Available online on 15.10.2018 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research



Open Access Research Article

# DESIGN AND IN VITRO EVALUATION OF EXTENDED RELEASE TABLET OF NATEGLINIDE

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## ABSTRACT

The aim of present study is to formulate and evaluate extended release matrix tablet of Nateglinide by direct compression method using different polymer like HPMC K4 and HPMC K15. Matrix tablet of nateglidine were prepared in combination with the polymer HPMC K4, HPMC K15, along with the excipients and the formulations were evaluated for tablet properties and *in vitro* drug release studies. Nateglinide matrix tablet prepared by using polymer such as HPMC K4 and HPMC K15, it was found that HPMC K15 having higher viscosity as compare to HPMC K4 therefore different concentration of polymer were studied to extend the drug release up to 12 h. The tablets of Nateglinide prepared by direct compression had acceptable physical characteristics and satisfactory drug release. The study demonstrated that as far as the formulations were concerned, the selected polymers proved to have an acceptable flexibility in terms of in-vitro release profile. In present the study the percent drug release for optimize batch was found to 94.62%. Hence it can be conclude that Nateglinide extended release matrix tablet can prepared by using HPMC. The swollen tablet also maintains its physical integrity during the drug release study.

**Keywords:** Tablet, *in-vitro* drug release, Nateglinide, HPMC

**Article Info:** Received 04 Sep, 2018; Review Completed 07 Oct 2018; Accepted 07 Oct 2018; Available online 15 Oct 2018

**Cite this article as:**

Mahajan N, Wanaskar K, Bhutada Y, Thenge R, Adhao V, Design and in vitro evaluation of extended release tablet of nateglinide, Journal of Drug Delivery and Therapeutics. 2018; 8(5-s):235-239

**DOI:** http://dx.doi.org/10.22270/jddt.v8i5-s.2012

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## INTRODUCTION

Oral drug delivery systems is the most convenient mode of drug administration compared to other dosage forms due to its high patient compliance and flexibility.[1] In conventional oral dosage forms drug dosage must be administered several times which results in fluctuating drug levels in plasma. These limitations of conventional dosage form can be overcome by formulation of sustained release dosage forms which provides drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with release profiles sustained by the special technological construction and design of the system[2-3]. An alternative to administration of another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations. Oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency. Controlled release formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduced dose and side effects and increased margin of safety for high potency drugs[4] . Nateglinide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). belongs to the meglitinide class of short secretagogues, which act by binding to β cells of the pancreas to stimulate insulin release[5]. The short biological half-life (nearly 1.5hr) favours development of sustained release formulations[6]. Nateglinide is dosed three times daily before meals there is a rapid rise in plasma insulin, with peak levels approximately 1 hour after dosing and a fall to baseline by 4 hours after dosing. However, fluctuations of drug concentration in plasma may occur, resulting in side

effects or re concentration at receptor side. As the drug is e plasma fluctuations are minimized, therefore sustain dosage form of Nateglinide is desirable.

## METHODS AND MATERIALS:

Nateglinide were obtained as a gift sample from Zydus cadila, Ahmadabad, India. HPMC K4 and HPMC K15 were obtained from JCPL, Jalgaon, India. Microcrystalline cellulose, talc, methanol, ethanol, hydrochloride acid were obtained from Molychem, Mumbai. All other chemicals used were of analytical grade.

**Preparation of matrix extended release Nateglinide tablet:**

Tablets of nateglinide were prepared by direct compression Techniques. The various formulation batches viz., F1, F2, F3, F4 and F5 were prepared by using different concentration of HPMC K4 and HPMC K15. Microcrystalline cellulose was used as diluent in each batch. Talc and magnesium stearate were used as a glidant and lubricant respectively. The entire ingredient were shifted through the screen (# 80) and thoroughly mixed using blender. Then adding talc and magnesium stearate and formulation were compressed by using tablet punching machine (Mini press II, Chamunda, Ahmedabad).

**Table 1: Formulation of Matrix Extended release Nateglinide tablets**

| Batch | Nateglinide | HPMC K4 | HPMC K15 | MCC | Talc | Magnesium stearate |
|---|---|---|---|---|---|---|
| F1 | 220 | ---- | 180 | 90 | 5 | 5 |
| F2 | 220 | 30 | 150 | 90 | 5 | 5 |
| F3 | 220 | 60 | 120 | 90 | 5 | 5 |
| F4 | 220 | 120 | 60 | 90 | 5 | 5 |
| F5 | 220 | 135 | 45 | 90 | 5 | 5 |

All weights are in mg

**Compatibility of Drug and Excipients**

The drug-excipients compatibility was studied by using Infrared spectroscopy. The sample of pure drug and other polymers over the range of 4000-400$^{cm-1}$ using Fourier Transform Infrared spectrophotometer (Shimadzu, Japan)

**Pre-compression properties of Powder blend**

**Angle of Repose**

The accurately weighed powder was taken in funnel. The height of the funnel was adjusted that the tip of the funnel touched the apex of the heap of the powder. The powder was transfer through the funnel freely onto the surface. The diameter of the powder cone was measured.

The angle of repose was calculated using the following equation.

$$\tan(\theta) = h/r$$

Where 'h' and 'r' are the height and radius of the powder cone respectively [7].

**Density**

The tap density (TBD) and loose bulk density (LBD) for the drug, polymers and excipients and in combination which was used in the research work was determined on the instrument. Two gram of drug powder was transfer into a 10 ml calibrated measuring cylinder. After initial volume was measured, then the cylinder was allowed to tap for specific time period. The total number of tap was calculated.

LBD = weight of the power/volume of the packing

TBD= weight of the powder/tapped volume of the packing

The compressibility index of all ingredients was calculated using following equation

Carr's index = [(TBD – LBD) 100/ TBD]

**Hausner's Ratio**

Hausner's ratio was determined by following equation [8]

Hausner's ratio = TBD/ LBD

**Evaluation of Nateglinide extended release tablets**

**1. Thickness and Diameter**

Method – Three samples were selected randomly from each batch and thickness was measured using venire caliper. Similarly one tablet from each batch was tested for diameter [9].

**2. Weight variation**

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. [9]

**3. Hardness**

Three samples were selected from each batch and hardness was measured using Monsanto hardness tester. [9]

**4. Friability**

Friability of the tablets was measured using Roche friabilator. Placed twenty tablets were weighed and tablets were rotated for 4 minutes at 25 rpm. The tablets were removed and weighed again after revolution. The percent friability was calculated using following formula. [9]

$$\% F = \{1-(w/w0)\}\ 100$$

Where,

% F = friability in percentage

W0 = Initial weight of tablets

W = Weight of tablets after revolution.

**5. Drug Content**

Five tablets were weighed individually, then place in a morter and powdered with a pestle. An amount equivalent to 25mg of drug (100mg) was extracted with 100ml of 0.1M HCl (pH1.2), stirred for 15 min using magnetic stirrer (Remi, Mumbai). It was filtered through a filter and appropriately diluted with 0.1 M hydrochloric acid and the drug content using UV-VIS spectrophotometer at 206 nm .

**6. In-vitro dissolution release of Nateglinide**

In vitro release of Nateglinide from formulated tablets was carried out 1.2 HCL for 2 hour and continued in phosphate buffer pH 6.8 for remaining hours. The studies were performed in USP dissolution apparatus II, (Dissolution Test Apparatus, Electrolab, India) 37 ± 0.5° C and 50 rpm speed. Samples were withdrawn at hourly interval and analyzed for Nateglinide content at 207 nm for PH 1.2 acid buffer and 206 nm for pH 6.8 phosphate buffers by using UV spectrophotometer (Shimazdu, Japan). [10]

**Kinetics of in-vitro drug releas**

To study the release kinetics of In-vitro drug release, data was applied to kinetic models such as zero order, first order, Higuchi and KorsmeyerPeppas.

Zero order: C = K0t K0 - zero-order rate constant expressed in units of concentration/time,

t - time in hrs.

First order: LogC = LogC0 – Kt / 2.303 Where, C0 - is the initial concentration of drug, K - first order constant, t - time in hrs.

Higuchi: Qt = Kt1/2 Where Qt - amount of the release drug in time t, K kinetic constant, t- time in hrs.

Korsmeyer peppas: Mt / M∞ = Kt n Where Mt - represents amount of the released drug at time t, M∞- Is the overall amount of the drug (whole dose) released after 12 hrs K- Is the diffusional characteristic of drug/ polymer system constant n- Is a diffusional exponent that characterizes the mechanism of release of drug. [11]

## RESULT & DISCUSSION

The FTIR of Nateglinide shows peaks at 1674, 1713, 2862-3096, 3296 which was correlates with peaks of mixture of drug and polymer, which conclude that the drug is compatible with polymer.

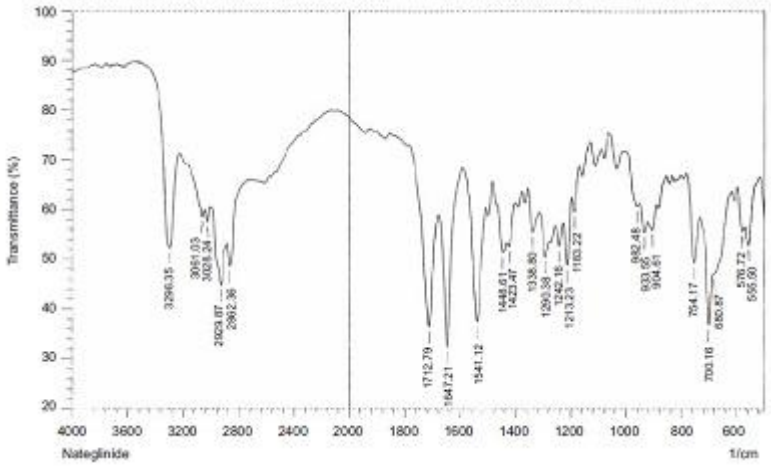


**Figure 1: FTIR spectra of Nateglinide**

**Table 2: Precompressional Parameter of the powder blend**

| Sr. No. | Angle of respose | Bulk density | Tapped density | Hausner's ratio | Cars index |
|---|---|---|---|---|---|
| **F1** | 28.36±0.022 | 0.625±0.021 | 0.680±0.024 | 1.088±0.058 | 8.03±0.066 |
| **F2** | 26.56±0.021 | 0.628±0.022 | 0.689±0.026 | 1.090±0.052 | 8.85±0.071 |
| **F3** | 27.82±0.024 | 0.632±0.020 | 0.675±0.024 | 1.068±0.056 | 6.37±0.045 |
| **F4** | 26.56±0.023 | 0.641±0.023 | 0.676±0.025 | 1.032±0.054 | 5.17±0.056 |
| **F5** | 29.19±0.032 | 0.640±0.022 | 0.675±0.016 | 1.054±0.066 | 5.18±0.053 |

The precompressional parameter shown in Table-2 showed that all the batches having angle of repose in between 26-30 shows that powder having good flow property. All batch shows Carr's index 5-9 therefore type of flow is good. Tapped density was found in range of 0.675-0.689.bulk density in range of 0.625-.0.641. All the batches shows Hausner's ratio less than 1.25. It was found within the limit.

**Table 3: Evaluation of Extended release matrix tablet of Nateglinide**

| Batch | Hardness ($kg/cm^2$) | Friability (%w/w) | Thickness (mm) | Diameter (mm) | Weight variation test (mg) | Drug Content |
|---|---|---|---|---|---|---|
| **F1** | 6.21±0.14 | 0.59±0.05 | 3.30±.0.057 | 12.00± 0.67 | 501±0.23 | 98±1.5 |
| **F2** | 6.26±0.09 | 0.71±0.04 | 3.29±.0.051 | 12.02± 0.23 | 502±0.26 | 100±1.7 |
| **F3** | 6.30±0.10 | 0.52±0.03 | 3.30± 0.053 | 12.03± 0.52 | 500±0.23 | 99±1.4 |
| **F4** | 6.20±0.13 | 0.59±0.04 | 3.31± 0.010 | 12.04± 0.34 | 501±0.22 | 99±1.5 |
| **F5** | 6.22±0.11 | 0.58±0.02 | 3.31± 0.056 | 12.02± 0.09 | 502±0.15 | 100±1.3 |

The hardness of all the tablet batches was found from 6.21-6.30. The friability of all tablet batches was found to be in the range of 0.52-0.71 %w/w. The diameter of each tablet was in range 12.00 to 12.04mm. The thickness of tablet was in range 3.28-3.30mm. Weight of all tablets was found in range of 500-502.

**Table 4: Dissolution study of extended release matrix tablet of Nateglinide**

| Time | Cumalative % drug release | | | | |
|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** |
| **30 min** | 4.38±0.29 | 4.75±0.15 | 8.83±0.56 | 11.35±0.34 | 12.25±0.76 |
| **1 hour** | 8.22±0.70 | 9.32±0.56 | 14.02±0.52 | 15.43±0.55 | 16.60±0.58 |
| **2 hour** | 10.03±0.94 | 11.40±0.71 | 15.81±0.66 | 21.01±0.32 | 22.37±0.55 |
| **4 hour** | 24.32±0.80 | 28.03±0.38 | 44.07±0.23 | 49.93±0.56 | 52.31±0.42 |
| **6 hour** | 29.85±0.79 | 39.95±0.56 | 53.38±0.26 | 61.39±0.52 | 62.83± 0.46 |
| **8 hour** | 36.27±0.58 | 46.41±0.32 | 58.44±0.38 | 70.12±0.59 | 71.32±0.75 |
| **10 hour** | 41.33±0.59 | 57.43±0.31 | 69.63±0.25 | 76.59±0.51 | 82.55±0.36 |
| **12 hour** | 45.74±0.61 | 65.03±0.58 | 76.82±0.55 | 84.79±0.34 | 94.62±0.57 |

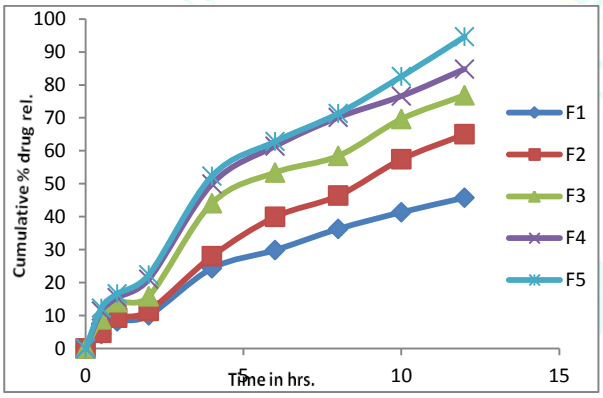


**Figure 2: Cumulative Percent drug release of Nateglinide**

There must be sufficient polymer content in a matrix system to form a uniform barrier. The barrier protects the drug from immediately releasing into the dissolution medium. If the polymer level is too low, a complete gel layer may not form, in most studies, increased polymer level in the formulation results in decreased drug-release rates. Because hydrophilic matrix tablets containing hydrophilic polymers absorb water and swell, the polymer level in the outermost hydrated layers decreases with time. The outermost layer of the matrix eventually becomes diluted to the point where individual chains detach from the matrix and diffuse into the bulk solution. The polymer chains break away from the matrix when the surface concentration passes a critical polymer concentration macromolecular disentanglement or surface erosion. The polymer disentanglement concentration is defined as the polymer concentration at the matrix surface. The surface concentration passes a critical polymer concentration of macromolecular disentanglement or surface erosion. It was observed that higher polymer levels result in slower release rate. As found in the concentration of HPMC K 15 decreases and HPMC K4 increases drug release increases. As it was found in F3, F4, and F5**.**

Cumulative percent drug release in F5 batch at the end of 12 hour was found to be 94.62% while in F4, F3, F2 and F1 was found to be 84.79%, 76.82%, 65.03%, 45.74% respectively.

The coefficient correlation (R2) was considered as main parameter for interpreting the release kinetics model. In the most of cases of (R2), value is higher for zero order than first order, so the formulation follows the zero order. It also follows the Higuchi model of drug release along with it also follows Korsemeyer – Peppas equation of drug release.

**Table 5: Kinetic treatment of data of dissolution profiles of formulations F1 – F5**

| Formulations | Parameter | Mathematical models | | | | |
|---|---|---|---|---|---|---|
| | | Zero order | First order | Hixoncrowell | Korsemeyer peppas | Higuchi plot |
| F1 | R 2 | 0.99332 | 0.87964 | 0.80564 | -0.31044654 | 0.9498211 |
| | Slop | 0.21944 | 0.0035 | 0.01966 | 1.22902064 | 0.1820864 |
| | Intercept | -2.0056 | 0.62549 | 1.65277 | -3.72165625 | 4.8092711 |
| F2 | R2 | 0.99742 | 0.86067 | 0.95966 | -0.31314875 | 0.951878 |
| | Slop | 0.15361 | 0.00248 | 0.01395 | 1.00346064 | 0.229591 |
| | Intercept | -0.4941 | 0.72354 | 1.97851 | -3.30499091 | 5.354839 |
| F3 | R2 | 0.98713 | 0.80564 | 0.9157 | -0.27661462 | 0.982296 |
| | Slop | 0.11218 | 0.00183 | 0.01029 | 0.85852773 | 0.2888078 |
| | Intercept | 6.92033 | 0.85765 | 2.69504 | -2.98043542 | 3.7652246 |
| F4 | R2 | 0.98694 | 0.81289 | 0.91883 | 0.28345074 | 0.9842822 |
| | Slop | 0.10829 | 0.00184 | 0.01016 | 0.86785966 | 0.2997375 |
| | Intercept | 6.42055 | 0.83947 | 2.60774 | -3.02264162 | 3.8181359 |
| F5 | R2 | 0.9805 | 0.80235 | 0.90852 | 0.33906093 | 0.9814 |
| | Slop | 0.09381 | 0.00175 | 0.0093 | 0.80497922 | 0.3467738 |
| | Intercept | 7.11308 | 0.8371 | 2.62102 | -2.90255647 | 3.2495836 |
| | Slop | 0.11081 | 0.00183 | 0.010232 | 0.860626629 | 0.2927849 |
| | Intercept | 7.15219 | 0.85635 | 2.698301 | -2.98790498 | 3.6531988 |

## CONCLUSION

It could be concluded from the results, that the tablets consist of the HPMC K15M used alone in the formulation a unlabe to sustained the release of drug (F1). The batch F5 consist of HPMC K4M and HPMC K15M (F5) showed sustained release upto 12 h. Hence Nateglinide extended release matrix tablet can prepared by using HPMC to prolong the release of drug for the treatment of diabetes.

## Acknowledgement:

Authors are thankful to Management and Principal Dr. Rajendra Gode College of Pharmacy, Malkapur, for providing necessary laboratory Facilities to carry out this research work.

**Conflict of Interest:** Author has no conflict of interest.

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