International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(2): March-April 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Research Article……!!!**

Received: 10-03-2015; Revised: 31-03-2015; Accepted: 01-04-2015

DEVELOP AND EVALUATE THE NATEGLINIDE DISPERSIBLE TABLET BY DIRECT COMPRESSION METHOD

Kameswara Rao S*, P Bhargava Bhushan Rao, R Jeevana, Ch Byula, M Santhi

Sri Siddhartha Pharmacy College, Ammavarithota, Nvzvid-521201, A.P, India

Keywords:

Nateglinide,

Hausnerratio,

Cross-povidone,

Cross-carmellose sodium

For Correspondence:

Kameswara Rao S

Sri Siddhartha Pharmacy College, Ammavarithota, Nvzvid-521201, A.P, India

E-mail:

contactkamesh87@gmail.com

ABSTRACT

The study was carried to formulate and evaluate dispersible tablet dosage form 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 disintegrates to formulate dispersible tablet of Nateglinide which disintegrates within few minutes thereby reducing the time of onset of action. Mannitol is selected as diluents, Sodium starch glycol ate, Cross-povidone, cross-carmellose sodium were selected as super disintegrates, citric acid and sodium bi carbonate is effervescent active ingredient in different concentrations. Aspartame as a sweetening agent, Magnesiumstearate as a Lubricant and glidant.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 99% - 100 % of Nateglinide, which is within the limit.As the concentrations of the Citric acid (preservative) & sodium bicarbonate (active ingredient respectively taking increases in the formulations F7 – F9 the disintegration time found to be decreased and the disintegration time for these formulations were 33, 31, 30 seconds respectively and the percentage drug release was also found to be increased for these formulations as 94 ,96, and 99 % respectively. From the above results it was found that as the concentration of citric acid decreased and sodium bi carbonate increases the disintegration and dissolution time was found to be improved, so considering the above results it was found that the F9 batch was found to be optimized batch and it pass all the pre-formulation parameters and evaluation results as per the IP limits.

INTRODUCTION

Nateglinide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the meglitinide class of short-acting insulin secretagogues, which act by binding to β cells of the pancreas to stimulate insulin release. Nateglinide is an amino acid derivative that induces an early insulin response to meals decreasing postprandial blood glucose levels.[1] Out of all the orally administered dosage forms; tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of change of various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The paediatrics and geriatrics patients are of particular concern. To overcome this, dispersible tablets and fast-disintegrating tablets have been developed. A mouth dissolving system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed inform of liquid. Recently mouth dissolving formulation is popular as NDDS because they are easy to administer and lead to better patient compliance. Paediatric and geriatric patient have difficulty in swallowing the conventional dosage forms. Mouth dissolving and fast dispersing drug delivery system may offer a solution to these problems. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy. Fast disintegrating tablets are gaining prominence as new drug-delivery systems. These dosage forms dissolve ordisintegrate in the oral cavity within a minute without the need of water or chewing. [2]

Nateglinide is rapidly absorbed following oral administration prior to a meal; absolute bioavailability is estimated to be approximately 73%. Peak plasma concentrations generally occur within 1 hour of oral administration. Onset of action is <20 minutes and the duration of action is approximately 4 hours.[3]

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. [4]

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 Nateglinide tablets of Nateglinide and to study the effect of functionality differences of super disintegrants on the tablet properties.[5]

MATERIALS AND METHODS

Nateglinide was a gift from Natco pharmaceuticals Pvt. Ltd, Hyderabad, India), and crospovidone and SSG were gifted from Hetero chemicals. Crosscarmellose 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.

Method of manufacturing Nateglinide dispersible tablets

Direct Compression Method

The Nateglinide dispersible tablets were prepared by using direct compression method.Nateglinide was sifted through 24 mesh, & excipientssuch as sodium starch glycol ate, crospovidine, Crosscarmellose sodium, mannitol and aspartame, magnesium state, sodium bi carbonate, citric acid, were passed through 60 mesh. 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.

Table No: 5 Composition of Nateglinide dispersible tablets.

S.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Nateglinide	60	60	60	60	60	60	60	60	60
2	Mannitol	116	116	116	116	116	116	96	93	86
3	Croscarmellose sodium	10	10	-	20	-	-	-	-	-
4	Cros-povidone	10	-	10	-	20	-	-	-	-
5	Sodium starch glycol ate (SSG)	-	10	10	-	-	20	-		-
6	Aspartane	2	2	2	2		2	2	2	2
7	Magnesium stearate	2	2	2	2	2	2	2	2	2
8	Sodium bi carbonate	-	-	-	-	-	-	36	38	42
9	Citric acid	-	-	-	-	-	-	4	6	8
	TOTAL (mg)	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**

Evaluation of Nateglinide dispersible tablets[6]

Wetting time:

A piece of filter paper folded twice and placed in a small petridish containing 5ml of distilled water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The wetted tablet was then weighed. Wetting time, S, was determined by using following formula. S = 10× Wb-Wa/Wb Where, Wa–weight of the tablet before water absorption. Wb – weight of the tablet after water absorption.

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 a vernier calipers. Three tablets from each formulation were used and average values of thickness and diameter were calculated.

Hardness:

The hardness of tablets was determined by using Monsanto Hardness tester and it is expressed in Kg/cm^2. The whole experiment was performed in triplicate

Friability:

The friability of the tablet was determined by using Roche friabilator.It is expressed in percentage. Twenty tablets 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.

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

Disintegration Test:

The test was carried out as per USP- 2008.One tablet was placed in six tubes of the basket. 0.1 HCL buffer of is used as the disintegration medium. The temperature of the liquid was maintained at 37^0 c ± 2^0 c. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets, not less than 16 of total of 18 tablets should disintegrate completely

Weight variation:

20 tablets were selected randomly and weighed accurately. 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 10 % and none should deviate by more than double that percentage. Standard deviation and average weight were calculated

Determination of moisture content by Karl Fisher Apparatus:

50 ml of methanol was taken in a dried titration flask and it was titrated with KFTS to obtain moisture free flask. 10 tablets were blended to get fine powder and 0.5 gm of powder sample was transferred to titration flask it was titrated with KFTS solution to the end point and moisture content was calculated by the following formula.

$$\text{Percentage of water} = \frac{\text{Volume of KFTS consumed x F x 100}}{\text{Weight of the sample in mg}}$$

Drug Content (Assay) By HPLC method

Separately inject 10 µl of diluents, five replicate injections of standard solution and two injections of sample solution in to the chromatograph, record the chromatograms and measure the peak responses.

In- Vitro Drug Release Study [7]

There are no standard methods yet developed for determining the in vitro drug release for dispersible tablets. The release rate of dispersible tablets of Nateglinide 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 ^{0}C ± 0.5 ^{0}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 217.0 nm.

Stability Study[9]

Stability testing is an integral part of formulation development. It generates information on which to base proposals for the shelf lives of drug substances and products and their recommended storage conditions. Stability data also are a part of the dossier submission to regulatory agencies for licensing approval. Stability testing ensures that a drug substance will be safe and effective throughout the shelf life of the product. However, meeting the potency and purity profiles established in the compendia can be challenging as pharmaceutical products become increasingly complex and diverse. The optimized formulation F9 packed in PVC blister pack then, they were stored at three different temperatures 4^0C±2^0C, 27^0C±2^0C and 45^0C±2^0C 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

Table 2: Evaluation parameters of dispersible tablets of Nateglinide

Batch	Wetting time (sec)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (sec)	Weight variation	Moisture content (% w/w)	Drug content %
F1	54.54	5.7	3.50	0.51	33.47	98±2.34	2.1	99
F2	55.56	5.7	3.48	0.94	31.56	100±3.5	2.2	100
F3	54.46	6.0	3.42	0.89	29.91	99±4.2	1.8	100
F4	56.37	5.8	3.58	0.61	35.42	101±1.3	2.2	100
F5	59.35	5.7	3.68	0.98	33.45	98±1.5	2.3	99
F6	54.25	5.9	3.71.	0.94	29.25	99±0.9	2.7	100
F7	59.90	5.6	3.45	0.50	33.25	101±0.7	2.0	99
F8	55.43	5.2	3.23	0.46	34.21	100±0.4	1.9	101
F9	56.08	5.4	3.36	0.39	31.24	100±1.2	1.6	101

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 **5.2 – 6.0 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 **3.36 – 3.71 Kg/cm^2.** Uniform hardness was obtained due to equal compression force. Tablets were evaluated by using Roche Friabilator and friability of tablets was observed in the range **0.39- 0.98.**Tablets were evaluated for disintegration time in the IP disintegration apparatus. The disintegration time was found in the range **29 – 33 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 **54 – 59 sec.** Tablets were evaluated by using assay method. The drug was obtained in the acceptable limit. The drug content was found in the range **99 – 101%.** Tablets are evaluated for the content uniformity test all the formulations are under the IP specifications.

In–vitro drug release studies

Table 3: Comparative Dissolution Profile of Nateglinide dispersible tablets in 0.1 HCL Buffer Solution

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	23	26	32	27	28	24	31	35	36
10	34	44	40	36	43	32	48	52	53
15	47	54	51	44	52	45	65	68	62
20	63	61	57	53	62	63	73	77	80
25	72	72	72	61	71	70	82	86	88
30	80	81	84	87	88	89	94	96	99

Average % Drug Release Of At 30 Mins

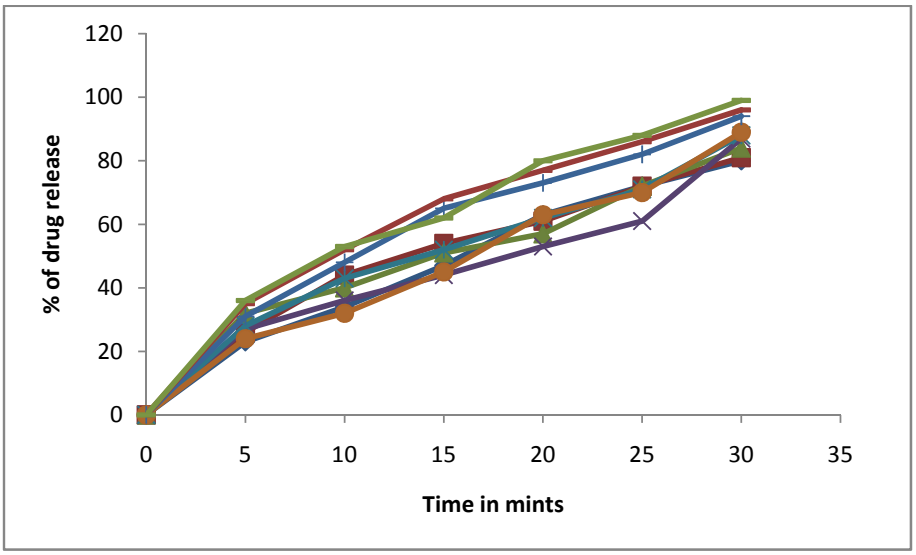

Fig.no:1: Comparative Dissolution Profile of Nateglinide dispersible Tablets in 0.1 HCL Buffer Solution.

In-vitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 25 rpm. The percentage drug release at the end of 30 min was found in the range **90 – 99 %.**Cross carmellose sodium and Cross providence is used as the super disintegrate in the formulation F1 at the concentrations of the 5, 5, % respectively.Cross carmellose sodium and sodium starch glycol ate is used as the super disintegrates in the formulation F2 at the concentrations the 5, 5, % respectively.Cross-povidone and sodium starch glycol ate is used as the super disintegrates in the formulation F3 at the concentrations of the 5, 5, % respectively.

Cross carmellose sodium is used as the super disintegrates in the formulation F4 at the concentrations of the 10 % respectively. Cross-povidone is used as the super disintegrates in the formulation F5 at the concentrations of the 10 % respectively. Sodium starch glycol ate is used as the super disintegrates in the formulation F6 at the concentrations of the 10%

respectively. Citric acid and sodium bi carbonate is used effervescent active ingredient in the formulation F7 – at the concentrations of 18, 2% respectively, F8 – at the concentrations of 19,3% and 21,4 % respectively. So F9 was best optimized formulation using effervescent 99% of drug release obtained, F9 was best formulation.

Table 4: In-vitro Dissolution profile of Nateglinide from optimized formulation F9and marketed (Starlix) product

Time in (mn)	0	5	10	15	20	25	30
Innovator	0	28	42	59	75	86	97
F9	0	36	53	62	80	88	99

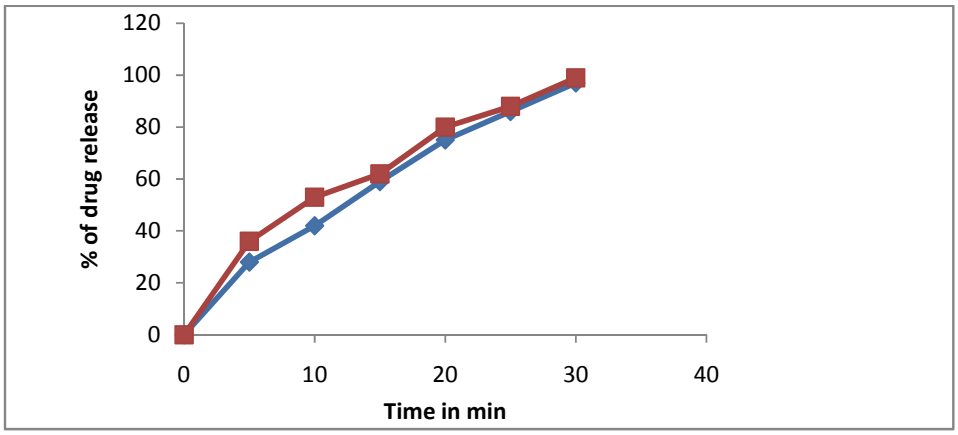

Fig .No:2 Comparison of in-vitro Dissolution data of Market product with Optimized Formulation (F9)

Finally concentration is increased to. This showed 99% drug released in 30 min. where perfect match with the Market product was obtained. So F9 was considered as optimized formulation.

Release kinetics: The release profile of the optimized formula F9 fitted best to Korsmeyer-Peppas model with R^2 value of 0.992. As the n value for the Korsmeyer-Peppas model was found to be greater than 1, it follows case-2 transport.

Stability studies:

According to ICH guidelines, 45 days stability study at $4^0C \pm 2^0C$, $27^0C \pm 2^0C$ and $45^0C \pm 2^0C$ for 45 days at RH 75±5% of optimized formulation (F9) 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 $4^0C \pm 2^0C$, $27^0C \pm 2^0C$ and $45^0C \pm 2^0C$ for 45 days at RH 75±5% for 45 days.

Table 6:Stability studies of Nateglinide tablets.

Parameters	After 15 days	After 30 days	After 45 days
Physical appearance	No change	No change	No change
Weight variation (mg)	100±3.34	100±2.55	100±4.23
Thickness (mm)	5.51	5.53	5.54
Hardness (kg/cm^2)	3.4	3.3	3.2
Friability (%)	0.41	0.43	0.43
Drug content (%/tablet)	100.34	99.81	99.0
Wetting time (sec)	58.96	60.12	65.51
Disintegration time (sec)	34.19	39.13	45.05
Percentage drug release	99	98.5	98

SUMMARY AND 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.Mannitol is selected as diluents, Sodium starch glycol ate, Cross-povidone, cross-carmellose sodium were selected as super disintegrates,citric acid and sodium bi carbonate is effervescent active ingredient in different concentrations. Aspartame as a sweetening agent, Magnesium stearate as a Lubricant and glidant. 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 99% - 100.% of Nateglinide, which is within the limit. As the concentrations of the Citric acid (preservative) & sodium bicarbonate (active ingredient respectively taking increases in the formulations F7 – F9 the disintegration time found to be decreased and the disintegration time for these formulations were 33, 31, 30 seconds respectively and the percentage drug release was also found to be increased for these formulations as 94 ,96, and 99 % respectively. From the above results it was found that as the concentration of citric acid decreased and sodium bi carbonate increases the disintegration and dissolution time was found to be improved, so considering the above results it was found that the F9 batch was found to be optimized batch and it pass all the pre-formulation parameters and evaluation results as per the IP limit. From the data obtained, it is observed from the formulation containing Citric acid - 4mg, sodium bi carbonate - 21mg in **Formulation F9**, shows Disintegration time in 30 seconds and the Percentage drug release is of 99 % at the end of 30min which satisfied all the tablet evaluation parameters for dispersible tablet. Hence

looking at all the satisfactory parameters F9 batch is selected as the optimized batch.The release profile of the optimized formula F9 fitted best to Korsmeyer-Peppas model with R^2 value of 0.999.The Market product was compared with the formulated F9 batch and shows less release compared with the optimized formulation F9 batch.

ACKNOWLEDGEMENT

The author would like to thank Mr. P. LaxmanRao, Assistant Professor, M.A.M. College of Pharmacy for for giving support and guidance for throughout research work. And also thankful to principal M.PrasadRAo for providing lab premises to conduct my research work.

REFERENCES

1. Lachmann, L., Liebermann, HA., Kiang, JL., The theory and practice of Industrial Pharmacy, 3rd Ed., Varghese Publishing House, Bombay, 1998, 430- 440.
2. Kuchekar, BS.,Badhan, AC., Mahajan, HS., Mouth dissolving tablets: A Novel drug delivery system, Pharma. Times, 2003, 35, 3-10.
3. Amin, AF., Shah, TJ., Bhadani, MN., Patel, MM., Emerging trends in orally disintegrating tablets, www.pharminfo.net, 2005.
4. Battue SK, Repay MA, Maunder S and Rio MY, Formulation and evaluation of rapidly disintegrating tablet Fenoverine tablets: Effect of superdisintegrants, Drug DevIndPharm, 2007, 33, 1225–1232.
5. Swamy PA, Areefulla SH, Shrisand SB, Gandra S and Prashanth B, Orodispersible tablets of meloxicam using superdisitegrant blends for improved efficiency, Ind J Pharm Sci, 2007, 69(6), 836-840.
6. Lachman L, Liberman H A, Kenig J. L: Theory and practice of industrial pharmacy, 3rd edition, 1987 Varghese Publication house, Bombay, 293.
7. Gazzi S, Chegonda KK, Chandra SRG, Kumar BV, Reddy P. Formulation and evaluation of dispersible tablets of paracetamol. AAPS. Pharm. Sci. Tech. 2009; 10: 530-539.
8. Edmund J. Elder. Et al., Preparation, Chracterisation and Scale-up of Ketoconazole with enhanced dissolution and Bioavailability. Drug Dev. and Ind. Pharmacy. 2007; 33: 755-765.
9. Brain R Matthews. Regulatory aspects of stability testing in Europe. Drug devInd Pharm. 1999; 25(7): 831-856.