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FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF NATEGLINIDE

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ABSTRACT

The study was carried to formulate and evaluate dispersible tablet obtaining Nateglinide. Nateglinide is a drug for the treatment of type 2 diabetes. The present study is an attempt to select best possible combination of diluents and disintegrantes to formulate fast dissolving tablets of Nateglinide which disintegrates within few minutes thereby reducing the time of onset of action. A combination of super disintegrants, i.e., sodium starch glycolate (SSG) and croscarmellose sodium (CCS) were used. IR spectroscopy showed that there is no interaction of the drug with the polymer. Direct Compression method was used to formulate the tablets. All the formulations were showed the acceptable flow properties and the pre-compression parameters like Bulk density, Tapped density and Hausner ratio. The post compression parameters like Hardness, Friability, Disintegration time, Weight variation, wetting time, Dispersion time values were found to be within the IP limits. The percentage Drug content of all tablets was found to be between 97.30% - 99.23 % of Nateglinide, which is within the limit. From the results it was found that the F6 batch was found to be optimized batch and it pass all the pre-formulation parameters and evaluation results as per the IP limits.

Keywords: Nateglinide, Type 2 diabetes, wetting time, Hausner ratio, Tapped density.

INTRODUCTION

An ideal regimen for disease therapy is the one, which instantly attains the desired concentration of the active pharmaceutical ingredient in plasma and maintains it for the entire duration of treatment which lies in the therapeutic range. This will be possible by administration of conventional dosage form in a particular dose and at a particular frequency[1]. Solid dosage form provides the best protection to the drug against light, temperature, humidity, oxygen, and stress during transportation. Amongst the solid oral dosage form tablets are widely used. The oral route of drug administration is a popular, convenient and widely accepted method of administering the drugs.The method of

preperation of oral dosage form has been changed drasticallly in last few years with the emergence of pre-compression, ultra-high-speed press, induced die feeding. The demand for the technologies has been increased threefold annually.The pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects.Dysphagia is seen to afflict nearly 35% of general population [2, 3]. 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. These tablets having various names such as orally disintegrating tablets (ODT), mouth dissolving (MD), fast melting, fast dissolving or-oro disperse[4, 5]. 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[6, 7]. 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 [8, 9]. 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, this dissolved rapidly. When the tabletcomes in to contact with water, it swelled,and the drug is absorbed in the normal way. Drugs are easily absorbed in stomach & it may produce rapid onset of action [10]. In such a cases Bioavailability of a drug is significantly greater than those observed from the conventional tablet dosage form[11, 12]. The growing importance of fast dissolving tablet was underlined recently. According to European Pharmacopoeia fast dissolving tablet means tablet which dissolves in the oral cavity in about 10 seconds to 3 minutes. Direct compression method was used for the formulation of Nateglinide tablets. As molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablet. Therefore, direct compression appears to be a better option for manufacturing of tablets [13]. So Nateglinide was found to be the best suitable candidate for preparation of Nateglinide tablets using direct compression technique. The objective of the present work is to develop tablets of Nateglinide and to study the effect of functionality differences of super disintegrants on the tablet properties.

MATERIALS & METHODS

Nateglinide was a gift from Natco pharmaceuticals Pvt. Ltd, Hyderabad, India), and crospovidone and SSG were gifted from Hetero chemicals. Cross carmellose sodium from modi Mundi chemicals, Aspartame from Micro Pharmaceutical Pvt Ltd, Magnesium stearate from yarrow chemicals. All other reagents and chemicals used were of analytical grade.

Preformulation Studies of Pure Drug and Excipients

The preformulation study relates to a pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug

substance. It gives the information needed to define the nature of the drug substance and provide frame work for the drug in combination with pharmaceutical recipients in the dosage form. Hence, the following formulation studies were performed on the obtained sample of the drug.

Table 1: Preformulation Study of Pure Drug (Nateglinide).

S. No.	Parameters	Result	Conclusion
1	Bulk Density	0.675 gm/ml	------
2	Tapped Density	0.75 gm/ml	-----
3	Carr's Index	10 %	Excellent Flow
4	Hausner Ratio	1.11	Better Flow
5	Melting Point	136-141° C	----
6	Solubility	Freely soluble in methanol, ethanol, chloroform. Practically insoluble in water.	

Table 2: Preformulation Study of the blend

Batch Code	Bulk Density	Tapped Density	Angle of repose	% Compressibility	Haussner's Ratio
F1	0.41	0.47	24.58	12.76	1.15
F2	0.44	0.52	25.91	15.38	1.18
F3	0.44	0.51	26.86	13.72	1.16
F4	0.47	0.54	24.43	12.96	1.14
F5	0.45	0.50	24.10	12.00	1.06
F6	0.46	0.53	24.77	13.20	1.15
F7	0.47	0.52	25.42	9.61	1.11

PREPARATION OF NATEGLINIDE FAST DISSOLVING TABLETS

Preparation of Nateglinide tablets using direct compression method

Weighed the drug, superdisintegrants, mannitol, micro crystalline cellulose, and aspartame accurately. All the materials were passed through 40 # screen before mixing. Then add the remaining excipients like talc and magnesium stearate. Mix well and pass through 80 # screen. The above ingredients were mixed in double cone blender for 25 mins and lubricants were added to the above ingredients. The lubricated blend was compressed by using oval shaped 9.0 punches. Formulations of tablets are represented in table-3.

Table 3: Composition of Nateglinide fast dissolving tablets

S. No.	Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7
1	Nateglinide	60	60	60	60	60	60	60
2	Croscarmellose Na	9	---	---	4.5	---	4.5	3
3	Na. Starch Glycolate	---	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
9	Mg Stearate	6	6	6	6	6	6	6
10	Mannitol	138	138	138	138	138	138	138
11	MCC	60	60	60	60	60	60	60
	Total (mg)	240	240	240	240	240	240	240

EVALUATION OF FAST DISSOLVING TABLETS [14]

Evaluation parameters of tablets mentioned in the Pharmacopoeia need to be assessed, but some, which require special concern or need to be modified, are discussed here.

Hardness

The hardness of tablets was determined by using Pfizer Hardness tester and it is expressed in Kg/cm2. The whole experiment was performed in triplicate.

Dimension (Diameter and Thickness): The Thickness and diameter were used to measure and provide information on the variation between tablets. The thickness and diameter of the tablets was determined using vernier calipers. Three tablets from each formulation were used and average values of thickness and diameter were calculated.

Friability testing

The friability of the tablet was determined by using Roche friabilator. It is expressed in percentage. 10 tablets (a sample equivalent to 6.5 grams should be taken if the tablets weigh less than 650 mg) are initially weighed W1 and transferred into the friabilator. The friabilator was operated at 25 rpm

for 4 minutes. The tablets were weighed again (W2). The percentage of friability was calculated by using following formula.

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight x 100}}{\text{Initial weight}}$$

Weight variation

20 tablets were selected randomly from the lot and weighed individually to check for weight variation. The weight divided by 20 provides an average weight of tablets. Not more than two of the individual weight deviates from the average weight by 7.5% and none should deviate by more than double that percentage. Standard deviation and average weight were calculated.

Wetting time

Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. Ten millimetres 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 the 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 centre of Petri dish and the time for the tablet to completely disintegrate into fine particles was noted.

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 following equation,

$$\mathbf{R = 100\ (Wb\text{-}Wa/Wa)}$$

Where wb - the weight of tablet before water absorption

Wa - the weight of tablet after water absorption.

In-Vitro drug release[15]

The release of the drug *in vitro* was carried out using rotating paddle apparatus (USP Type II The dissolution medium consisted of 900 ml of 0.1 HCL buffer. The release study was performed at 37°C ± 0.5°C with a rotation speed of 25 rpm. The 5ml of sample was withdrawn at time interval of 5, 10,15,20,25, minutes up to 30 min and replaced with 5 ml of dissolution medium the amount of Nateglinide released was determined by UV Spectrophotometer at 210 nm.

Stability study

Selected formulations were subjected to stability studies as per I.C.H. Guidelines. Selected formulations packed in PVC blister pack then; they were stored at three different temperatures $40^0C\pm2^0C$, $27^0C\pm2^0C$ and $45^0C\pm2^0C$ for 45 days at RH 75±5%. At 15 days intervals, the tablets were evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time.

RESULTS AND DISCUSSION

The present study was carried out to develop fast dissolving tablets of Nateglinide to enhance absorption and bioavailability by increasing solubility of the drug using superdisintegrants.

Determination of UV Absorption Maxima of Nateglinide – UV scanning was done for 10 mcg/ml drug solution from 200-400 nm in 0.01 N HCl as a blank using double beams UV/VIS spectrophotometer. The wavelength maximum was found to be at 210 nm.

Drug Excipient Compatibility Study

Compatibility of the drug with excipients 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. The samples were taken for FT-IR study.

Calibration Curve

The different concentration (1 to 10 µg/ml) of Nateglinide were prepared with 0.01N HCl and analyzed through UV at 210 nm using corresponding media as a blank. The absorbance obeys the Beers-Lamberts law at the range 1 to 10 µg/ml. The data are shown in Table no. 4 and Fig. No.1.

Table 4: Standard calibration curve of Nateglinide

S. No.	Concentration (mcg/ml)	Absorbance
1	1	0.0089
2	2	0.031
3	3	0.0544
4	4	0.0841
5	5	0.1051
6	6	0.1233
7	7	0.1496
8	8	0.1655
9	9	0.1833
10	10	0.1996

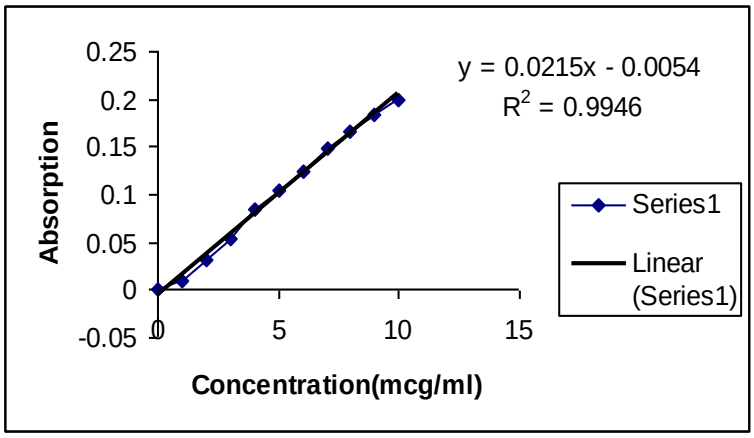

Fig. 1: Standard Calibration Curve of Nateglinide

Table 5: Regression Analysis

Parameters	Value
R^2	0.9946
Slope	0.0215
Intercept	0.0054

By preliminary identification test, it was concluded that the drug complied the preliminary identification. From scanning of the drug in 0.01N HCl dissolution media, it was also concluded that the drug had a maximum wavelength of 210nm.

From standard calibration curve of Nateglinide in 0.01N HCl dissolution media, it was observed that the drug obeys Beer-Lamberts law in the concentration range of 1-10 µg/ml in the media.

Table 6: Evaluation of Fast Dissolving Tablets of Nateglinide

Formula code	Hardness (kg/cm^2)	Friability (%)	Drug-Content (%)	Thickness (mm)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio	Avg. Wt. (mg)
F1	4.0	0.61	98.84	3.2	135	152	70.41	297
F2	4.0	0.56	98.76	3.3	170	193	72.34	296
F3	3.5	0.75	98.57	3.2	122	142	75.23	305
F4	3.5	0.63	97.30	3.4	57	72	77.87	302
F5	3.5	0.84	98.76	3.1	48	61	82.56	301
F6	3.0	0.59	99.10	3.4	30	42	89.33	297
F7	3.5	0.48	99.23	3.5	40	53	85.66	298

From the above table it is clearly indicating that tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications, less than 10%. Tablets were evaluated by using Vernier caliper. The thickness of the tablets was found in the range 3.1 – 3.5 mm. Uniformity thickness was obtained due to uniform die fill. Tablets were evaluated by using Pfizer Hardness tester. Hardness of the tablets was found in the range 3.0 – 4.0 Kg/cm2. Uniform hardness was obtained due to equal compression force. Tablets were evaluated by using Roche Friabilator and friability of tablets was observed in the percentage range 0.48- 0.84. Tablets were evaluated for disintegration time in the IP disintegration apparatus. The disintegration time was found in the range 42 – 180 sec. The tablets are evaluated for the uniformity dispersion in which all the tablets were dispersed in few seconds in purified water and all the formulations were under the IP limits. Tablets were evaluated for wetting time test. The wetting time was found in the range 40 – 170 sec. Tablets were evaluated by using assay method. The drug was obtained in the acceptable limit. The drug content was found in the range 97.30 – 99.23%. Tablets are evaluated for the content uniformity test all the formulations are under the IP specifications. The fast dissolving formulations was formed by using super

disintegration such as croscarmellose, crospovidone, sodium starch glycolate, and Amberlite. Here we conclude that combination of polymers is very effective than the single polymer. And also concluded that F6 Formulation which is having crospovidone, is more effective than the other polymers. Crospovidone shows less disintegration time than the other polymer due to wicking and capillary effect.

IN VITRO DRUG RELEASE

The release of the drug *in vitro* is determined by estimating the dissolution profile. *In- vitro*, drug release studies were performed and the results of in-vitro drug release studies of all the developed formulation in respective tables. The percentage cumulative drug release was plotted against time to obtained drug release profiles. The results are shown in respective Table No.7.

Table 7: Comparative Dissolution Profile of Nateglinide dispersible tablets in 0.01 HCL Buffer Solution

Time (min)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
2	60.30	62.31	64.53	64.09	65.53	72.21	68.39
4	68.20	66.01	70.49	69.66	69.26	74.27	70.09
6	79.82	70.92	81.03	78.42	83.24	85.37	85.37
8	88.93	75.43	89.74	86.53	92.81	92.14	91.84
10	94.53	92.77	95.69	95.89	97.56	100.05	98.67

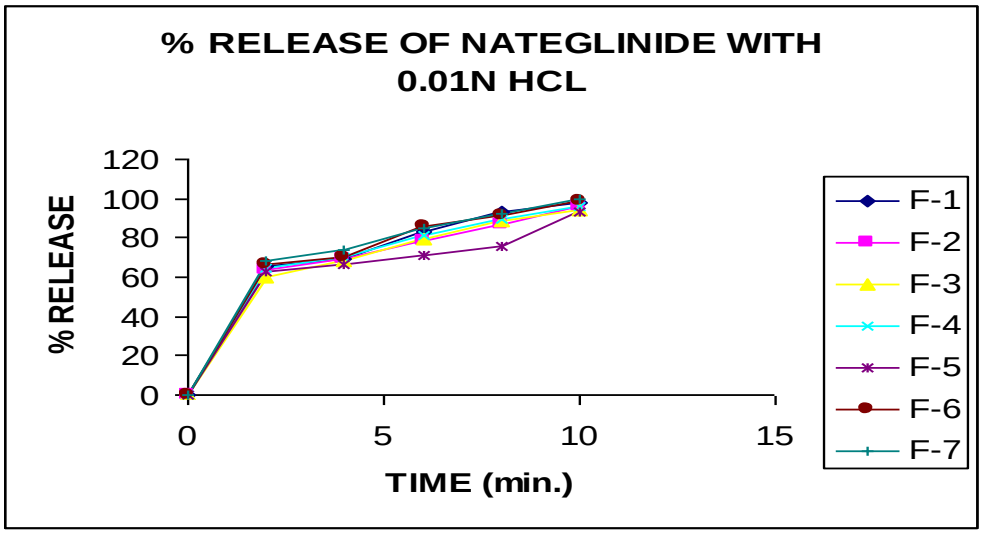

Fig. 2: Comparison of % drug release of various formulations

Stability Studies of Fast Dissolving Tablets [16]

According to ICH guidelines, 45 days stability study at 4^0C ±2^0C, 27^0C ±2^0C and 45^0C ±2^0C for 45 days at RH 75±5% of optimized formulation (F6) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 40C±20C, 270C±20C and 450C±20C for 45 days at RH 75±5% for 45 days.

Table 8: Stability studies of formulation F6 at room temperature.

Parameters	After 15 days	After 30 days	After 45 days
Physical appearance	No change	No change	No change
Drug content(%)	100.23	99.98	99.91
Disint. Time (sec.)	30	30.5	31.4
Wetting Time(sec.)	42	43	44
Hardness(kg/cm^2)	3.5	3.5	3.4
Friability%	0.48	0.48	0.46
	Cumulative %Drug Release		
Time	**After 15 days**	**After 30 days**	**After 45 days**
2	72.21	72.01	71.86
4	74.27	73.37	72.27
6	85.37	84.59	82.91
8	92.14	91.40	91.12
10	100.05	99.97	99.90

CONCLUSION

The present study is an attempt to select best possible combination of diluents and disintegrates to formulate dispersible tablet of Nateglinide which disintegrates within few minutes thereby reducing the time of onset of action. Four super-disintegrating agents are used at lower, medium & higher concentration. Seven formulations were designed. All the Super-disintegrants 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 used as a diluent and superdisintegrants. Each formulation was composed of drug and excipients in various proportions. The bulk density of the powdered mixture was found to be 0.41 - 0.47 gm/cm^3, tapped density where found out to be 0.47 – 0.53 gm/cm^3 for all formulations. % Compressibility, Haussner's ratio to be found between IP limit.The angle of Repose was found in the range of (28) º. Drug content was found to be (97-100) %. Friability (%) was found to be below 1%. Hardness was found to be (3-4) kg/cm^2. *In-vitro*

drug release shows that formula has crospovidone which has less disintegration time as compared to the other super disintegrants. And sodium starch glycolate shows higher disintegration time than others. Comparatively, disintegrating time of tablets containing crospovidone < croscarmellose < sodium starch glycolate. The faster disintegration of crospovidone tablets may attribute to its rapid capillary activity and pronounced hydration with little tendency to gel formation. Thus, these results can suggest that the disintegration times can be decreased by using a wicking type of Disintegrants (crospovidone). So Batch No. F6 is best due to less disintegration time and high water absorption ratio. Increase in thickness of all tablets was noticed particularly pronounced in crospovidone tablets. These results indicate that, at higher relative humidity, tablets containing a high concentration of superdisintegrants get softened and hence, must be protected from atmospheric moisture. In our formula concentration of crospovidone is less so, these problem has been not arisen. Fast dissolving tablets prepared from superdisintegrants must be protected from atmospheric moisture.

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