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Design, Development and In-Vitro Evaluation of Orodispersible Tablets of Nateglinide Using Direct Compression Method

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ABSTRACT

Nateglinide is the meglitinide derivative class of blood glucose lowering agent. It's used for the treatment of type 2 diabetes mellitus condition most in pediatric and geriatric populations. the Novel drug developments In fast disintegration/dissolving tablets this have a convenient dose in pediatric, elderly patients and who have trouble in swallowing tablets.so the present study and aim of formulation convenient of administration and patient acceptability friendly dosage from i.e. fast dissolving tablet nateglinide was carried out using formulation techniques direct compression with the addition of superdisintegrants. Superdisintegrants such as croscarmellose sodium, crospovidone, and sodium starch glycolate. Different binders using and optimized superdisintegrants concentration. The tablets evaluated for friability, hardness, weight variation, wetting time, disintegration time, and content uniformity. The formulation optimized by evaluation of *in-vitro* dissolution study, drug-excipient compatibility and accelerated stability study. The formulation was concluded fast disintegration tablets of nateglinide were formulated successfully with desired characteristics and rapid onset of action. And enhanced the patient convenience and compliance.

INTRODUCTION:

Tablets may be defined as solid pharmaceutical dosage forms containing medicament or medicaments with or without suitable excipients & prepared either by compression or molding. Recently pharmaceutical preparations used for elderly patients have been investigated to improve the compliances and quality of life of patients.[1] Recent advances in Novel Drug Delivery System (NDDS) aims to enhance the safety and efficacy of a drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is "Mouth/Fast Dissolving Tablet". This is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Innovators and inventor companies have given these tablets various names such as orally disintegrating tablets (ODT), mouth dissolving (MD), fast melting, fast dissolving or disperse [2][3]. The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide the patient with a conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Other categories that experience problems using conventional oral dosage forms includes are the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to unavailability of water. These problems led to the development of a novel type of solid oral dosage form called "Fast Dissolving Tablets". On placing the fast-dissolving tablet in the mouth, it has dissolved rapidly. When the tablet comes to contact with water it swallowed or swelled? And the drug is absorbed in the normal way. Drugs are easily absorbed in stomach & it may produce rapid onset of action. In such a cases Bioavailability of a drug is significantly greater than those observed from the conventional tablet dosage form. The growing importance of fast dissolving tablet was underlined recently. According to European Pharmacopoeia, fast dissolving tablet means tablet which disintegrates within three minutes. For rapid dissolution or disintegration of a dosage form, water must rapidly penetrate into the tablet matrix to cause quick disintegration & instantaneous dissolution of the tablet. Several techniques are used to achieve these fundamentals, to formulate fast-dissolving tablet. Some of the techniques are Freeze Drying, Moulding, Sublimation, Spray Drying, Direct compression [4] [5].

Nateglinide is chemically (-)-N-[(trans-4-isopropylcyclohexane)carbonyl]-D- Phenylalanine, Clinically, Antidiabetics are the most frequently prescribed drugs Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta- cells in the pancreatic islets. Nateglinide interacts with the ATP- sensitive potassium (K+ ATP) channel on pancreatic beta- cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. Nateglinide is available in marketing as tablets form. Conventional Nateglinide tablets available in markets are not suitable for quick onset of action. Besides, the conventional tablets also show poor patient compliance particularity by the geriatric and pediatric patients who experience difficulty in swallowing, and by those who are bedridden or who are traveling and do not have an easy access of water. To provide the patients with the most convenient mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without the need of water, anytime, anywhere, such tablets are called as mouth dissolve tablets [7].

MATERIALS AND METHODS:

MATERIALS:

Nateglinide was purchased from (**Glen mark pharmaceutical Pvt. Ltd**) Croscarmellose sodium (CCS) Sodium starch glycolate, Crospovidone was obtained as **Colorcon Asia Pvt. Ltd**., Alginic acid NF, Soy polysaccharides, Calcium Silicate. Was purchased from **Loba chemicals**. All others ingredients were of analytical grade'.

METHODS:

Preparation nateglinide standard stock solution (10 mcg/ml.) in 0.01N HCl solution

Nateglinide (100mg) was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in 0.01 N HCl and volume was made up to the mark with 0.01 N HCl to get a 1000 mcg/ml solution. One ml of the above solution was then further diluted to 100 ml with 0.01 N HCl to get a stock solution of 10 mcg/ml.

Calibration curve of nateglinide in 0.01N HCl solution:

From the stock solution 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml were transferred to 10 ml volumetric flasks and were diluted with the 0.01 N HCl, up to the mark to obtain nateglinide concentration of 2, 3, 4, 5, 6, 7, 8, 9 and 10 µg/ml respectively. The absorbance of each solution was measured at 210 nm.

Preformulation studies:

Melting point determination:

The melting point is the temperature at which the pure liquid and solid exist in equilibrium. In practice, it is taken as an equilibrium mixture at an external pressure of 1 atmosphere; this is sometimes known as the normal melting point. The Thiel's tube method of melting point determination in nateglinide was used in the present study. Melting point was found to be in the range of 136-141○C which is in compliance with the official value.

Drug-excipient Compatibility study:

Compatibility of the drug with recipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes in the chemical constitution of the drug after combined it with the excipients recipients. The samples were taken for FT-IR study.

FTIR Studies:

IR spectra of a drug in KBr pellets at moderate scanning speed between 4000400 cm-1 was carried out using FTIR (Jasco FTIR 6100 type A). The peak values (Wave number) and the possibility of the functional group present the comparison of these results with nateglinide chemical structure and polymers in standard IR spectrum.

Solubility studies:

It determined by dissolving drug substance is freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in chloroform and in the ether.

Optimization of super disintegrants:

Selection of excipients and optimization of their concentration:

The most important parameter that needs to be optimized fast disintegrating tablets is the disintegration time. The tablets were prepared using different excipients binders and super disntegratants and then evaluated various parameters like hardness and disintegration time .this formulations of fast disintegrating tablets select the best combination. Four super-disintegrating agents are used at lower, medium & higher concentration. Seven formulations were designed. All the Super-disintegrates such as croscarmellose, crospovidone, sodium starch glycolate, were maintained 3% in all the formula and amberlite added in all formula as a 3% individually. Microcrystalline cellulose and mannitol were used as diluents. Here microcrystalline cellulose is also a super disintegrant. Each formulation was composed of drug and excipients in various preparation. This design technique was used to optimize and obtain a better formulation. Then the combination with lower disintegration time, optimum hardness and friability were selected and further study [8] [9].

Optimization of super disintegrant sodium starch glycolate (primo gel)

The tablets and capsules which require rapid disintegration include the super disintegrants and its optimum concentration is a prerequisite for optimal bioavailability. Superdisintagrants reduce the disintegration time which turns enhance the drug dissolution rate. The proper choice of super disintegrants importance to the formulation of rapidly disintegrating dosage forms.

Formulation F1-F7 was prepared to study the effect type and concentration of super disintegrants in table 1 tablets were prepared to direct compression method. Weight quantity of nateglinide with different concentrations of super disintegrant (starch glycolate sodium) along with excipients mixed in geometric progression in a dry mortar. Then blend and pass through sieve number 80 for direct compression. The powder blend was then compressed into a tablet using 10mm punch rotary tablet compression machine [9] [10].

Optimization of croscarmellose sodium or (microcrystalline cellulose) and other binders along with optimized concentration super disintegrant.

Formulation F1-F7 was prepared to study the effect type and concentration of super disintegrants. Tablets were prepared to direct compression method. Weight quantity of nateglinide with different concentrations of super disintegrant (croscarmellose) along with excipients mixed in geometric progression in a dry mortar. Then blend and pass through sieve number 80 for direct compression. The powder blend was then compressed into a tablet using 10mm punch rotary tablet compression machine [9] [10].

PREPARATION OF NATEGLINIDE FAST DISSOLVE TABLETS:

Preparation of nateglinide tablets using dry granulation technique.

Weighed the Nateglinide, and superdisintegrants, mannitol, microcrystalline cellulose, and aspartame accurately. All the materials were passed through 40 mesh screen prior to mixing. Then add the remaining excipients like talc and magnesium stearate. Mix well and pass through 80 mesh screen. The resulting granules were compressed into tablets using a rotary tablet machine [11].

EVALUATION OF FAST DISSOLVING TABLETS OF NATEGLINIDE:

Mechanical Strength:

Tablets should possess adequate strength to withstand mechanical shocks of handling in manufacturing, packaging, and shipping. Crushing strength and friability are two important parameters to evaluate a tablet for its mechanical strength [12] [13].

Crushing Strength:

This is the force required to break a tablet by compression in the radial direction, it is an important parameter in the formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study, the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported [12] [13].

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P.

Table 1: Weight variation specification as per IP.

Sr. No.	Average weight of tablet	% Deviation
1	80mg or less	±10
2	more than 80mg less then 200mg	±7.5
3	250mg or more	±5

Friability testing:

The crushing test may not be the best measure of potential behavior during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measured in "Electro lab friabilator". Ten preweighed tablets were rotated at 25 rpm for 4 min, the tablets were then reweighed and the percentage weight loss was calculated using,

$$F = ((W1 – W2/W1) \times 100)$$

Rapidly Disintegrating Property

To evaluate the tablets for their rapid disintegration properties, the following tests were carried out.

Wetting time:

Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. Ten millimeters of water containing Eosin, a water-soluble dye, is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach an upper surface of the tablet is noted as a wetting time.

Modified disintegration test: The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for ODT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a Petri dish (10 cm diameter) was filled with 10 ml of water. The

tablet was carefully put in the center of Petri dish and the time for the tablet to completely disintegrate into fine particles was noted [14].

Water absorption Ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using the following equation,

$$R = 100 (Wb-Wa/Wa)$$

Where Wb is the weight of tablet before water absorption Wa is the weight of tablet after water absorption.

***In-vitro* dispersion time:**

Tablet was added to 10 ml of .001N HCL, (pH 1.2) at 37+0.5ºc. The time required for complete dispersion of a Tablet was measured.

***In-Vitro* drug release**

The release of the drug *in-vitro* was determined by estimating the dissolution profile.

Dissolution test:

USP 2 Paddle apparatus was used and the paddle was allowed to rotate at 50 rpm. 0.01 N HCl (900 ml) was used as a dissolution medium.

Determination of amount of drug dissolved form tablets was carried by Schimadzu UV 1601 spectrophotometer at 210 nm [14] [15].

Stability study:

Selected formulations were subjected to stability studies as per I.C.H. Guidelines. Following conditions were used for stability studies [16] [17].

30˚C/65 % RH analyzed at a time interval of 10 days till a period of 30 days 40˚C/75 % RH analyzed at a time interval of 10 days till a period of 30 days.

RESULTS AND DISCUSSION

Standard calibration curve of nateglinide at 210nm is 0.01NHCL:

From the stock solution 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml were transferred to 10 ml volumetric flasks and were diluted with the 0.01 N HCl, up to the mark to obtain nateglinide concentration of 2, 3, 4, 5, 6, 7, 8, 9 and 10 µg/ml respectively. The absorbance of each solution was measured at 206 nm. (fig.2)

Table 2: Summary of validation parameters proposed UV method:

Sr. No.	Parameters	Value
1	absorption maximum ((λmax))	210nm
2	Beer's Law limit (µg/mL)	1-5
3	Regression equation (y=mx+c)	y=0.0215x+0.079
5	slope	0.0215
6	intercept	0.0079
7	Coefficient of correlation ($R^{2)}$	0.9947

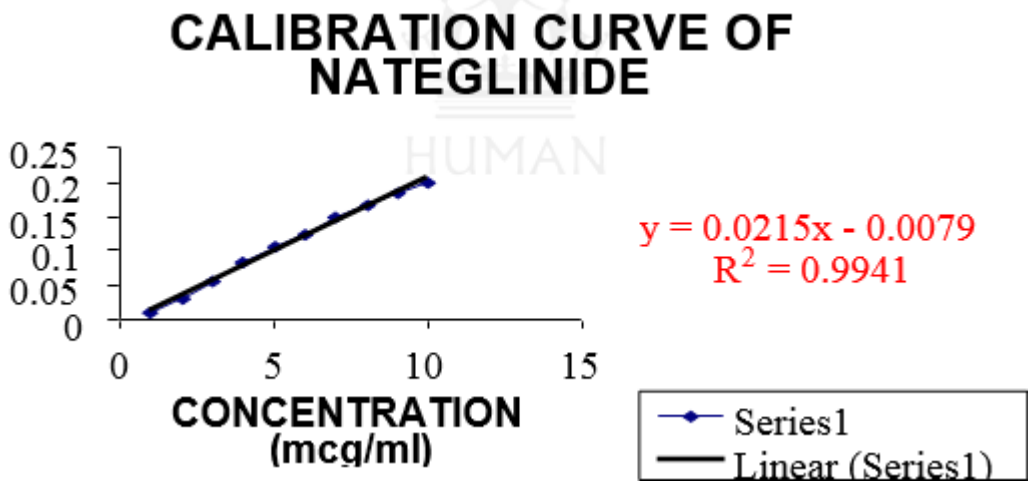
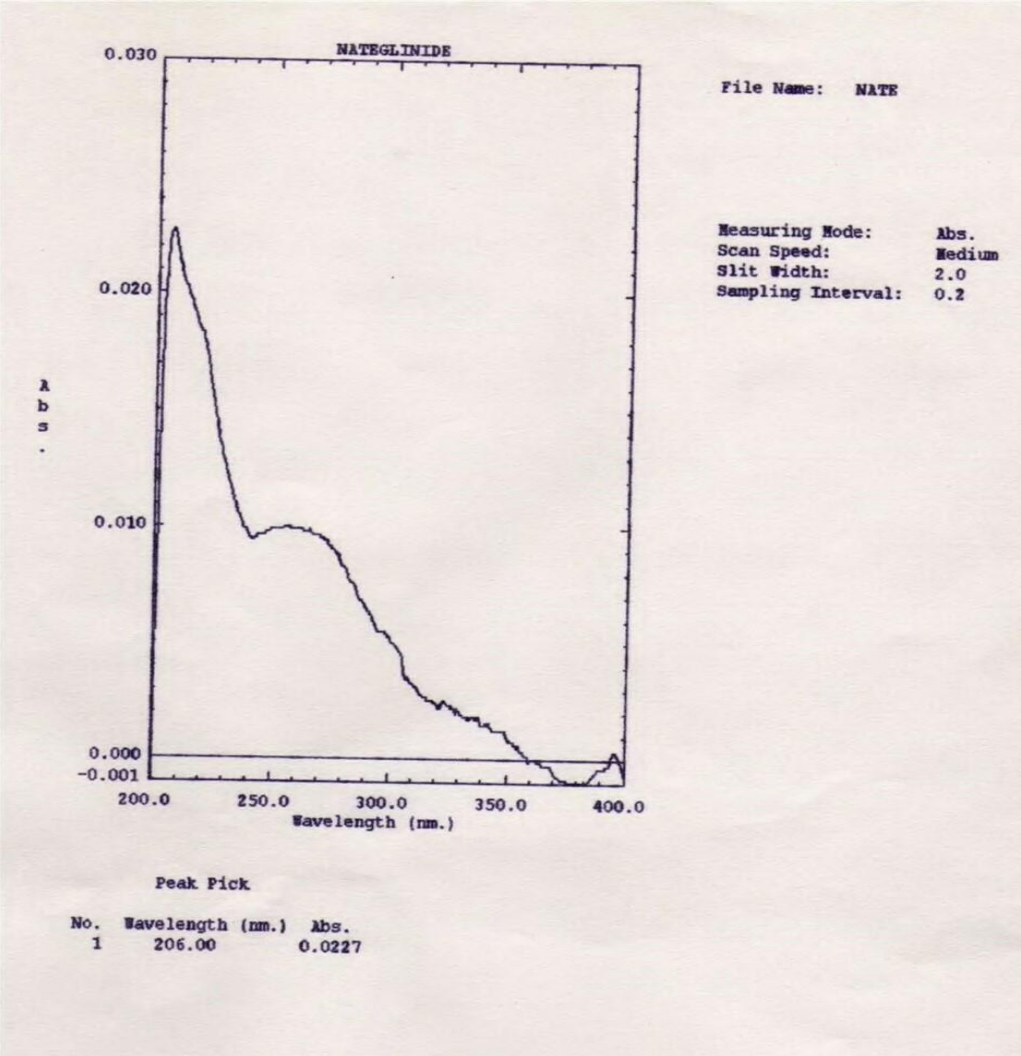


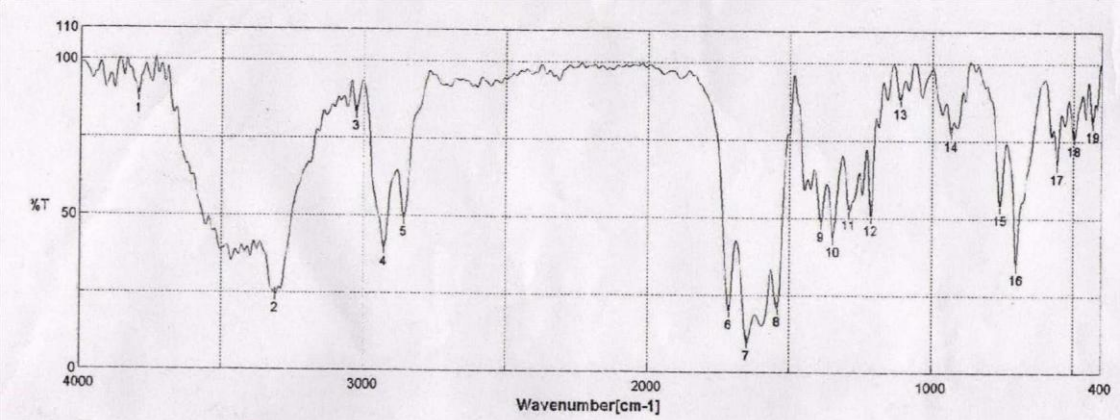
Fig. 1: Calibration curve of nateglinide

Drug excipients- compatibility studies:

Prepare KBr pellets with drug and excipients in a force of 8 tons, IR spectra of the drug in KBr pellets at moderate scanning speed between 4000 to 400 cm^{-1} was carried out using FTIR (Jasco FTIR 6100 type A). Given below on IR spectrum. Fourier-transform infrared

spectrum of nateglinide, (fig.2) the infrared spectrum of nateglinide + croscarmellose, (fig.3) the spectrum of nateglinide + crospovidone, (fig.4) the spectrum of nateglinide + sodium starch glycolate. (fig.5)

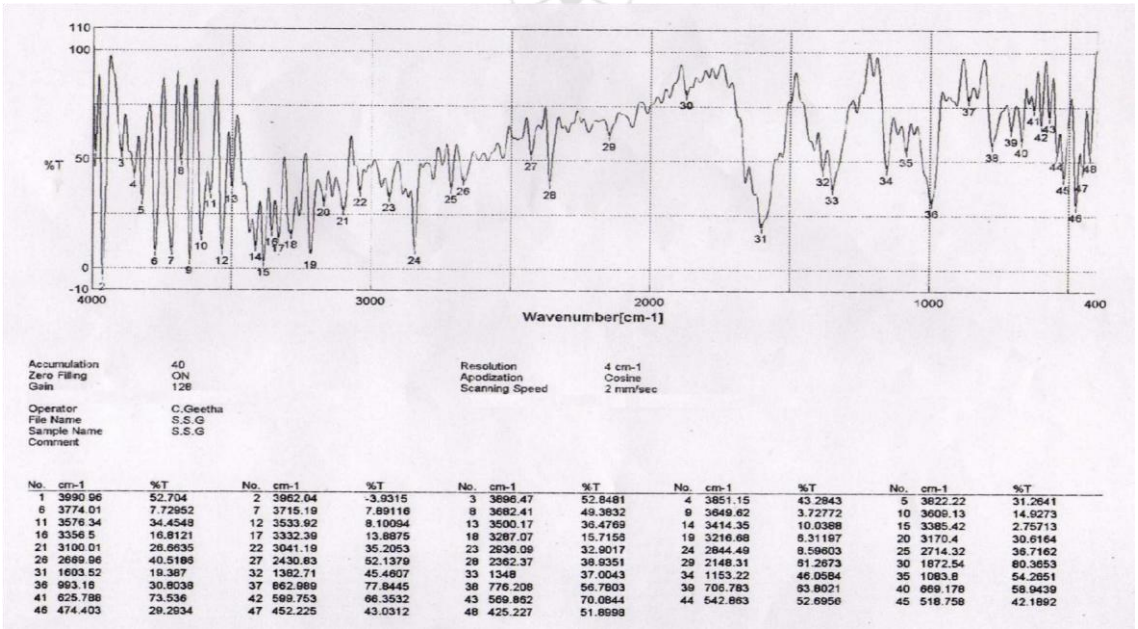




Accumulation	40
Zero Filling	ON
Gain	8
Operator	C.Geetha
File Name	Pure drug
Sample Name	Pure drug
Comment	
Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3795.22	88.186	2	3309.25	24.4521	3	3027.69	83.1914	4	2926.38	39.6067	5	2858.95	49.2268
6	1713.44	19.8403	7	1648.84	9.91197	8	1541.81	20.9789	9	1387.53	48.4029	10	1346.07	43.5741
11	1290.14	52.3543	12	1213.01	50.4431	13	1110.8	88.1294	14	933.378	77.6494	15	755.959	53.9055
16	699.069	34.7354	17	557.327	67.1539	18	496.58	76.2872	19	431.977	80.8481			

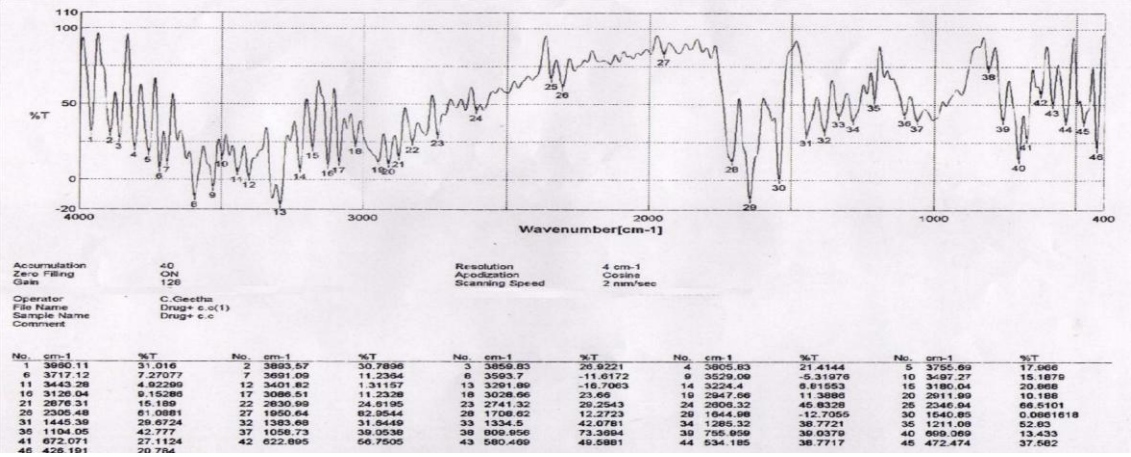
Fig 2: Fourier-transform infrared spectrum of nateglinide



Accumulation	40
Zero Filling	ON
Gain	128
Operator	C.Geetha
File Name	S.S.G
Sample Name	S.S.G
Comment	
Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec

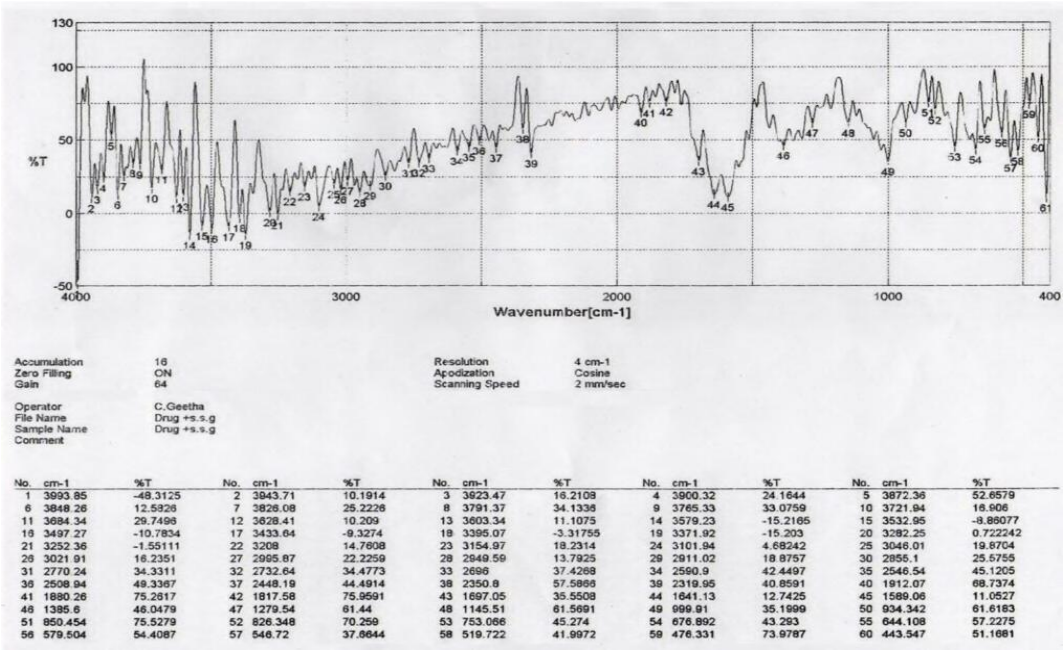
No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3990.96	52.704	2	3962.04	-3.9315	3	3896.47	52.8481	4	3851.15	43.2843	5	3822.22	31.2641
6	3774.01	7.72952	7	3715.19	7.89116	8	3682.41	49.3632	9	3649.62	3.72772	10	3609.13	14.9273
11	3576.34	34.4548	12	3533.92	8.10094	13	3500.17	36.4769	14	3414.35	10.0388	15	3385.42	2.75713
16	3356.5	16.8121	17	3332.39	13.8875	18	3287.07	15.7158	19	3216.68	5.31197	20	3170.4	30.6164
21	3100.01	26.6635	22	3041.19	35.2053	23	2936.09	32.9017	24	2844.49	8.59603	25	2714.32	36.7162
26	2669.96	40.5186	27	2430.83	52.1379	28	2362.37	38.9351	29	2148.31	51.2673	30	1872.54	80.3653
31	1603.52	19.387	32	1382.71	45.4607	33	1348	37.0043	34	1153.22	46.0584	35	1083.8	54.2651
36	993.18	30.8038	37	862.989	77.8445	38	776.208	56.7803	39	706.783	93.8021	40	669.178	58.9439
41	625.788	73.536	42	599.753	66.3532	43	569.862	70.0844	44	542.863	52.6956	45	518.758	42.1892
46	474.403	29.2934	47	452.225	43.0312	48	425.227	51.8998						

Fig 3: Fourier-transform infrared spectrum of nateglinide + croscarmellose



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3990.11	31.016	2	3893.57	30.7836	3	3859.83	26.9221	4	3805.83	21.4144	5	3755.69	17.966
6	3717.12	7.27077	7	3691.09	11.2364	8	3593.7	-11.6172	9	3529.09	-5.31976	10	3497.27	15.1878
11	3443.28	4.92299	12	3401.82	1.31157	13	3291.89	-16.7063	14	3224.4	8.81553	15	3180.04	20.868
16	3128.04	9.15288	17	3086.51	11.2328	18	3028.66	23.66	19	2947.66	11.3886	20	2911.99	10.186
21	2876.31	15.189	22	2830.99	24.8195	23	2741.32	29.2543	24	2696.32	46.8328	25	2346.94	66.5101
26	2305.48	61.0881	27	1950.64	82.9544	28	1706.62	12.2723	29	1644.98	-12.7055	30	1540.85	0.0861618
31	1445.39	29.6724	32	1383.69	31.8449	33	1334.5	42.0781	34	1285.32	38.7721	35	1211.08	52.63
36	1104.05	42.777	37	1058.73	39.0538	38	809.956	73.3994	39	755.959	39.0379	40	669.069	13.433
41	672.071	27.1124	42	622.895	56.7505	43	580.469	49.5881	44	534.185	38.7717	45	472.474	37.582
46	425.191	20.784												

Fig 4: Fourier-transform infrared spectrum of nateglinide + crospovidone:



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3993.85	-48.3125	2	3943.71	10.1914	3	3923.47	16.2108	4	3900.32	24.1644	5	3872.36	52.6579
6	3848.28	12.5826	7	3826.08	25.2228	8	3791.37	34.1338	9	3765.33	33.0759	10	3721.94	16.906
11	3684.34	29.7498	12	3628.41	10.209	13	3603.34	11.1075	14	3579.23	-15.2165	15	3532.95	-8.86077
16	3497.27	-10.7834	17	3433.64	-9.3274	18	3395.07	-3.31755	19	3371.92	-15.203	20	3282.25	0.722242
21	3252.36	-1.55111	22	3208	14.7608	23	3154.97	18.2314	24	3101.94	4.68242	25	3046.01	19.8704
26	3021.91	16.2351	27	2965.87	22.2259	28	2949.59	13.7925	29	2911.02	18.8757	30	2855.1	25.5755
31	2770.24	34.3311	32	2732.64	34.4773	33	2696	37.4268	34	2590.9	42.4497	35	2546.54	45.1205
36	2508.94	49.3367	37	2448.19	44.4914	38	2350.8	57.5866	39	2319.95	40.8591	40	1912.07	68.7374
41	1880.26	75.2617	42	1817.58	75.9591	43	1697.05	35.5508	44	1641.13	12.7425	45	1589.06	11.0527
46	1385.6	46.0479	47	1279.54	61.44	48	1145.51	61.5691	49	999.91	35.1999	50	934.342	61.6183
51	850.454	75.5279	52	826.348	70.259	53	753.086	45.274	54	676.892	43.293	55	644.108	57.2275
56	579.504	54.4087	57	546.72	37.8644	58	519.722	41.9972	59	476.331	73.9787	60	443.547	51.1681

Fig 5: Fourier-transform infrared spectrum of nateglinide + sodium starch glycolate:

Evaluation of the blend:

Weight quantity of nateglinide with different concentrations of super disintegrant along with excipients mixed in geometric progression in a dry mortar. Then blend and pass through sieve number 80, after evaluated pre-formulation parameters.

Table 3: The blend was evaluated for tapped density, bulk density, % compressibility, and Hausner s ratio.

Sr. No.	Batch Code	Bulk Density gm/cm^3	Tapped Density gm/cm^3	Angle of Repose (Ɵ)	Compressibility Index (%)	Hausners Ratio
1	F1	0.41	0.47	24.58	12.76	1.15
2	F2	0.44	0.52	25.91	15.38	1.18
3	F3	0.44	0.51	26.86	13.72	1.16
4	F4	0.47	0.54	24.43	12.96	1.14
5	F5	0.45	0.50	24.10	12.00	1.06
6	F6	0.46	0.53	24.77	13.20	1.15
7	F7	0.47	0.52	25.42	9.61	1.11

Formulation of Optimization of super disintegrant sodium starch glycolate (primo gel)

Formulation F1-F7 was prepared to study the effect type and concentration of super disintegrants in table 1 tablets were prepared to direct compression method. Weight quantity of nateglinide with different concentrations of super disintegrant (starch glycolate sodium) along with excipients mixed in geometric progression in a dry mortar. Then blend and pass through sieve number 80 for direct compression. The powder blend was then compressed into a tablet using 10mm punch rotary tablet compression machine.

Table 4: the formula for 1 tablet (300mg) of different concentrations of sodium starch glycolate

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Nateglinide	60	60	60	60	60	60	60
2	Croscamellose Na	3	3	3	3	3	3	3
3	Na.Starchglycolate	2 10%	3 20%	4 30%	5 40%	6 50%	7 60%	8 60%
4	Crospovidone	3	3	3	3	3	3	3
5	Amberlite	6	6	6	6	6	6	6
6	Povidone	12	12	12	12	12	12	12
7	Aspartame	6	6	6	6	6	6	6
8	Mg. Stearate	6	6	6	6	6	6	6
9	Mannitol	142	141	140	139	138	137	136
10	MCC	60	60	60	60	60	60	60

(All ingredients were taken in mg)

Optimization of croscarmellose sodium or (microcrystalline cellulose) and other binders along with optimized concentration super disintegrant.

Formulation F1-F7 was prepared to study the effect type and concentration of super disintegrants. Tablets were prepared to direct compression method. Weight quantity of nateglinide with different concentrations of super disintegrant (croscarmellose) along with excipients mixed in geometric progression in a dry mortar. Then blend and pass through sieve number 80 for direct compression. The powder blend was then compressed into a tablet using 10mm punch rotary tablet compression machine.

Table 5: the formula for 1 tablet (300mg) for the optimization of croscarmellose sodium, or microcrystalline cellulose with optimized concentration of sodium starch glycolate and crospovidone.

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Nateglinide	60	60	60	60	60	60	60
2	Croscamellose Na	2 10%	4 20%	6 30%	8 40%	---	---	--
4	Crospovidone	---	---	---	---	3	6	9
3	Na. Starch Glycol Late	3	3	3	3	3	3	3
5	Amberlite	9	9	9	9	9	9	9
6	Povidone	12	12	12	12	12	12	12
7	Aspartame	6	6	6	6	6	6	6
8	Mg. Stearate	6	6	6	6	6	6	6
9	Mannitol	142	141	138	141	141	139	135
10	MCC	60	60	60	60	60	60	60

Optimization of fast dissolving tablets of nateglinide:

Weighed the Nateglinide, and superdisintegrants, mannitol, microcrystalline cellulose, and aspartame accurately. All the materials were passed through 40 mesh screen prior to mixing. Then add the remaining excipients like talc and magnesium stearate. Mix well and pass through 80 mesh screen. The resulting granules were compressed into tablets using a rotary tablet machine

Table 6: Optimization of fast dissolving tablets of nateglinide:

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Nateglinide	60	60	60	60	60	60	60
2	Croscamellose Na	9	---	---	4.5	---	4.5	3
3	Na.Starchglycolate	---	9	---	4.5	4.5	---	3
4	Crospovidone	---	---	9	---	4.5	4.5	3
5	Amberlite	9	9	9	9	9	9	9
6	Povidone	12	12	12	12	12	12	12
7	Aspartame	6	6	6	6	6	6	6
8	Mg.Stearate	6	6	6	6	6	6	6
9	Mannitol	138	138	138	138	138	138	138
10	MCC	60	60	60	60	60	60	60

All the quantities are in mg.

Evaluation of fast dissolving tablets of nateglinide:

Table 7: F1-F7 optimization formulations evaluation parameters:

test	hardness kg/cm^3	friability (%)	drug Content (%)	thickness (mm)	dis integration time (sec)	wetting time (sec)	water absorption ratio	Avg wt. (mg)
F1	40	0.61	98.84	3.2	135	152	85.24	297
F2	40	0.56	98.76	3.3	170	193	92.69	296
F3	35	0.75	98.57	3.2	122	142	78.80	305
F4	35	0.63	97.30	3.4	57	72	79.05	302
F5	35	0.84	98.76	3.1	48	61	73.40	301
F6	30	0.59	99.10	3.4	30	42	71.14	297
F7	35	0.48	99.23	3.5	40	53	75.08	298

BAR DIAGRAM

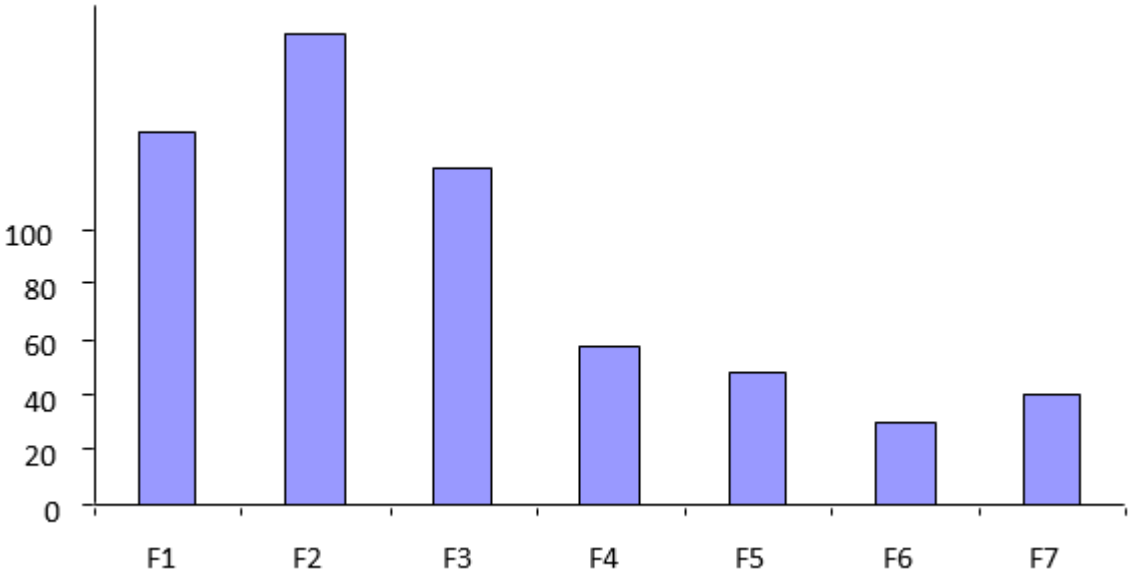


Fig. 6: Comparison of disintegration time of various formulation:

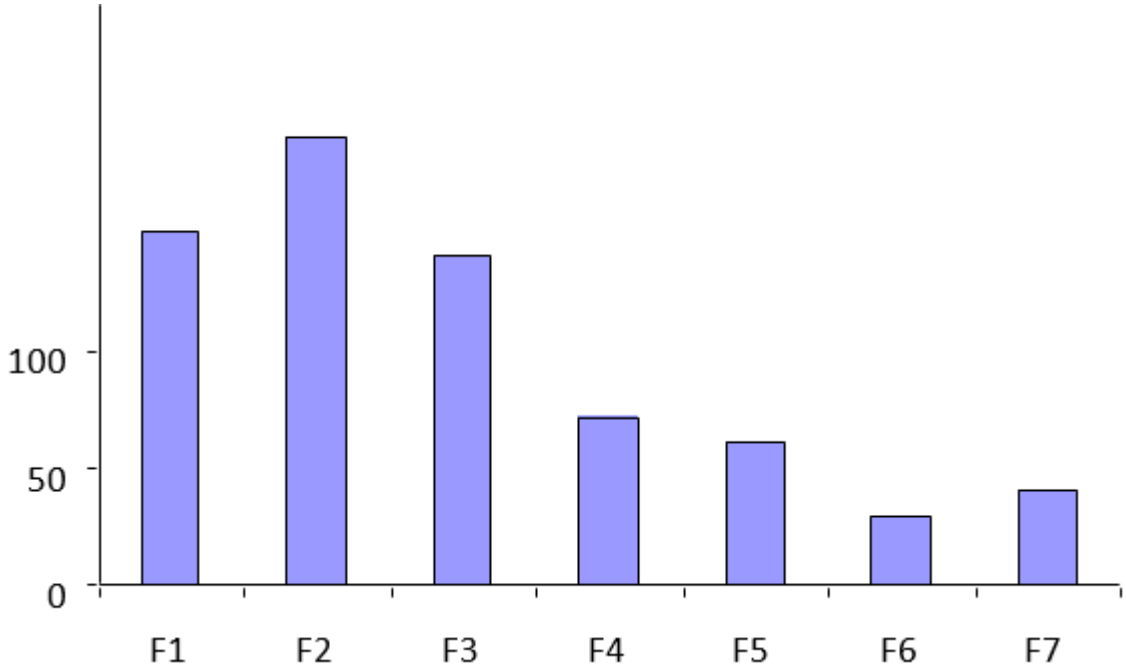


Fig. 7: Comparison of wetting time of various formulation

***In-vitro* drug release:**

Release of the drug *in-vitro*, is determined by estimating the dissolution profile.

USP 2 Paddle apparatus was used and the paddle was allowed to rotate at 50 rpm. 0.01 N HCl (900 ml) was used as a dissolution medium

Table 8: Dissolution Profile of Pure Nateglinide standard: (0.01NHcl) solution:

Sr. No.	Time(min)	absorbance	concentration (mcg)	cumulative amount in 900ml(mg)	% drug release
1	5	0.0576	2.68	24.12	40.20
2	10	0.0751	3.494	31.44	52.41
3	15	0.0936	4.355	39.19	65.33
4	30	0.1039	4.836	43.52	72.54
5	45	0.1096	5.100	45.90	76.50
6	60	0.1186	5.518	49.66	82.78

Table 9: Dissolution Profile of Batch F1: Table 10: (0.01NHcl) PH 1.2 with phosphate buffer PH 6.1

Sr. No.	Time(min)	absorbance	concentration (mcg)	cumulative amount in 900ml(mg)	% drug release
1	2	0.0864	4.020	36.18	60.30
2	4	0.0976	4.542	40.92	68.20
3	6	0.1143	5.316	47.89	79.82
4	8	0.1273	5.921	53.35	88.93
5	10	0.1353	6.295	56.71	94.53

Table 10: Dissolution Profile of Batch F2: table 11: (0.01NHcl) PH 1.2 with phosphate buffer PH 6.

Sr. No.	Time(min)	absorbance	concentration (mcg)	cumulative amount in 900ml(mg)	% drug release
1	2	0.0893	4.154	37.38	62.31
2	4	0.0945	4.396	39.60	66.01
3	6	0.1015	4.732	42.55	70.92
4	8	0.1080	5.023	45.25	75.43
5	10	0.1428	6.645	59.86	92.77

Table 11: Dissolution Profile of Batch F3: table 12: (0.01NHcl) PH 1.2 with phosphate buffer PH 6.1

Sr. No.	Time(min)	absorbance	concentration (mcg)	cumulative amount in 900ml(mg)	% drug release
1	2	0.0924	4.300	38.71	64.53
2	4	0.1009	4.694	42.29	70.49
3	6	0.1160	5.396	48.61	81.03
4	8	0.1284	5.976	53.84	89.74
5	10	0.1370	6.372	57.41	96.69

Table 12: Dissolution Profile of Batch F4: table 13: (0.01NHcl) PH 1.2 with phosphate buffer PH 6.1

Sr. No.	Time(min)	absorbance	concentration (mcg)	cumulative amount in 900ml(mg)	% drug release
1	2	0.0918	4.272	38.45	64.09
2	4	0.0997	4.639	41.79	69.66
3	6	0.1122	5.222	47.5	78.42
4	8	0.1239	5.762	51.91	86.53
5	10	0.1373	6.386	57.53	95.89

Table 13: Dissolution Profile of Batch F5: table 13: (0.01NHcl) PH 1.2 with phosphate buffer PH 6.1

Sr. No.	Time(min)	absorbance	concentration (mcg)	cumulative amount in 900ml(mg)	% drug release
1	2	0.0937	4.358	39.22	65.53
2	4	0.0992	4.613	41.56	69.26
3	6	0.1192	5.544	49.94	83.24
4	8	0.1328	6.181	55.68	92.81
5	10	0.1396	6.497	58.53	97.56

Table 14: Dissolution Profile of Batch F6 : (0.01NHcl) PH 1.2 with phosphate buffer PH 6.1

Sr. No.	Time (min)	absorbance	concentration (mcg)	cumulative amount in 900ml (mg)	% drug release
1	2	0.1034	4.812	43.32	72.21
2	4	0.1063	4.945	44.56	74.27
3	6	0.1222	5.685	51.22	85.37
4	8	0.1319	6.136	55.28	92.14
5	10	0.1402	6.503	58.58	97.63

Table 15: Dissolution Profile of Batch F7 :(0.01NHcl) PH 1.2 with phosphate buffer PH 6.1

Sr. No.	Time (min)	Absorbance	Concentration (mcg)	Cumulative amount in 900ml (mg)	% drug Release
1	2	0.0980	4.559	41.03	68.39
2	4	0.1003	4.667	42.05	70.09
3	6	0.1222	5.686	51.22	85.37
4	8	0.1315	6.116	55.10	91.84
5	10	0.1412	6.571	59.20	98.67

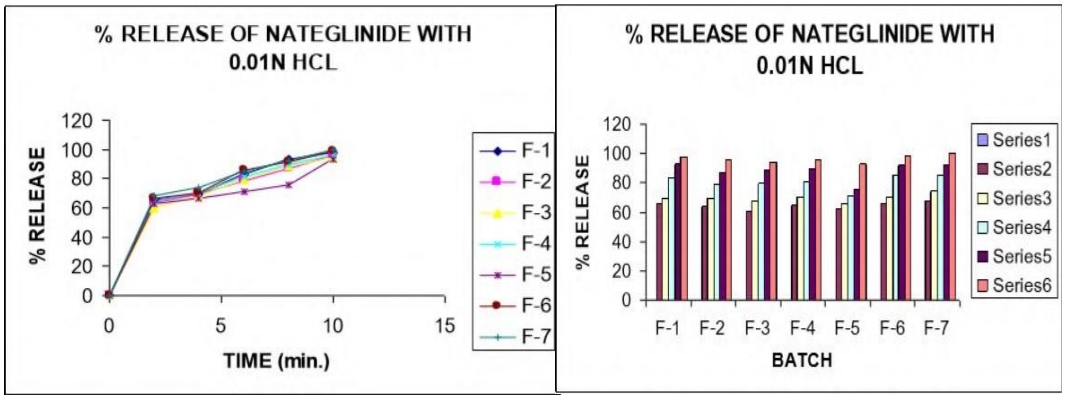


Fig. 8: Comparison of % drug release of various formulation

STABILITY STUDIES FDT TABLETS;

ACCELERATED STABILITY TESTING

Since the period of stability testing is of 2 years, it is time consuming and expensive also. Therefore it is essential to develop a method that will help in rapid prediction of long term stability of drug. Accelerated Stability testing is defined as the validated method by which the product stability may be predicted by storage of products under conditions that accelerate the change in defined and predictable manner. The stability studies of formulated tablets were carried out at 40ºC and at room temperature for two months. The effects of temperature and time on the physical characteristics of the tablets were evaluated. The stability study was carried out when the room temperature was 20 to 25ºC. The different parameters which were studied are Drug content (%), *In-vitro* Disintegrate. Time (secs), Wetting Time (secs), *in-vitro* dissolution rate.

Table 16: Stability studies of formulation F7 at room temperature:

Sr. No.	**Parameters**	**Controlled**	**After 15 days**	**After 1 month**
1	Drug content (%)	100.23	99.94	99.90
2	disintegrant time (sec.)	30	31	31
3	wetting time (sec.)	42	43.2	44.5
4	hardness kg/cm^3	3.5	3.4	3.3
5	friability %	0.48	0.47	0.45
S.no	**Time**	**cumulative % of drug release**		
		controlled	**after 15 days**	**after 1 month**
1	2	72.21	71.96	71.21
2	4	74.27	72.87	72.27
3	6	85.37	82.67	81.94
4	8	92.14	91.29	90.86
5	10	100.05	99.93	99.77

Table 17: Stability studies of formulation F7 at temperature 40°C

S.No	Parameters	Controlled	After 15 Days	After 1 Month
1	Drug content (%)	100.23	99.88	99.96
2	disintegrant time (sec.)	30	30	31
3	wetting time (sec.)	42	43.7	44.6
4	hardness kg/cm^3	3.5	3.6	3.3
5	friability %	0.48	0.48	0.45
S.no	**Time**	**Cumulative % of drug release**		
		Controlled	**After 15 days**	**After 1 month**
1	2	72.21	72.06	71.86
2	4	74.27	73.37	72.27
3	6	85.37	84.59	82.91
4	8	92.14	91.49	91.12
5 5	10	100.05	99.97	99.90

CONCLUSION:

From the present study investigation, it can be concluded the oral fast dissolving tablets nateglinide are superior in drug release when compared to the marketed formulation. The fast dissolving tablets were prepared by superdisntagrats like crospovidone, sodium starch glycolate, croscarmellose sodium, by direct compression method .this formulations shown good mechanical strength, drug release, disintegration time, and stability. nateglinide administered in the form of the fast dissolving tablets potential novel dosage form for pediatric, geriatric and other also general population by providing fast drug release and better patient compliance. And this method using commercially available super disintegrants. Simple and economic in bulk manufacturing pharmaceuticals.

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