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Formulation and Evalution Of Sustained Release Effervescent Floating Tablets of Nateglinide

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Abstract: Nateglinide is a novel, exceedingly physiologic, glucose regulator lately ratified for the handling of type-2 diabetes mellitus. Nateglinide has a rapid commencement and diminutive duration of insulinotropic action those outcomes in decline of glucose level. The persistence of this study is to develop a floating tablet of Nateglinide to boost its bioavailability and sustained action. Tablets were prepared by direct compression method, using Ethyl cellulose, Carbopol 930 and pvpk-30. Tablets were evaluated for in vitro drug release features like hardness, thickness, friability, weight variation and floating properties. Additional tablets were evaluated for In vitro drug release studies for 24 hours. The tablets unveiled controlled and prolonged release while moving over the dissolution medium, polymer rearrangement played a critical role.

Key words: Nateglinide, floating tablets, ethyl cellulose, sodium bicarbonate, sustained drug release.

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I. INTRODUCTION

Oral transport of drugs is utmost preferred, versatile and expedient route of drug administration as of ease to use, cost-effective and safe[1]. Drug bioavailability of Oral controlled drug delivery is prejudiced by numerous factors gastrointestinal physiology Physiochemical properties of drug. Dosage form features[2]. Patients associated factors gastric residence time. Gastro retentive drug delivery has established momentous curiosity in the earlier few decades as most conventional oral delivery system. The improvement of a long term oral controlled- release dosage forms have been challenging principally because of the journey of the dosage forms through the gastrointestinal tract[3]. The gastro retentive dosage forms have impending for use as controlled-release drug delivery systems and can daze these complications by elongating the retention time (Drugs remain in the gastric region for several hours) of a dosage form in the GI tract, thereby enlightening the oral bioavailability, dropping drug leftover and refining solubility for drugs that are less soluble in a high pH environment[4] Diabetes Mellitus (DM) is a metabolic condition characterized by hyperglycemia, glycosuria, negative nitrogen balance, all these fallouts into an extensive range of pathological changes such as congealing of capillary basement membrane, increase in vessel wall matrix and cellular proliferation ensuing in vascular obstacle like lumen narrowing, atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular inadequacy, hence diabetes is one of the foremost sources of death and debility in the world.[5]

Insulin is the supreme key directing hormone in the governor of glucose homeostasis, comprising of 51 amino acids communal between two intramolecular chains (alpha and beta chain) concealed from beta cells of pancreatic islets. DM is of two type[6].

Type-I: Insulin dependent diabetes mellitus (IDDM)
DM supervenes due to abridged or no secretion of insulin from beta cells of pancreatic islets which could be due to extermination of beta cells by autoimmune disease (type-IA/antibodies) or by some idiopathic disorder antibodies) or drugs/chemicals/pathogens. Circulating insulin level is low or very low and patients are inclined to Ketosis.

Type-II: Non-insulin dependent diabetes mellitus (NIDDM)
There is no destruction or moderate decay in beta cells, insulin level is typical or great or low, the grounds of DM may be lessening in number of insulin-receptors (down regulation), condensed the sensitivity of peripheral tissues. Peculiarly amplified secretion of insulin and obesity. The chemical structure of Nateglinide is shown in the fig 1.

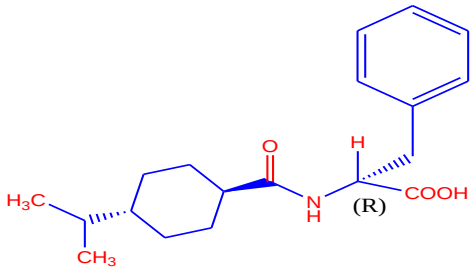

Figure 1: Chemical structure of Nateglinide**.**

II. MATERIALS AND METHODS

Materials:
Nateglinide was a gift sample obtained from UNICHEM laboratories Ltd., Mumbai. Ethyl cellulose was purchased from LOBA Chemical laboratory reagents & fine chemicals along with Carbopol 930, Magnesium sterate, Talc fine powder. Citric acid and sodium bicarbonate were purchased from Merck, Mumbai.

Pre formulation study
Pre formulation studies were conducted to identify the compatibility of drug with polymers. These studies were conducted by using FTIR method. In this method, the sample along with KBr was used to get the IR spectrum. The IR spectra of pure drug and physical mixtures containing drug and polymers were produced and analysed.

Method:
The floating tablets of Nateglinide were prepared by direct compression method.
For the preparation of floating tablets, the active ingredient was thoroughly mixed with the gas forming agent (Sodium bicarbonate) using a mortar and pestle for 15 minutes, magnesium sterate and talc were added to the above blend for flow parameters.
In all the formulations the amount of Nateglinide was kept constant at 120 mg. The different formulation chart of floating tablets are represented in table 1.

Table: 1 Formulation chart of floating tablets.

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Nateglinide	120	120	120	120	120	120	120	120	120	120
Ethyl Cellulose	90	100	120	100	120	90	150	180	180	180
Carbopol 930	120	120	120	50	80	40	30	80	45	65
Sodium bicarbonate	80	70	50	80	50	80	50	50	75	65
Citric acid	35	25	35	50	50	60	75	25	30	25
PVP k-30	25	35	25	40	40	40	30	15	20	15
Talc	10	10	10	20	20	20	25	10	10	10
Magnesium state	20	20	20	40	40	40	20	20	20	20

Evaluation Tests: (Pre Compression Studies)

Bulk density (dB): Density is determined by dividing weight of powder by volume of powder in g/cm3. Bulk density is determined by weight of dry powder and the bulk volume in a graduated cylinder.
Tapped density (dT): Tapped volume is measured by tapping of cylinder filled with bulk powder from a constant height on flat horizontal surface for 100 times. This tapped volume gives tapped density by dividing weight of dry powder by tapped volume.
Hausner ratio: The Hausner ratio is a number that is correlated to the flow ability of a powder or granular material. It is calculated by the formula, HR= dT/dB. (1)
A Hausner ratio greater than 1.25 is considered to be an indication of poor flow ability.
Carr index: It is also known as compressibility index. Carr index gives the important properties of powdergranules and is calculated by following equation,

$$CI = dT- dB / dT \times 100 \quad (2)$$

Angle of repose (Ɵ): It is calculated by fixed funnel method. The values obtained for angle of repose of all formulations are tabulated in table 2. The values were found to be in the range from 48˚.58′ to 58˚.01′ this indicate poor flow properties of powder. The angle of repose is determined by using following equation,
$\Theta = \tan^{-1} 2H/d$ (3)

Table: 2 Pre compression studies:

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's Ratio (HR)	Carr's Index (%)	Angle of repose (˚)
F1	0.43 ± 0.030	0.56 ± 0.054	1.13 ± 0.052	14.83 ± 0.77	31°. 50
F2	0.44 ± 0.034	0.55 ± 0.044	1.12 ± 0.060	11.89 ± 0.25	33°.62
F3	0.46 ± 0.028	0.54 ± 0.041	1.14 ± 0.031	12.52 ± 0.16	34°.53
F4	0.47 ± 0.019	0.56 ± 0.063	1.15 ± 0.047	15.32 ± 0.29	32°.01
F5	0.45 ± 0.043	0.54 ± 0.032	1.12 ± 0.063	13.08 ± 0.45	29°. 59
F6	0.46 ± 0.035	0.57 ± 0.061	1.13 ± 0.058	10.39 ± 0.87	28°. 29
F7	0.45 ± 0.021	0.66 ± 0.045	1.19 ± 0.041	9.98 ± 0.12	26°. 46
F8	0.46 ± 0.037	0.56 ± 0.063	1.14 ± 0.061	9.47 ± 0.48	24°. 29
F9	0.44 ± 0.024	0.54 ± 0.032	1.11 ± 0.031	9.29 ± 0.11	23°.53
F10	0.47 ± 0.029	0.66 ± 0.045	1.12 ±0.0587	10.72 ± 0.36	24°.17

Post Compression Studies: The post compression parameters such as tablets hardness, weight variation, friability, drug content and disintegration time were studied. All the studies were carried out by using standard procedures listed in Indian Pharmacopeia limits.
In-Vitro Buoyancy Study In-vitro buoyancy of each formulation was determined by floating lag time (FLT) and total floatation time (TFT). Tablet of each formulation were individually placed in a 200 ml beaker containing 0.1N HCl solution at 37± 0.5^0C. Time required for the tablet to rise to surface and float was FLT and the total time taken to remain buoyant without disintegration was TFT.
In vitro drug release: The release of Nategilinde from floating tablets was determined by using Dissolution type II test apparatus.
Drug Content Uniformity: The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of pH 7.4 Phosphate buffer, followed by stirring 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by spectrophotometer (UV-1700 pharmaspec, SHIMADZU) at 216 nm using pH 7.4 Phosphate buffer as blank.

Characterization of drug in Floating tablets: Characterization studies was done for pure drug and the mixture of pure drug and polymer for compatibility studies which was done by using FT-IR and DSC.
Comparison studies: Comparison of optimized formulation with the marketed product (Starlix 120 mg) by using *In vitro* drug release studies.
Stability studies: The stability studies were carried out on optimized formulation i.e. F2. The formulations were stored at 40 ^{o}C / 75 RH for three months to assess the quality of product. Samples were withdrawn after 1, 2 & 3 months and retested for physical properties, drug content, floating lag time and *in vitro* drug release.

III. RESULTS AND DISCUSSIONS

Pre formulation studies:
Fourier transform infrared spectroscopy (FTIR): Infrared (IR) spectroscopy studies of pure drug and excipients were recorded in a FTIR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum for each showed the wavelength of absorbed light which is a characteristic of the chemical bonds in the sample. Each spectrum was derived in the region of 4000-400 cm-1. Figure 2 shows the FT-IR spectra of pure drug Nateglinide and Figure 3 shows the FT –IR spectra of formulation F9. Table 3 is the FTIR spectral data of Nateglinide and physical mixture.

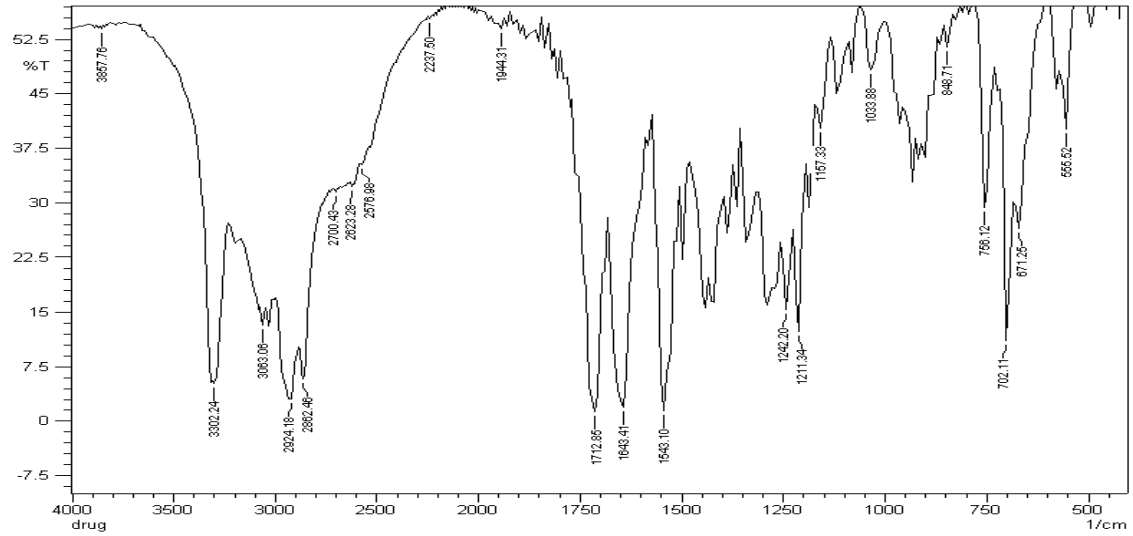

Figure: 2 FT-IR spectra of pure drug Nateglinide

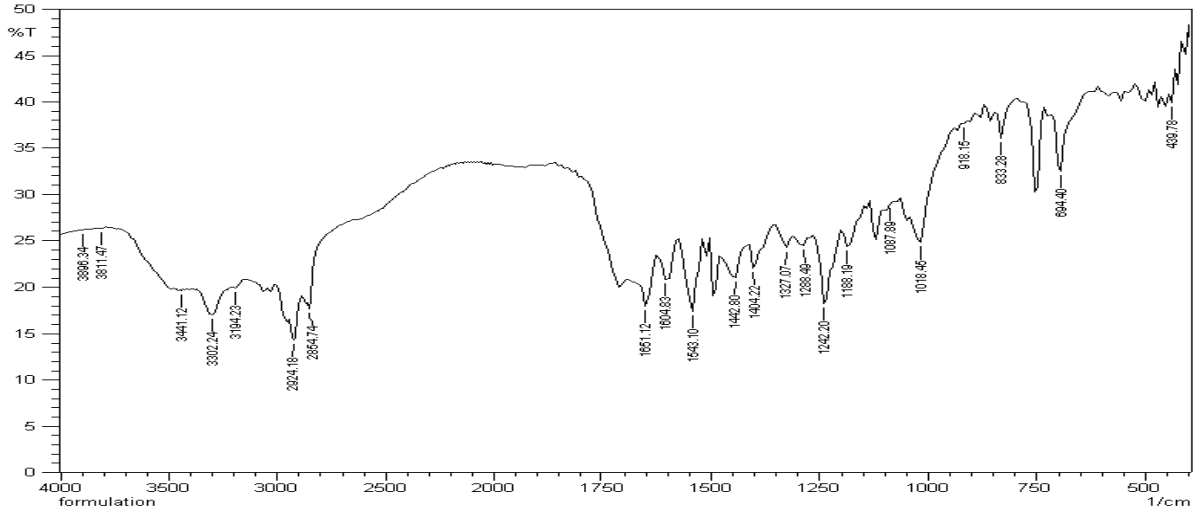

Figure: 3 FT –IR spectra of formulation F9

Table: 3 FTIR spectral data of Nateglinide and physical mixture.

Group	**Frequency range cm^{-1}**	**Peak position of Nateglinide in cm^{-1}**	**Optimized formulation in cm^{-1}**
Secondary NH stretching	3350 - 3250	3302	3302
Aromatic C-H stretching	3000 - 3050	3043	3046
Aliphatic C-H bending	2800 - 2990	2924	2995
O-H stretching	3450 - 3370	3300	3441
C-O	1100 - 1250	1211	1242
C-N	1250 - 1300	1252	1288

Differential scanning calorimetry (DSC):

The possibility of occurrence of any drug - excipients interactions in the formulation was predicted by conducting DSC studies. A sharp endothermic peak related to the melting point of pure drug Nateglinide was found at 146.5 ºC. For drug sample and the proposed formulation, the thermo gram did not show any significant shift in endothermic peak. Based on the thermo grams of DSC, it is confirmed that there is not much interaction between Nateglinide and the proposed excipients and DSC thermo gram of pure drug Nateglinide is represented in figure 4 and Figure 5 shows the DSC thermo gram of formulation (F9).

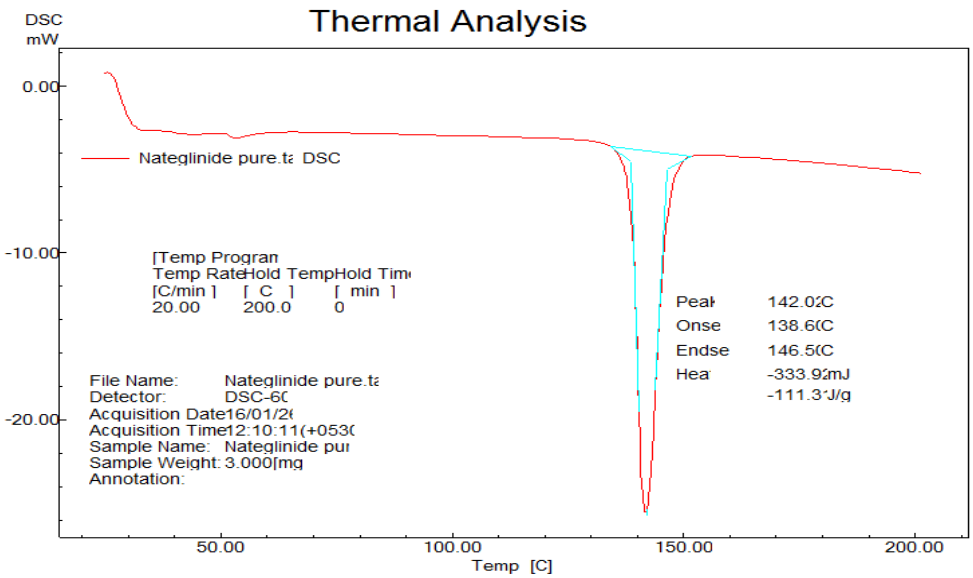

Figure: 4 DSC thermo gram of pure drug Nateglinide

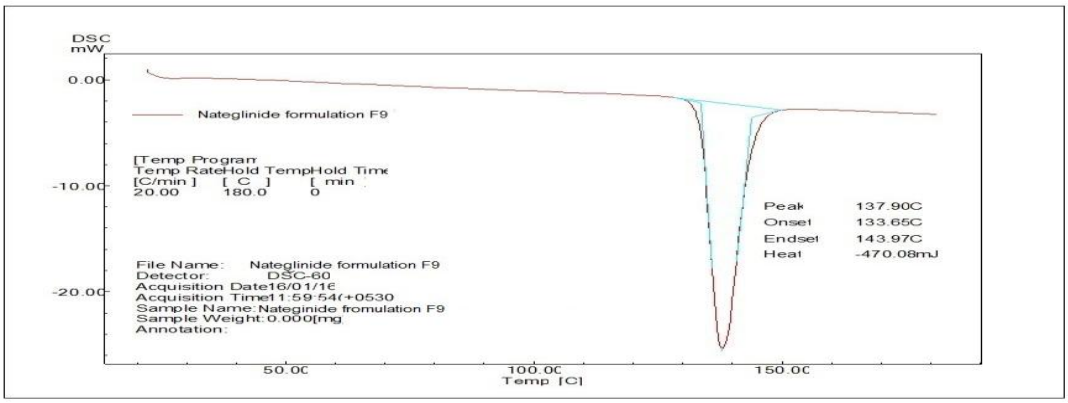

Figure: 5 DSC thermo gram of formulation (F9)

Post compression studies: All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and drug content are evaluated as shown in table.
Weight variation: Since all the materials were free flowing, the obtained tablets were having uniform weight and found to be within specific variations as per pharmacopoeia specifications, less than 10 %.
Thickness: Thickness of the tablets was found in the range of 4.9 to 5.7 which is acceptable as per pharmacopeia specifications.
Hardness: It was found to be in the range of 4.6 – 5.8 kg/cm^2 which comply with Pharmacopeia limits.
Friability: Tablets were evaluated by using Roche friabilator and found to be in the range of 0.35 – 0.63 within the pharmacopeia's limits and comply with the standards. Post compression studies are shown in table 4.

Table: 4 Post compression studies

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)
F1	493 ± 0.264	4.9 ± 0.05	5.2 ± 0.234	0.42 ± 0.081
F2	496 ± 0.325	5.5 ± 0.04	5.4 ± 0.542	0.47 ± 0.064
F3	498 ± 0.187	5.3 ± 0.04	4.6 ± 0.789	0.35 ± 0.043
F4	502 ± 0.257	5.5 ± 0.2	5.8 ± 0.612	0.52 ± 0.055
F5	508 ± 0.178	5.4 ± 0.04	5.4 ± 0.564	0.56 ± 0.087
F6	495 ± 0.247	5.6 ± 0.07	5.6 ± 0.329	0.48 ± 0.076
F7	496 ± 0.352	5.5 ± 00.3	5.7 ± 0.345	0.63 ± 0.054
F8	492 ± 0.278	5.6 ± 0.04	5.2 ± 0.343	0.59 ± 0.062
F9	499 ± 0.236	5.6 ± 0.03	5.5 ± 0.237	0.35 ± 0.078
F10	504 ± 0.186	5.7 ± 0.06	5.4 ± 0.752	0.44 ± 0.098

***In vitro* floating lag time and floating duration:** The formulations like F1, F2 shown floating lag time after a min, formulation F3, F4 shown floating lag time below 1 minute and above 20 sec with the total floating duration time below 20 hrs. In the rest of the formulations F5 to F10 the floating lag time was found to be below 12 sec, with the total floating duration time above 20 hrs. Formulation F9 was found to be the one with rapid flotation time 3 sec with the total duration 24 hrs is mentioned in table – 5.

Table: 5 Drug content uniformity

Formulation	Drug content (%)	Buoyancy lag time (sec)	Total floating time (hrs)
F1	99.84 ± 0.60	70	12
2	98.52 ± 0.42	65	13
F3	100.32 ± 0.48	45	14
F4	98.67 ± 0.71	22	16
F5	99.38 ± 0.38	08	21
F6	99.12 ± 0.66	11	24
F7	99.28 ± 0.12	10	24
F8	101.58 ± 0.34	9	>24
F9	100.99 ± 0.14	3	>24
F10	97.76 ± 0.20	8	>24

***In-Vitro* drug release studies:**

The in vitro dissolution studies have been carried out for all the formulations from F1 to F10. The release of Nategilinde form the gastro retention floating tablets varied according to the composition. The drug release from formulation F1 was up to 12 hours. The % drug release from formulation from formulation F3 was not extended up to 6hrs and immediate drug release pattern was observed; formulation F2 and F4 was extended to 16 hrs and f5 to 20 hrs. From formulation F6 to F10 controlled drug release was observed till hour 24. Highest % drug release has been noticed in F9 with 98.92 % at hour 24. The samples were analyzed at 216 nm by UV spectrophotometer (UV1700 pharmaspec, SHIMADZU) results are shown in table 6.

Table 6: % In vitro drug release studies

Cumulative drug release (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.5	33.62 ± 1.77	28.42 ± 2.94	42.32 ± 2.73	29.72± 1.83	17.25± 2.84	19.78± 2.41	19.86 ± 1.34	14.11± 1.29	14.26± 3.27	14.13 ± 2.56
1	47.15 ± 4.57	37.41 ± 1.6	54.64 ± 3.14	39.67± 2.01	28.21± 1.39	28.32± 3.1	26.72± 4.61	20.74± 3.27	21.85± 1.59	21.71 ± 3.34
2	57.34 ± 3.59	48.21 ± 2.57	78.81 ± 2.26	53.24± 3.23	41.32± 2.72	34.65± 1.72	35.21± 3.15	27.12± 4.28	30.38± 2.92	29.25 ± 1.56
4	71.84 ± 2.65	63.92 ± 1.49	94.59 ± 3.7	66.78± 1.86	57.15± 1.48	48.12± 3.13	40.93± 2.06	34.12± 1.89	38.59± 2.77	33.28 ± 2.21
6	80.12 ± 5.46	72.92 ± 3.35	97.32 ± 4.82	74.55± 2.74	63.29± 2.4	60.25± 1.99	49.18± 1.82	41.59± 2.56	45.89± 1.67	40.52 ± 1.56
8	92.35 ± 2.97	86.77 ± 2.57	-	81.42± 3.09	79.42 ± 4.66	72.88± 2.59	54.72± 0.92	51.79± 0.84	51.51± 2,53	52.72 ± 4.28
12	95.29 ± 1.77	93.15 ± 1.71	-	94.83± 4.61	88.24± 2.12	91.33± 1.42	63.28± 3.29	68.39± 3.45	63.78± 4.08	67.29 ± 2.29
16	-	96.12 ± 2.09	-	97.12± 4.38	95.82± 2.4	92.32± 3.67	72.28± 2.57	79.28± 1.59	75.48± 4.28	78.81 ± 4.46
20	-	-	-	-		96.72± 2.27	89.61 ± 1.29	87.34± 2.63	89.51± 3.19	86.82 ± 3.26
24	-	-	-	-	-	96.92± 2.49	95.12± 2.28	94.82± 2.92	98.92± 3.26	93.92 ± 3.28

In the dissolution study of formulation F1, F2, F3 and F4, F5 was revealed that only one formulation F5 have released the drug in controlled manner till 20 hours or more, formulation F3, F4 released more than 15 hrs, whereas remaining formulation failed to release for prolonged period of time, as shown in figure 6.

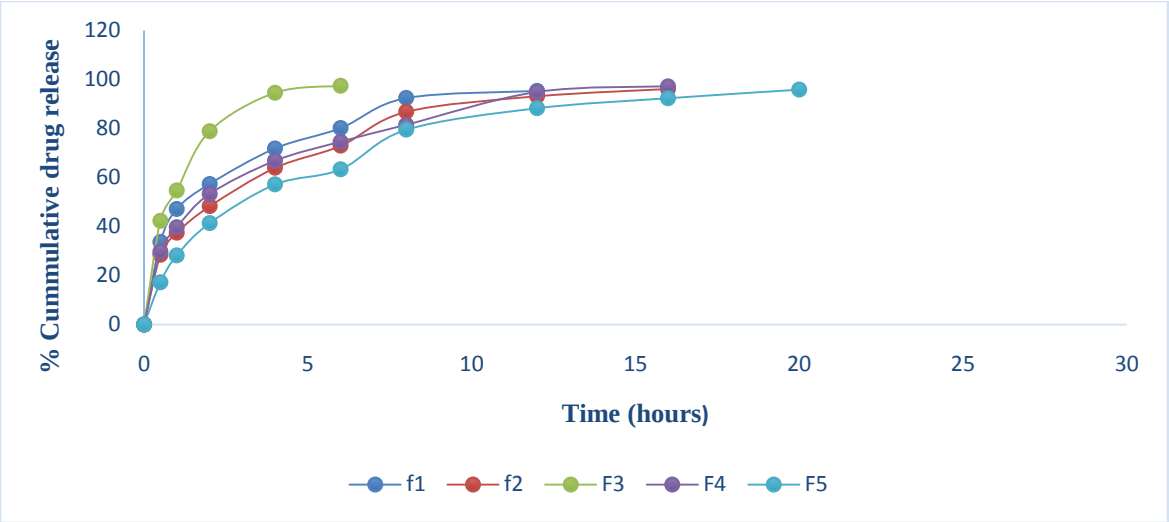

Figure: 6 Cumulative % release of Nateglinide from formulation F1-F5

In the dissolution study of formulation F6, F7, F8 and F9, F10 it was revealed that formulation F9 had controlled release 98.92 % at hour 24 when compared to the remaining formulations like F7, F8 and F10 at hour 24, as represented in figure 7.

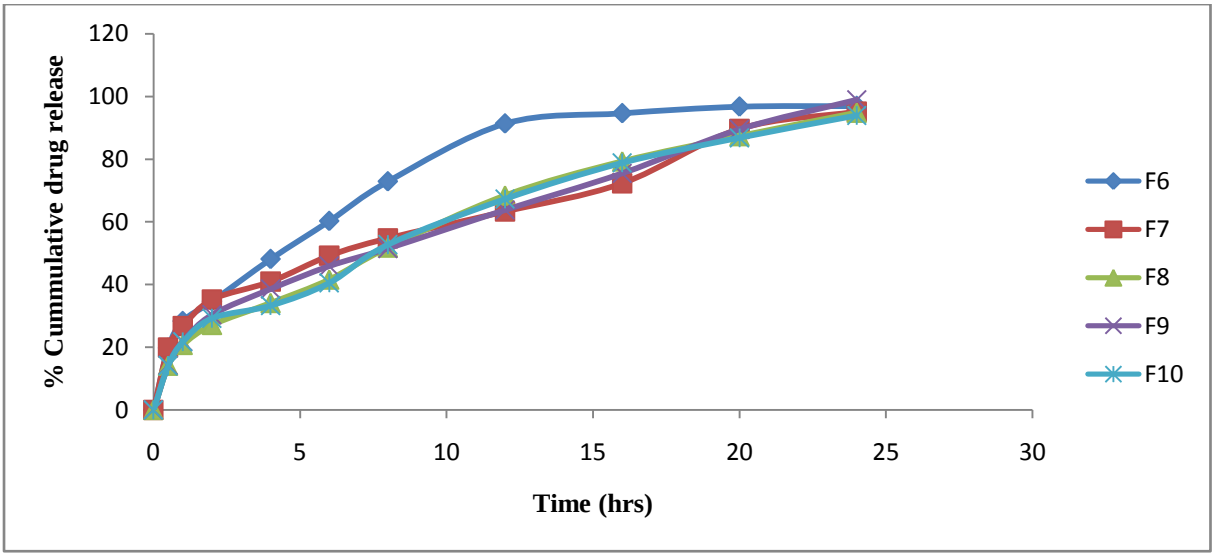

Figure: 7 Cumulative % release of Nateglinide from formulation F6-F10

Comparison studies: The comparison studies of formulation F9 with marketed products reveals the maximum release of marketed product was found to be 97.92 % release at hour 8, on the other hand formulation F9 gives the sustained release until the hour 24 with the percentage drug release of 98.94 %, which helps in reducing the dosing frequency of drug form 3 times a day to 1 time a day, as mentioned in table 7.

Table: 7 Comparison of formulation F9 with marketed product

S.no	Time (hrs)	Marketed formulation	F9
1	0.5	36.42 ± 1.76	14.28 ± 3.26
2	1	56.82 ± 2.52	23.85 ± 1.54
3	2	71.89 ± 3.56	32.48 ± 2.96
4	4	80.21 ± 2.65	40.56 ± 2.84
5	6	86.95 ± 4.32	46.89 ± 1.59
6	8	97.92 ± 1.68	54.32 ± 2.65
7	12	-	65.78 ± 4.32
8	16	-	75.82 ± 4.26
9	20	-	89.96 ± 3.89
10	24	-	98.94 ± 3.73

Stability studies[7,8]: The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The optimized tablets were subjected to stability studies for three months at 40 °C ± 2 °C / 75 % ± 5 % RH in a humidity chamber. The products were evaluated for their physical properties and *in vitro* drug release profiles over a period of three months listed in table 8.

Table: 8 Stability data of floating tablets

S. No	Parameters	Initial 0 days	1 month	2 months	3 months
1	Average weight (mg) 500 ± 5.0	501 ± 0.4	500 ± 0.3	499 ± 0.5	499 ± 0.2
2	Hardness (kg/cm^2)	5.5 ± 0.5	5.4 ± 0.3	5.2 ± 0.2	5.2 ± 0.2
3	Thickness (mm)	5.6 ± 0.3	5.4 ± 0.2	5.4 ± 0.2	5.4 ± 0.1
4	*In vitro* dissolution	98.92 %	97.91 %	96.96 %	96.11 %

IV. SUMMARY

The present study demonstrates the feasibility of prolonging the gastric residence time floating tablets; it also reveals the effects of sodium bicarbonate on the buoyancy lag time with ethyl cellulose and carbopol930, which has predominant effect on total floating time and drug release. The tablets showed controlled release pattern after immediate initial release. In vitro release studies discloses that formulation F9 showed maximum floating time with maximum % drug release (98.92%) which deliberated as the successful formulation.

V. CONCLUSION

Nateglinide is a potent drug for treatment of diabetes mellitus type II but it has a rapid onset and short duration of insulinotropic action. Gastro retentive formulation improves bioavailability, prolonged duration of action, reduced drug waste and dosing frequency. Thus, conclusion can be made that the stable floating dosage form can be developed for Nateglinide controlled release floating tablets.

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