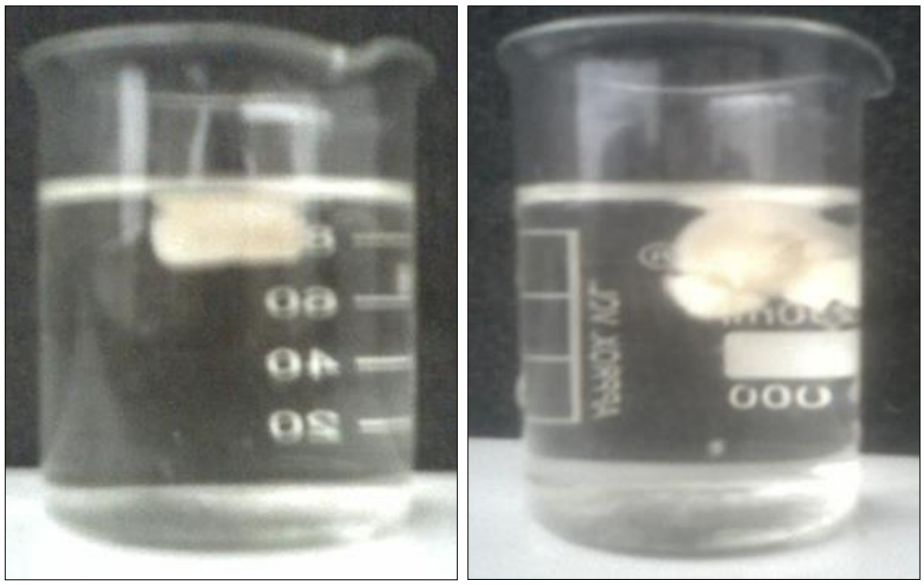
	Parameters				
Formulation Code	**Angle of Repose (θ)**	**Loose Bulk Density gm/cm3**	**Tapped Bulk Density gm/cm3**	**Hausner's Ratio (HR)**	**Compressed ability Index (%)**
A1	26.32±1.2	0.29±0.04	0.35±0.03	1.32±0.28	26.03±1.03
A2	27.53±1.7	0.21±0.02	0.37±0.06	1.30±0.14	29.30±1.25
A3	29.14±1.5	0.31±0.03	0.39±0.05	1.40±0.18	30.67±1.23
A4	25.87±1.7	0.24±0.01	0.32±0.04	1.35±0.17	23.50±1.43
A5	31.53±1.4	0.28±0.08	0.35±0.06	1.28±0.11	24.60±1.67
A6	30.12±1.7	0.30±0.04	0.34±0.03	1.24±0.14	22.79±1.34
A7	26.67±1.6	0.22±0.07	0.36±0.02	1.39±0.16	30.80±1.54
A8	27.73±1.3	0.24±0.04	0.33±0.07	1.40±0.17	32.75±1.40
A9	30.79±1.8	0.25±0.03	0.45±0.03	1.39±0.10	38.29±1.39
B1	30.49±1.4	0.23±0.09	0.40±0.05	1.48±0.14	34.32±1.37
B2	31.56±1.1	0.28±0.05	0.34±0.04	1.50±0.10	37.76±1.45
B3	30.70±1.7	0.30±0.06	0.40±0.01	1.39±0.16	28.56±1.64
B4	31.24±1.8	0.22±0.02	0.33±0.07	1.58±0.13	39.45±1.40
B5	27.97±1.4	0.26±0.08	0.39±0.04	1.55±0.19	28.44±1.45
B6	28.67±1.6	0.30±0.04	0.45±0.03	1.47±0.13	30.23±1.56
B7	30.56±1.3	0.23±0.06	0.32±0.05	1.52±0.16	38.21±1.52
B8	29.45±1.4	0.25±0.03	0.39±0.01	1.50±0.12	34.23±1.67
B9	27.34±1.5	0.26±0.02	0.44±0.07	1.56±0.16	38.32±1.70
C1	27.82±1.8	0.22±0.09	0.32±0.05	1.60±0.15	30.42±1.29
C2	31.40±1.9	0.30±0.08	0.36±0.03	1.30±0.18	25.65±1.34
C3	26.63±1.3	0.27±0.06	0.47±0.07	1.55±0.13	35.67±1.54
C4	32.40±1.5	0.26±0.03	0.35±0.09	1.46±0.09	33.66±1.33
C5	29.92±1.3	0.29±0.01	0.42±0.05	1.49±0.15	29.23±1.56
C6	31.56±1.2	0.28±0.06	0.43±0.06	1.39±0.14	39.41±1.60
C7	29.93±1.4	0.22±0.03	0.40±0.04	1.54±0.11	34.34±1.65
C8	31.78±1.3	0.28±0.08	0.41±0.06	1.40±.13	31.54±1.34

All values are mean ± SD, (N=3)

Results are shown in Table 8 results revealed that floating bio adhesive sustained release layer powder blend can withstand to direct compression method for formulation of tablets. Formulation of floating bio adhesive sustained release tablets Floating bio adhesive sustained release layer tablets were prepared according to the compositions given in Table 6,7,8.

Determination of buoyancy lag time (BLT)

At 0 min (a) After 60 min. (b)



After 8 hr. (c) After 12 hr. (d)

Fig 15: Photograph shows floating behavior a) Tablet at 0 min, b) Tablet after 60 min c) Tablet after 8 hr, d) Tablet after12 hrs (Batch AC2).

This test was only performed to check the floating behavior of floating bioadhesive sustained release layer while disintegration test was only performed to check the disintegration of immediate release layer. The buoyancy of bilayer floating tablet was studied at 37±0.5 °C in 200ml of 1.2 pH buffer (Simulated gastric fluid without pepsin). The buoyancy lag time (BLT) was measured by using stop watch and total floating time was observed visually, as shown in Fig. 8.34 until they are consumed. Floating lag time was observed less than 144 sec for all batches. Total floating time was observed more than 12 hrs.

Conclusion

This study aimed to develop floating tablets for prolonged gastric residence time using barium sulfate, a radiopaque material, in a live animal model. An *in vitro* environment was used to test a variety of tablet formulations, and the results showed that tablets containing thirty percent barium sulphate exhibited the most desirable floating behavior while still preserving their structural integrity. The *in-vivo* evaluation showed that tablets from formulations A6 and C2 were able to successfully float in the stomach of the rabbit for more than eight hours. On the other hand, formulation C2 stayed stable during the observation period, which suggests that it may stick to the stomach lining.

There are a number of advantages that floating drug delivery systems (FDDS) provide, including a longer period for the drug to remain in the stomach and a controlled release of the drug, which may result in enhanced drug absorption and bioavailability. When designing FDDS, however, there are problems that must be overcome, such as striking a balance between buoyancy and drug release.

This is because large amounts of barium sulphate might have a deleterious impact on the floating behavior of the tablet. In addition, certain single-unit FDDS have an "all-or-nothing" emptying mechanism, which might result in variations in the administration of the medicine and the possibility of local irritation at the release site. In conclusion, this study demonstrates the potential of FDDS for achieving prolonged gastric retention time and suggests future research should focus on optimizing formulation design and investigating drug release characteristics and *in-vivo* performance in larger animal models.

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