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Research Article

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF NATEGLINIDE

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ASBTRACT

In the present investigation an attempt was made to formulate mouth dissolving tablets using BCS class II drug Nateglinide, i.e. low solubility and high permeability drug. The aim of present work was to formulate mouth dissolving tablets of Nateglinide using superdisintegrants like sodium starch glycolate (SSG), crospovidone, Avicel PH 102 and pregelatinized starch. All tablet batches were prepared by direct compression technique. All batches were evaluated for hardness, friability, disintegration time and dissolution rate. An effective, pleasant tasting mouth dissolving tablet from Batch F6 was found to have a better hardness of 3 kg/cm^2, disintegration time of 30 seconds and *in vitro* drug release of not less than 98.33% within 45 minutes.

Keywords: Nateglinide, SSG, FDT, Pregelatinized starch, Direct compression technique.

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 agingincluding 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 formfor oral administration, which when placed in mouth,rapidly dispersed or dissolved and can be swallowed inform of liquid. Recently mouth dissolving formulation ispopular as NDDS because they are easy to administer andlead 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 theneed 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 dissolvecompletely 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 superdisintegrants on the tablet properties.[5]

MATERIALS AND METHODS

Nateglinide was a gift from Cadila pharmaceuticals Pvt. Ltd, Ahmedabad, India), and crospovidone and SSG were gifted from Colorcon Asia Pvt Ltd (Mumbai). All other reagents and chemicals used were of analytical grade.

Preparation of Nateglinide tablets [6,7]

The superdisintegrants (Crospovidone, sodium starch glycolate, Avicel PH 102 and pregelatinized starch) in varying concentration (5-10%) were used to develop the tablets. All the materials were passed through 80 # screens prior to mixing. All the materials were directly compressible so this uniformly mixed blend wascompressed into tablets using concave face round toolingon multistation tablet compression machine. The composition ofthe batches is shown in Table 1.A minimum of 50 tablets were prepared for every batch. The tablets so obtained were evaluated for their organoleptic properties.

Table 1: Formulation of Nateglinide mouth dissolving tablets

Ingredients	F1	F1	F3	F4	F5	F6	F7	F8
Nateglinide	60	60	60	60	60	60	60	60
SSG	5	10	-	-	-	-	-	
Crospovidone	-	-	5	10	-	-	-	-
Pregelatinized starch	-	-	-	-	5	10	-	-
Avicel PH 102	-	-	-	-	-	-	5	10
Mannitol	125	125	125	125	125	125	125	125
Lactose	100	95	100	95	100	95	100	95
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
Total (mg)	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Evaluation of Nateglinide tablets

1. Uniformity of weight

The weights were determined to within ±1mg by using Sartorius balance (Model CP- 224 S). Weight control isbased on a sample of 20 tablets. Determinations were made in triplicate.

2. Tablet hardness

The hardness of the tablets was determined by diametric compression using a dial type hardness tester (Model no.1101, Shivani Scientific Ind). A tablet hardness of about4-5 kg is considered adequate for mechanical stability.Determinations were made in triplicate.

3. Tablet friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of aknown weight (W_0) or a sample of 20 tablets arededusted in a drum for a fixed time (100 revolutions) andweighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below.The weight loss should not be more than 1 %.

Determination was made in triplicate.

% Friability = W_0- W/ W_0 *×100*

4. In-vitro disintegration test

The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electrolab, Mumbai, India) distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

5. Wetting time

The wetting time of the tablets can be measured using asimple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter.Ten millimetres of water-containing Eosin, a water-solubledye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet isnoted as a wetting time.

6. Tablet thickness

Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using Varnier calipers. The thickness was measured by placing tablet between two arms of the Varnier calipers.

7. In-vitro dissolution study[8]

The release rate Nateglinide from mouth dissolving tablets was determined using United State Pharmacopoeia (USP)XXIV dissolution testing apparatus II (paddle method).The dissolution test was performed using 900 ml of pH 6.8 phosphate buffer, at 37± 0.5^{0}C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 5, 10, 15, 20, 25 and 30min. The samples were replaced with fresh dissolution medium ofsame quantity. The samples were filtered through a 0.45µ membrane filter. Absorbance of these solutions was measured at 209 nm using a Shimadzu UV-1601 UV/Visdouble beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

8. Accelerated stability studies[2,7,8]

In order to determine the change in *in-vitro* release profile on storage, stability study of the effective batch was carriedout at 400 C in a humidity chamber having 75% RH.Sample were withdrawn after three month interval andevaluated for change in in-vitro drug release pattern,hardness and disintegration time.

RESULT AND DISCUSSION

The use of superdisintegrants for preparation of mouth dissolving tablets is highly effective and commerciallyfeasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorba large amount of water when exposed to an aqueous environment. The absorption of water results in breakingof tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well. Prepared fast-dissolving tabletgets dispersed in the mouth quickly and releases the drugearly as compared to its formulated conventional tablet.

Table 2 shows the results for evaluation of mouth dissolving tablets of the Nateglinide for F1to F8 batches.

Table 2: Evaluation parameters of mouth dissolving tablets of Nateglinide

Batch	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
F8	3.5	0.47	99.25	3.7	49	73	80.27	302

From the observations of Table 2, the Batch F6 was found to be more significant as compared to the other batches i.e. disintegration time of just 30 seconds was obtained.

Following Figure 1 shows the cumulative percentage of Nateglinide released from formulated tablet with different concentration of sodium starch glycolate, crospovidone, Avicel PH 102 and SSG. It is clear that the dissolution of Nateglinide has improved considerably in formulation F6 as compared to other batches.

Also the mouth dissolving tablets of batch F6 gets dispersed in the mouth quickly and releases the drug early as compared to the conventional directly compressible tablet. Amongst four different superdisintegrants used, i.e. sodium starch glycolate, crospovidone,Pregalatinized starch and Avicel PH 102, the order of enhancement of the dissolution rate superdisintegrants was found to be Pregelatinized starch>Avicel PH 102> crospovidone>Sodium starch glycolate. The prepared tablets in all the formulations possessed goodmechanical strength with sufficient hardness in the range of 3 to 4 kg/cm^2. Friability values below 1% were indication of good mechanical resistance of the tablets. Also all the tablets from each formulation passed weight variation test, as the % weightvariation was within the pharmacopoeial limits. The percentage drug content of all the tablets was found to be withinthe acceptable limits. The wetting time for all the six formulations was performed in triplicate. In vitrodispersion is a special parameter in which the time taken by the tablet to produce complete dispersion was measured which was found to be reduced in tablets containing pregalatinized starch which may be attributed to the wicking type of disintegrant (pregelatinized starch) formed thus facilitating the disintegrates to bring about faster disintegration. However, tablets

containing pregelatinized starch showed the fastest disintegration, as shown in Figure 1. In vitro dissolution studies for F6 tablets confirmed the results. F6 tablets shown good and rapid dissolution efficiency. The study shows that the dissolution rate of Nateglinide can be enhanced to agreat extent by direct-compression technique with the addition of superdisintegrants.

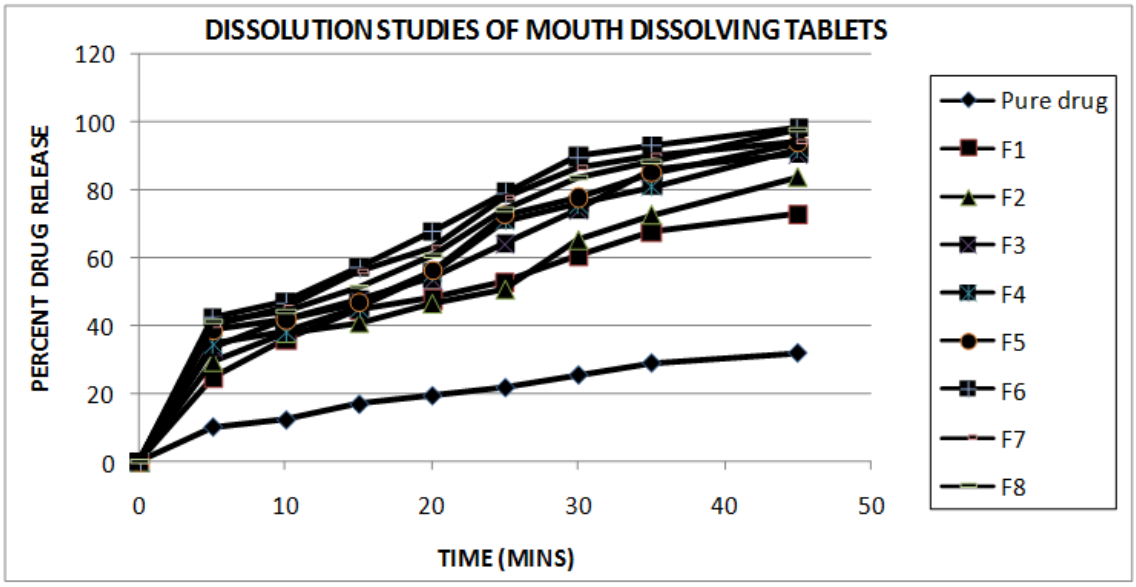

Fig. 1: Dissolution pattern for mouth dissolving tablets of Nateglinide

The F6 tablets were subjected to the accelerated stability studies for three months and evaluated for the in-vitro drug release pattern, hardness and disintegration time. The results for the stability studies are as shown in Figure 2 as follows:

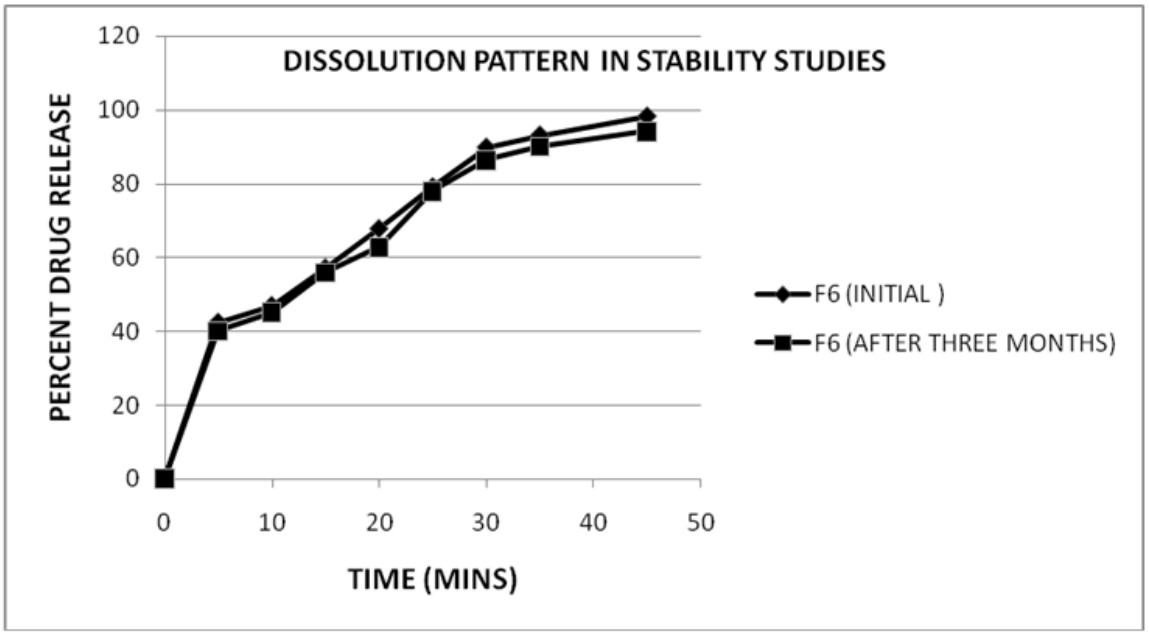

Fig. 2: Dissolution pattern of F6 tablets before and after stability studies

The results of disintegration time and wetting time during and after stability studies are as shown in Table 2 as follows:

S. No.	Parameter	Batch F6 (Initial)	Batch F6 (After 3 months)
1.	Disintegration time	30 seconds	35 seconds
2.	Wetting time	42 seconds	52 seconds

From the disintegration test, dissolution test and wetting time results of the F6 batch tablets, it can be concluded that the mouth dissolving tablets of Nateglinide are stable and do not undergo significant changes in their physicochemical characteristics.

Thus the studies shows that the Nateglinide can be formulated as mouth dissolving tablet using pregelatinized starch as a superdisitegrant and quick disintegration time of just 30 seconds can be obtained for rapid onset of action of the Nateglinide.

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