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Impact of Concentration of Superdisintegrant on the Disintegration Time of Film Coated Tablets of Nateglinide

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ABSTRACT

Nateglinide is an insulin secretogogues, meglitinide anti-diabetic drug used for the treatment of type II Diabetes mellitus. Film coated means 2% coating immediate release tablets. Superdisintegrants used for the formulation of immediate release tablets to decrease the disintegration time of tablets and disaggregate the granules into fines. Current investigation aims to access the impact of gradient concentration of sodium starch glycolate, Crosscarmellose sodium on the disintegration time also drug release rate of tablets. The drug-excipients interaction study was carried out by Fourier Transform Infra-red and Different Scanning Calorimeter. The six formulations were formulated by using 2, 4, 6 % concentration of Superdisintegrants. The hardness of each formulation was in between 100 to 140 N. The disintegration time of formulation containing 6% (F-6), 4% (F-5) and 2 % (F-4) concentration of Crosscarmellose sodium was about 7.0, 6.0 and 3.0 min respectively. The formulation having sodium starch glycolate concentration of 2% (F-1), 4% (F-2), 6% (F-3) about 8.0, 6.0 and 4.0 min respectively. As the concentration of Superdisintegrants get on increase the disintegration time was decrease. The formulation containing sodium starch glycolate had more disintegration time than Crosscarmellose sodium containing tablets.

Keywords: Secretogogues, Diabetes mellitus, Superdisintegrants.

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INTRODUCTION

Despite increasing interest in controlled release drug delivery systems, more attention has been paid to formulate poorly soluble drugs as conventional tablets intended to be swallowed to disintegrate and release their medicaments rapidly in the gastro intestinal tract for bioavailability. Bioavailability of a poorly soluble drug from a solid oral dosage form depends on the release of the drug substance from the dosage form, *i.e.*, disintegration of the solid oral dosage form which will increase the wettability of the drug by increasing the surface area of the drug particles[1-3]. Maglitinide derivative, Nateglinide is an insulin secretogogues anti-diabetic drugs used for the treatment of type II diabetes mellitus[4,5] which increase the secretion of insulin in case of type II diabetes and it is poorly soluble drug[3].The poor aqueous solubility of Nateglinide gives rise to difficulties in the formulation of tablets with a desired dissolution rate. This highlights the importance of proper choice of superdisintegrants. The importance of proper choice of superdisintegrant Crosscarmellose sodium, Sodium Starch glycolate, etc and their consistency of performance which are of critical importance to increase the rate of disintegration and dissolution of drug particles[1,2]. By increasing the surface area and its consistency of performance which is of critical importance to increase the rate of dissolution and hence its bioavailability[6,7]. Nateglinide taking before a meal reduces the risk of hypoglycaemia. Nateglinide lowers blood glucose concentrations by stimulating the release of insulin from functioning β-cells of pancreatic tissue. There are various factors like hardness, concentration of binders, disintegrants etc. which affect the disintegration time and rate of dissolution of the drug.

The objective of present investigation was to access the impact of gradient concentration of sodium starch glycolate, crosscarmellose sodium on the disintegration time of tablets.

MATERIALS AND METHODS:

Materials:

Nateglinide are obtained from Cadila Pharmaceuticals Ltd, Croscarmellose Sodium and Sodium Starch Glyolate (FMC Corporation, Ireland), Instacoat Universal (Ideal cure Ltd) and other additives were procured commercially. All the reagents and solvents used were of analytical grade[17].

Preparation core Tablets:

The granules were prepared by wet granulation technique. The respective ingredients (Drug, diluents and additives) were passed through sieve no. 40# and blended in a rapid mixer granulator. Activation of Povidone K-30 was done using purified water and the prepared

granules were dried. Addition of half quantity of Superdisintegrants in intragranular stage and half in the extragranular stage[8,9,15].The tablets were compressed in 20 station CADMAC (CMD4) rotary tablet punching machine, Ahemedabad by using 17.5 x 7.5 mm punch, D tooling capsule shape, plane on both sides punch set.

Table 1: Formulation of Nateglinide Tablets

Ingredients	**F1** mg/tab **2% SSG**	**F2** mg/tab **4% SSG**	**F3** mg/tab **6% SSG**	**F4** mg/tab **2% CCS**	**F5** mg/tab **4% CCS**	**F6** mg/tab **6% CCS**
Intragranulation and Extragranulation:						
Nateglinide USP	120.0	120.0	120.0	120.0	120.0	120.0
Lactose Monohydrate (Pharmatose 200M)	301.27	288.67	276.07	301.27	288.67	276.07
Microcrystalline Cellulose (Avicel PH 101)	152.83	152.83	152.83	152.83	152.83	152.83
Crosscarmellose Sodium (Ac-Di-Sol) (CCS)	--	--	--	12.6	25.2	37.8
Sodium Starch Glycolate (SSG)	12.6	25.2	37.8	--	--	--
Sodium Lauryl Sulphate	6.3	6.3	6.3	6.3	6.3	6.3
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Povidone K30 (PVP K30)	12.5	12.5	12.5	12.5	12.5	12.5
Collidal Silicon Dioxide	13.1	13.1	13.1	13.1	13.1	13.1
Magnesium Stearate	11.4	11.4	11.4	11.4	11.4	11.4
Total	**630.0**	**630.0**	**630.0**	**630.0**	**630.0**	**630.0**

Preparation of Film coated Tablets:

The tablets were coated in Conventional pan coater by Aqueous coating technique. Coating agents used as polymer in immediate release tablets[8,9]. Mainly Instacoat Universal (Ideal cure Ltd.) used as coating agent.

Table 2: Film Coating

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Instacoat IC-U-6964	12.6	12.6	12.6	--	--	--
Instacoat IC-U-6994	--	--	--	12.6	12.6	12.6
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

EVALUATION OF BLEND AND TABLETS:

The prepared granules were evaluated by Loss on drying, bulk density, tapped density, Carr's Index, haussner`s ratio and angle of repose. The prepared tablets (F_1-F_6) were evaluated for friability, hardness and disintegration time (Table 3).

a) Bulk density, tapped density and Carr's index:

10 grams of granules were introduced into a clean, dry 100 ml measuring cylinder and the volume was recorded. The cylinder was then tapped 25 times from a constant height

and the tapped volume was read. The bulk density and tapped density were calculated as the ratio of the granules mass and the respective volumes[10,11]. Carr's index (I) was calculated using the equation:

$$\mathbf{I = Dt - Db/Dt \times 100}$$

Where Dt is the tapped density of the powder and Db is the bulk density of the powder.

b) Angle of repose:

The fixed funnel method was employed for determining the angle of repose. The granules were poured carefully until the apex of the conical pile just touches the tip of the stem of the funnel[10]. The angle of repose was calculated using following equation,

$$\boldsymbol{Tan\ \theta = h\ /\ r}$$

Where H is the height of the pile and R is the radius of the base of the conical pile.

EVALUATION OF TABLETS:

Hardness

The tablet crushing strength was tested by commonly used Monsanto type tablet hardness tester (Erweka). A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, is recorded[11,12].

Friability Test

Tablet strength was tested by Roche Friabilator (Electrolab). Pre-weighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets[11,12].

Disintegration time

The disintegration time was determined by using disintegration test apparatus. The tablet was placed in each of the six tubes of the apparatus. For film coated tablets, use water as the liquid. Add a disc to each tube. Operate the apparatus for 30 minutes, unless otherwise stated in the individual monograph. If coated tablets fail to comply because of adherence to the discs, repeat the test on a further 6 tablets omitting the discs. The tablets comply with the test if all 6 tablets have disintegrated (Table 4,6) [13,14].

***In vitro* dissolution studies:**

Drug release profile was evaluated *in vitro* using a dissolution test apparatus (Electro Lab, TDT-08L, Mumbai, India). The USP XIII Type II (paddle type) method was selected to perform the dissolution profile of Nateglinide. For immediate release film coated tablets Dissolution medium was used 0.01 N HCl containing 0.5% (w/v) of sodium lauryl sulphate; 1000 ml. The dissolution for all the formulations was carried out according to US Pharmacopoeia[15] for Time interval of

sampling was 10, 20, 30, 40, 50 and 60 min. Rotation speed was 50 rpm. Volume adjust 900 ml and temperature maintained 37 ^{0}C ± 0.5 ^{0}C. Samples (10 ml) were withdrawn at regular intervals and filtered through membrane filter (pore size 0.22 µm)[8]. The samples were analysed by UV Spectrophotometer. The reported ƛmax of Nateglinide is 210 nm. The Drug releases of film coated tablets are given in Table 7.

$$\%\ \boldsymbol{Drug\ Release} = \boldsymbol{At \times Wstd \times 5 \times 900 \times P/AS \times DS \times 50 \times LC \times 1}$$

Stability studies:

Stability studies were carried out at 25°C / 60% RH, 30°C / 75% RH and 40°C/ 75% RH for the selected formulation for 3 months. Formulation F6 selected for stability study. After specified time intervals checked parameters like Average weight, Hardness, Disintegration time and *In vitro* Dissolution. The physical appearance of the samples kept for stability studies were checked each month and found that there was no difference in the appearance (Table 8-10).

Evaluation of optimized formulation:

The optimized formulation was evaluated by Similarity factor (f_2) study.

Similarity factor (f_2): The similarity factor is then defined to be the logarithmic reciprocal square root trans-formation of one plus the mean squared (the average sum of squares) difference in observed average cumulative percent dissolved between the test and reference formulations over all sampling time points.[9,16],

In similarity factor, comparison of therapeutic performances of two medicinal products containing same active substance is critical mean assessing possibility of alternative using between the innovative and any essentially similar medicinal product[16]. The similarity factor study carried out by dissolution profile of selected formulation F6 compare with innovator product which is Starlix from Novartis Pharmaceuticals Ltd (Table 11-12).

RESULT AND DISCUSSION:

Pre-compression parameters:

The pre-compression parameters like bulk density, tapped density and Carr's index, Haussner's ratio and angle of repose have been performed. The angle of repose, compressibility index (%) and haussner`s ratio for all prepared granules were found to be in the range of 28 to 31°, 9.0 to 12.0, and 1.0 to 1.16 respectively, which indicate a good flow property of the powders. This showed that the granules were free flowing and may be used for compression shown in table 3.

Post-compression parameters:

The punches used to compress the tablets were 17.5 x 7.5 mm punch, D tooling capsule shape,

plane on both sides punch set. The average weight was found to be within the prescribed limit. Since mechanical integrity is of paramount importance in successful compressed immediate release formulation, the hardness of tablets were determined in triplicate and found to be in the range of 100 to 140 N. Friability was observed in between 0.03 to 0.07% w/w, which were below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets in Table 4.

Table 3: Evaluation of Pre-compression parameter (Blend)

Parameter	F1	F2	F3	F4	F5	F6
Loss on drying (%)	1.32±0.2	1.60±0.06	1.87±0.2	1.41±0.09	1.40±0.21	1.90±0.3
Bulk density (gm/ml)	0.38±0.02	0.40±0.037	0.41±0.01	0.37±0.02	0.40±0.037	0.39±0.01
Tapped Density	0.43±0.014	0.46±0.02	0.45±0.014	0.42±0.031	0.45±0.03	0.43±0.03
Carr's Index (%)	11.62±0.9	13.04±0.92	9.8±0.7	11.90±0.93	11.11±0.78	9.3±0.62
Haussner`s ratio	1.14±0.16	1.15±0.1	1.11±0.03	1.14±0.1	1.13±0.1	1.12±0.26
Angle of Repose (Ɵ)	28.13±2	31.2±1.9	26.07±1.67	27.28±1.75	29.9±1.44	27.34±1.8

*Each value is the mean ± SD (n=3)

Table 4: Evaluation of Post-compression parameter (Core Tablets)

Parameter	F1	F2	F3	F4	F5	F6
Avg. weight (mg)	628.0±1.6	633.7±1.75	632.6±2.64	632.5±2.05	633.3±1.25	631.5±1.76
Hardness (N)	136.1±1.27	129.7±0.41	103.5±0.5	135.3±0.45	127.6±1.5	107.9±2.45
Friability (%)	0.03±0.006	0.06±0.002	0.04±0.007	0.02±0.001	0.08±0.005	0.07±0.006
Thickness (mm)	4.91±0.26	4.91±0.036	4.90±0.043	4.89±0.043	4.93±0.026	4.96±0.026
DT (min)	8.0±0.043	6.0±0.034	4.0±0.049	7.0±0.062	6.0±0.17	3.0±0.051

***** Each value is the mean ± SD (n=3)

Table 5: Drug content for Film-coated formulations

Parameters	F1	F2	F3	F4	F5	F6
Drug content (%)	98.3	101.99	99.6	98.52	102.1	99.3

Physico-chemical properties of film coated tablets

As per the result, decrease the Disintegration time of Nateglinide tablets by using different concentration (2%, 4% and 6%) of Superdisintegrants like Sodium Starch Glycolate, Crosscarmellose Sodium. The Disintegration time (in triplicate) of formulation containing 6% (F-6), 4%(F-5) and 2 % (F-4) of Crosscarmellose Sodium was about 9.0, 8.0 and 4.0 min respectively. The formulation having Sodium Starch Glycolate of 2% (F-1), 4% (F-2), 6% (F-3) had Disintegration time of about 10.0, 7.0 and 5.0 min respectively. As the concentration of Superdisintegrants get on increase the Disintegration time was decrease. The formulation containing Sodium Starch Glycolate had more Disintegration time than Crosscarmellose Sodium containing tablets. The Disintegration time of F-6 formulation was the lowest among (4.0 min) all formulations. It may be inferred that Crosscarmellose Sodium may be the suitable Superdisintegrants for the development of immediate release tablet of Nateglinide. So Optimized

formulation is F6.

Table 6: Evaluation of Film coated Tablets

Parameters	F1	F2	F3	F4	F5	F6
Average weight (mg)	645.2±2.1	643.1±1.64	644.9±3	641.7±2.85	645.3±1.53	643.8±2.7
Thickness (mm)	5.03±0.045	5.03±0.71	5.0±1.5	5.02±0.99	5.01±0.98	5.04±1.0
Disintegration test (min)	10±1.2	7.0±1.7	5.0±0.052	9.0±2.34	8.0±0.52	4.0±0.5

***** Each value is the mean ± SD (n=3)

***In-vitro* dissolution studies:**

In vitro dissolution studies were performed for all the formulations using USP apparatus II tablet dissolution tester employing paddle type at 50 rpm using For immediate release film cated tablets Dissolution medium was used 0.01 N HCl containing 0.5% (w/v) of sodium lauryl sulphate; 1000 ml. The drug release was evaluated using UV spectroscopy. The drug release data for formulation F1-F6 is given in the Table 6. All the formulations F1-F6 have demonstrated at time intervals 10, 20, 30, 40, 50 and 60 min. The drug release was found to be within specified limits for F3 and F6. The drug release of F3 was 84.67±0.03 at 30 min and for F6 was 86.34±0.022 at 30 min. The specified limit for immediate tablets of Nateglinide is 85% in 30 min. Among all formulations, the formulation F6 was considered optimum because its drug release is above 85%. So it is in the specified limit.

Table 7: *In vitro* dissolution studies (% of Drug Release)

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	21.5±0.058	30.9±0.49	41.8±0.39	23.14±0.06	35.0±0.09	44.32±0.45
20	40.0±0.7	47.7±0.78	68.4±0.76	44.0±0.06	52.1±0.34	69.8±0.38
30	52.4±0.088	67.1±0.43	84.67±0.03	57.13±0.56	69.5±0.69	86.34±0.022
40	64.9±0.78	78.64±0.04	88.2±0.67	68.2±0.5	80.9±0.7	89.4±0.79
50	68.3±0.03	82.4±0.67	94.7±0.07	74.2±0.03	83.52±0.89	95.37±0.09
60	73.2±0.78	86.1±0.08	97.6±0.45	79.34±0.08	87.81±0.43	98.7±0.23

***** Each value is the mean ± SD (n=3)

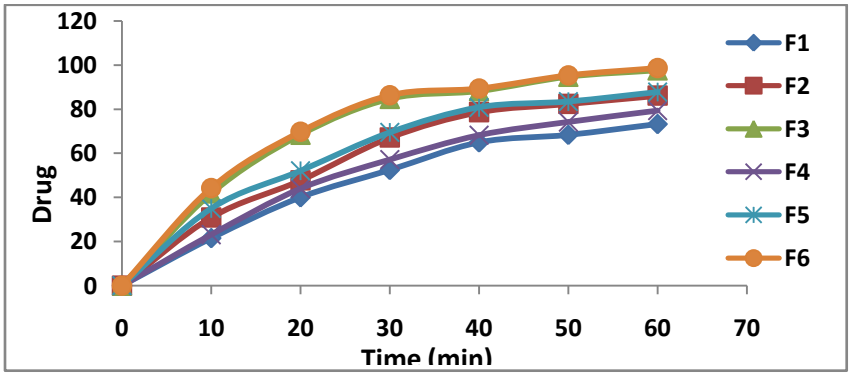

Figure 1: *In-vitro* release patterns of formulations F1 to F6

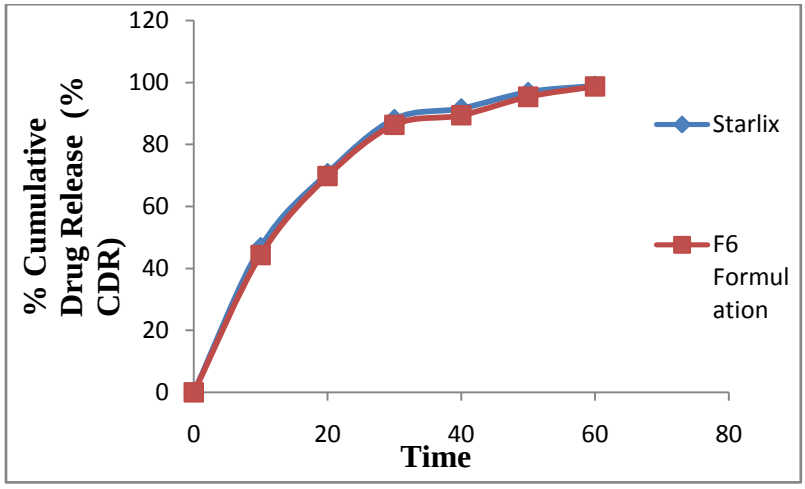

Figure 2: % Drug Release of Starlix and F6 formulation

Table 8: Physical parameter of stability batch F6

Parameter	Time in months	Stability condition		
		25°C / 60% RH	30°C / 75% RH	40°C/ 75% RH
Avg. wt. (mg)	**0**	643.8±2.1	644.1±1.85	644.3±2.4
	1	645.4±2.0	642.89±1.68	643.1±2.08
	2	656.08±2.6	662.60±2.8	661.90±3.0
	3	650.36±2.4	649.45±1.93	651.86±1.56
Hardness (N)	**0**	111.4±0.5	110.4±1.2	108.5±0.7
	1	109.2±1.1	106.8±0.6	100.3±0.53
	2	105.0±0.9	103.9±1.4	97.7±0.54
	3	103.7±0.67	100.8±0.6	93.1±0.69
Disintegration time	**0**	5.0±0.5	5.0±0.053	4.0±0.4
(min.)	**1**	3.0±0.67	3.0±0.75	3.0±0.08
(In water)	**2**	2.0±0.06	2.0±0.4	1.0±0.03
	3	2.0±0.07	2.0±0.09	0.35±0.1

***** Each value is the mean ± SD (n=3)

Table 9: Dissolution studies for formulation F6 kept for stability studies at different temperature and humidity condition

Time in Months	Dissolution in 0.01 N HCl containing 0.5% (w/v) of SLS		
	25°C ±2°C/ 60%±5%RH	30°C ± 2°C / 75%±5%RH	40°C ±2°C/ 75%±5%RH
0	98.2 ±0.78	98.2±0.07	98.2 ±0.73
1	98.9±0.025	96.2 ±0.07	94.2±0.032
2	99.4 ±0.015	96.9 ±0.03	91.8±0.015
3	101.2 ±0.02	99.4±0.015	87.6 ±0.022

***** Each value is the mean ± SD (n=3)

Stability studies:

The stability studies were performed on selected formulation where the drug release was optimum in 0.01 N HCl containing 0.5% (w/v) of sodium lauryl sulphate (i.e. F6) at 25^0C ± 2^0C /

60% ± 5% RH, 30^0C ± 2^0C / 65% ± 5% RH and 40^0C ± 2^0C / 75% ± 5% RH. The samples were analysed for Physical parameter like average weight, Hardness and Disintegration time. The *in vitro* dissolution studies in 0.01 N HCl containing 0.5% (w/v) of sodium lauryl sulphate; 1000 ml. The drug content analysis also showed that the products were stable. Further the formulations did not show any significant difference in dissolution rate after a study period of 3 months.

Table 10: Assay for formulation F6 kept for stability studies at 25°C ±2°C 60%±5%RH, 30^0C ± 2^0C / 65%±5%RH and 40°C±2°C 75%±5%RH

Parameters	25°C±2°C/60%±5%RH	30°C ± 2°C/65%±5%RH	40°C±2°C75%±5%RH
Initial	102.2	102.2	102.2
1 month	101.7	101.7	101.3
2 month	101.3	103.36	102.44
3 month	101.97	102.6	103.0

***** Each value is the mean ± SD (n=3)

f) Similarity factor (f_2) of selected formulation F6 and Innovator product (Starlix):

Table 11: % Drug release of Starlix (R_t) and F6 formulation (T_t)

Time (min)	% Drug release of Starlix (R_t)	% Drug release of F6 formulation (T_t)	$\sum Rt - Tt$
10	46.83	44.32	2.51
20	70.7	69.8	0.9
30	88.17	86.32	1.85
40	91.6	89.4	2.2
50	96.89	95.37	1.52
60	98.9	98.7	0.2

$\sum Rt - Tt = 9.18$

Table 12: Similarity factor (f_2) value of Reference (Starlix, Novartis Pharmaceuticals Ltd.) and Test (Selected Formulation F6)

Product	Therapeutic Range	Similarity factor (f_2) value
Nateglinide	50-100	70.5

CONCLUSION:

In six formulations of Nateglinide tablet, two different superdisintegrant used which are Sodium starch glycolate and Crosscarmellose sodium in different concentrations like 2, 4 and 6%. In F1, F2 and F3 formulation about 2, 4 and 6 % of Sodium starch glycolate respectively and in F4, F5 and F6 formulation about 2, 4 and 6% of Crosscarmellose sodium. By evaluating tablets it concluded that powder blend showed good flow property and its disintegration time was very less. As the concentration of superdisintegrants get on increase the Disintegration time was decrease. The formulation containing Sodium starch glycolate had more Disintegration time than Crosscarmellose sodium containing tablets. The Disintegration time of F-6 formulation was the

lowest among (4.0 min) all formulations. It may be inferred that Crosscarmellose sodium may be the suitable superdisintegrants for the development of immediate release tablet of Nateglinide so F6 was consider as an optimized formulation.

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