



DESIGN AND IN VITRO/IN VIVO EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF NATEGLINIDE

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ABSTRACT:

Aim: Nateglinide is a quick acting anti-diabetic medication whose potent activity lasts for a short duration. One of the dangerous side effects of nateglinide administration is rapid hypoglycemia, a condition that needs to be monitored carefully to prevent unnecessary fatalities. The aim of the study was to develop a longer lasting and slower releasing formulation of nateglinide that could be administered just once daily.

Methods: Matrix tablets of nateglinide were prepared in combination with the polymers hydroxypropylmethylcellulose (HPMC), eudragits, ethyl cellulose and polyethylene oxide and the formulated drug release patterns were evaluated using in vitro and in vivo studies.

Conclusion: Of the seventeen formulated matrix tablets tested, only one formulation labelled HA-2 that contained 15% HPMC K4M demonstrated release profile we had aimed for. Further, swelling studies and scanning electron microscopic analysis confirmed the drug release mechanism of HA-2. The optimized formulation HA-2 was found to be stable at accelerated storage conditions for 3 months with respect to drug content and physical appearance. Mathematical analysis of the release kinetics of HA-2 indicated a coupling of diffusion and erosion mechanisms. In-vitro release studies and pharmacokinetic in vivo studies of HA-2 in rabbits confirmed the sustained drug release profile we had aimed for.

Keywords: Hydroxypropylmethylcellulose, Matrix tablets, Nateglinide, Sustained release

1. INTRODUCTION

Nateglinide, a D-phenylalanine derivative is an anti-diabetic drug that is quick but short acting and controls postprandial blood glucose (PBG) effectively. Nateglinide belongs to the meglitinide class of anti-diabetic drugs used to treat type 2 diabetes by stimulation of

pancreatic beta cells that results in the release of proinsulin. Nateglinide immediate-release tablets are administered twice or thrice a day.^{1,2} A sustained release formulation of nateglinide would enable control of both PBG and FBG (fasting blood glucose) with the novel advantage of improving patient compliance by decreasing multiple drug administration and

minimizing side effects such as hypoglycemia and hepatic impairment.^{3,4} The usual dose of nateglinide administered is three times a day. By using a higher 24-hr dose of nateglinide in a single matrix tablet, the drug is released at a slower rate thus preventing extremely high and low concentrations of nateglinide in plasma. This helps to avoid the side effects of hypoglycemia and hepatic impairment associated with high concentration and the lack of drug activity when its concentration in plasma is low. A slower release formulation would therefore enhance the therapeutic effects of nateglinide. Oral drug delivery system is the most accepted route for drug delivery, its benefits being easy administration and flexibility in dosage form design.⁵ There are several approaches for retarding drug release from dosage form.⁶ Matrix tablets composed of drug and release retarding polymers offer the simplest approach in designing a sustained release system.⁷ The goals of the present study were to develop a once-daily sustained-release dosage form of nateglinide in tablet form using different polymers in varying proportions and to determine which combination best fit the desired release profile. The prepared tablets were evaluated with respect to physicochemical parameters including in-vitro drug release, stability, surface morphology and in vivo pharmacokinetics in rabbits.

2. EXPERIMENTAL MATERIALS

Nateglinide, hydroxypropylmethylcellulose (K4M, K15M and K100M) and polyethylene oxide N80F were obtained from Lupin Laboratories Ltd, Pune, India. Eudragit RS 100 and Eudragit RL 100 were obtained from Vikram Thermolab Ahmedabad, India. Magnesium stearate, talc, lactose, hydrochloric acid and methanol, were purchased from S.D. Fine-Chem Limited, Merck, Loba Chemie Mumbai, India respectively. All other chemicals used were of analytical grade.

3. EXPERIMENTAL METHODS

3.1. PREPARATION OF NATEGLINIDE TABLETS

Tablets were prepared by direct compression. The investigated formulations are shown in Table 1. The respective powders (drug, polymers and excipients) were passed through 60# sieve. The powders were blended thoroughly using a mortar and pestle after which 500 mg of each mixture were weighed and manually fed into the die of a single punch tableting machine (Rimix tableting machine, Gujarat, India) equipped with 10.5 mm flat punches.

3.1.1. Conventional tablets for rabbits

Doses for rabbits were calculated using following formula of Gosh.^{8,9} According to the dose calculated for rabbits (48.30 mg), the same formula was proportionately reduced and compressed into tablets using 2.5 mm flat punch.

Rabbit dose = $0.07 \times$ human dose

Where, human dose = 345 mg, rabbit weight = 2 kg and rabbit dose = 48.300 mg. The rabbit dose was found to be 1.5 times the observed value.

3.2. Evaluation of prepared tablets

3.2.1. Thickness and diameter

The prepared matrix tablets were evaluated for thickness, hardness, friability and drug content. Thicknesses of randomly selected tablets were determined using screw gauge. Hardness of the tablets was determined using Monsanto Hardness tester. Friability of tablets was determined using Roche Friabilator according to the official method IP.¹⁰ The values are expressed as the mean of three measurements (\pm SD).

3.2.2. Drug content

For determination of drug content, tablets were crushed and 100 mg of powder was dissolved in 100 ml of methanol. The filtrate further diluted with phosphate buffer (pH 6.8)

was analyzed spectrophotometrically (UVe1601PC, Shimadzu, Japan) at 210 nm. Drug content was calculated using a standard curve generated using various concentrations of nateglinide in phosphate buffer (pH 6.8).

3.2.3. In vitro dissolution study

An *in-vitro* dissolution study of formulated matrix tablets was carried out in 900 ml 0.5% sodium lauryl sulphate (SLS) in 0.01 N HCl, followed by 900 ml of Phosphate buffer (pH 6.8) with type II paddle dissolution apparatus (Electrolab, TDL-08L, Mumbai, India) run at 50 rpm. The temperature of the medium was maintained at $37 \pm 0.5^\circ\text{C}$. Samples (5 ml) were withdrawn at predetermined intervals and read at 210 nm using a spectrophotometer.

3.2.4. Determination of swelling: eroding behavior

The swelling-eroding behavior of matrix tablets was determined using the method described by Al-Taani and Tashoush.¹¹ One matrix tablet was weighed and placed in a dissolution apparatus.

The swollen weights of tablets were calculated after placing the mixture in a vacuum oven at 40°C for 48 h. The following formula was used for calculating % swelling

$$\% \text{ Swelling} = S/R \times 100$$

Where, S is the weight of the matrix after swelling and R is the weight of the eroded matrix.

$\% \text{ Erosion} = T - R/T \times 100\%$ where, R is the weight of the eroded matrix and T is the initial weight of the matrix.

3.2.5. Scanning electron microscopy

A SEM study of the optimized formulation was carried out confirming drug release mechanism. SEM photograph of the matrix tablets were taken at 0 h, 2 h, 12 h and 24 h of dissolution.

3.2.6. Stability

The tablets were kept under accelerated storage conditions $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity according to ICH guidelines using a stability chamber (Thermolab, Mumbai) for a period of three months. The samples were withdrawn at predetermined time intervals and evaluated for drug content and physical parameters.

3.2.7. In vivo pharmacokinetic study

An *in vivo* pharmacokinetic study was conducted in accordance with the ethical guidelines for investigations in laboratory animals and approved by the Institutional Animal Ethics Committee (IAEC), Sri Satya Sai University of Technology and Medical Sciences, Sehore/IAEC/COP/21/2018. All procedures and care of the rabbits were in accordance with institutional guidelines for animal use in research. Twelve Rabbits (New Zealand, White) weighing 2.30 ± 0.12 kg (divided into two groups) were fasted overnight. Tablets were administered orally via gastric intubation. The first group received conventional tablet while the second group received optimized extended release tablet of nateglinide. Rabbits were held in rabbit restrainers during blood sampling. Blood samples were collected from ear veins at predetermined intervals of 0.5, 1, 2, 4, 8, 12 and 24 h post dose into heparinized tubes.¹² Plasma samples were obtained following centrifugation of blood at $3500 \times g$ for 5 min at 4°C and kept frozen at -70°C until analysis.

3.2.8. Analysis of plasma nateglinide concentration using HPLC¹³

A sensitive HPLC (HPLC-LC-2010C HT, Shimadzu, Japan) method was used for the estimation of nateglinide in plasma. The mobile phase consisted of acetonitrile and phosphate buffer (pH 3) 50:50 v/v. The column was C18 (250 cm \times 4.6 mm) Hypersil BDS, The mobile phase was delivered at a flow rate of 1.0 ml/min, the detection wavelength was 210

nm. All assays were performed at ambient temperature.

3.2.9. Preparation of sample solutions

Rabbit plasma (100 ml) were pipetted into centrifugal tubes, 10 ml of IS (gliclazide) 500 mgmL⁻¹ was added and vortexed for 10 s. Then 100 µl methanol and acetonitrile 100 µl were added and vortexed for 30 s and centrifuged at 10000 rpm for 10 min at 4 °C. The supernatant layer (200 ml) was separated out, 100 ml of mobile phase was added to make up the volume to 300 ml and then 50 ml was injected into HPLC system. Pharmacokinetic analysis was performed by means of noncompartmental pharmacokinetic data analysis software PK Solutions 2.0 TM.

4. RESULTS

4.1. Evaluation of prepared tablets

The tablets exhibited uniform thickness and hardness. The friability and drug content were also within the acceptable limits.

4.2. *In vitro* release profile

Release parameters of the tablet formulations are summarized in Fig. 1. Nateglinide release from the prepared tablets was slow, spanning a period of 24 h and rested on the grade of the controlled release polymer. The results of dissolution studies indicated that HA-1, ES-1, EL-1, EC-1 and PO-1 released 7.31, 2.27, 0.50, 0.99 and 3.93% of nateglinide at the end of 0.5 h; at 24 h, 91.14, 78.22, 77.45, 60.40 and 78.43% of nateglinide was released. Since formulation EC-1 containing ethyl cellulose showed incomplete release in the 24 h, further studies were discontinued. A study was undertaken to determine the release profile of nateglinide matrix tablets with different viscosity grades of HPMC and thereby select a suitable polymer. HPMC K15M and HPMC K100M were selected for formulation and their release profile compared with HPMC K4M matrix tablets. Results indicate that the tablet formulations HA-1(HPMC K4M), HB-1(HPMC K15M) and HC-1(HPMC K100M) released 7.31,

3.39 and 1.02% at the end of 0.5 h and 91.14%, 85.28% and 64.75% of nateglinide at the end of 24 h. The release profile of HC-1 was retarded when compared to the formulations HA-1 and HB-1. Hence HA-1 and HB-2 were selected for the further studies. In formulations HA-1, HA-2 and HA-3 containing 20%, 15% and

10% HPMC K4M respectively, the percentage release was 7.31, 9.35 and 10.72% respectively at the end of 0.5 h and 91.14, 96.62 and 97.92% at the end of 24 h. In the cases of formulations HB-1, HB-2 and HB-3 containing 20%, 15% and 10% HPMC K15M respectively, the percentage releases were 3.93, 5.00 and 7.14% respectively at the end of 0.5 h and 85.28, 94.44 and 96.12% at the end of 24 h. Release studies illustrate incomplete drug release with formulation HA-1 and with formulation HA-3 it was observed that tablet integrity was lost resulting in complete release within 12 h. Since release of nateglinide with 15% of HPMC K15M and 10% of HPMC K15M were lower compared with same concentrations of HPMC K4M, formulation HA-2 was selected for further studies. For formulations ES-1, ES-2 and ES-3 containing 20%, 15% and 10% Eudragit RS-100, the percentage releases were 2.27, 4.24 and 4.99% respectively at the end of 0.5 h and 78.22, 90.39 and 97.06% at the end of 24 h (Table 2). For formulations EL-1, EL-2 and EL-3 which contain 20%, 15% and 10% Eudragit RL 100, the percentage releases were 0.50, 2.53 and 2.77 respectively at the end of 0.5 h and 77.45, 92.53 and 94.34% at the end of 24 h (Table 2). These results indicate that lower percentage of Eudragit exhibit satisfactory release over a period of 24 h. Eudragits were not considered for further studies since inadequate amount of nateglinide was released at 0.5 h. Matrix tablets with the polymer polyethylene oxide, PO-1, PO-2 and PO-3, exhibited better release with reduction in polymer concentration. Percentage release found with 20%, 15% and 10% polyoxyethylene were 78.43%, 82.39%,

and 90.30% respectively; also, 10% polymer showed an initial release of 7.56% in 0.5 h (Table 2) .The results indicate that 10% polyoxyethylene has potential for extended release formulation and further trials are needed to assess this potential. Formulation HA-2 (15% HPMC K4M) was selected for further studies. Figs. 2 and 3 represent the percentage swelling and percentage matrix erosion respectively as a function of time. The matrix tablets underwent both swelling and erosion at the same time after placement in the dissolution media. SEM study of the optimized formulation taken at 0 h, 2 h,12 h and 24 h of dissolution are shown

in Fig. 4.

4.3. In vivo pharmacokinetic study

The retention time of nateglinide and gliclazide was 11.5 and 7.55 min respectively (Fig. 5). The

plasma concentrations of conventional nateglinide and extended release formulation over time

are presented in Figs. 6 and 7 respectively. The pharmacokinetic parameters of conventional nateglinide and extended release formulation are presented in Table 3.

4.4. Stability studies

Accelerated stability studies conducted for the optimized batch of nateglinide extended release matrix tablets (HA-2) showed no change in drug appearance and assay after storage at 40 °C for 3 months. The drug content was 97% at the end of 90 days and appearance was unchanged indicating that the optimized formulation is fairly stable at accelerated storage condition.

Table 1: Formulation of different batches of matrix tablets.

| Ingredients (mg/tablet) | Batch Code | | | | | | | | | | | | | | | | | |
|---------------------------|------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|-----|
| | HA-1 | HA-2 | HA-3 | HB-1 | HB-2 | HB-3 | HC-1 | EC-1 | ES-1 | ES-2 | ES-3 | EL-1 | EL-2 | EL-3 | PO-1 | PO-2 | PO-3 | |
| Nateglinide | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 | 345 |
| Lactose | 45 | 70 | 95 | 45 | 70 | 95 | 45 | 45 | 45 | 70 | 95 | 45 | 70 | 95 | 45 | 70 | 95 | 95 |
| HPMC K4M | 100 | 75 | 50 | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** |
| HPMC K15M | ** | ** | ** | 100 | 75 | 50 | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** |
| HPMC K100M | ** | ** | ** | ** | ** | ** | 100 | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** |
| Ethyl Cellulose | ** | ** | ** | ** | ** | ** | ** | 100 | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** |
| Eudragit RS-100 | ** | ** | ** | ** | ** | ** | ** | ** | 100 | 75 | 50 | ** | ** | ** | ** | ** | ** | ** |
| Eudragit RL-100 | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | 100 | 75 | 50 | ** | ** | ** | ** |
| Polyethylene oxide N 80 F | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | ** | 100 | 75 | 50 | 50 |
| Mag. Stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total Tab. Wt. | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

** Indicates that ingredient is not included.

Table 2: release data of formulations.

| Formulation | % Release at 0.5 h | % Release at 24 h |
|-------------|--------------------|-------------------|
| HA-1 | 7.31 ± 1.23 | 91.14 ± 1.98 |
| HB-1 | 3.39 ± 1.67 | 85.28 ± 2.56 |
| HC-1 | 1.02 ± 3.12 | 64.75 ± 3.67 |
| HA-2 | 9.35 ± 5.23 | 96.62 ± 4.10 |
| HA-3 | 10.72 ± 0.89 | 97.92 ± 2.78 |
| HB-2 | 5.00 ± 4.12 | 94.44 ± 2.67 |
| HB-3 | 7.14 ± 3.90 | 96.12 ± 1.78 |
| ES-1 | 2.27 ± 1.56 | 78.22 ± 2.13 |
| ES-2 | 4.24 ± 2.67 | 90.39 ± 2.94 |
| ES-3 | 4.99 ± 4.24 | 97.06 ± 3.45 |
| EL-1 | 0.50 ± 0.98 | 77.45 ± 1.45 |
| EL-2 | 2.53 ± 1.56 | 92.53 ± 2.15 |
| EL-3 | 2.77 ± 3.12 | 94.34 ± 4.67 |
| PO-1 | 3.93 ± 0.98 | 78.43 ± 3.44 |
| PO-2 | 6.32 ± 1.67 | 82.39 ± 3.14 |
| PO-3 | 7.56 ± 2.13 | 90.30 ± 3.23 |

All values are expressed as Mean ± SE, n = 3. HA-1 (HPMC K4M 20%), HA-2(HPMC K4M 15%), HA-3(HPMC K4M 10%). HB-1 (HPMC K15M 20%) HB-2(HPMC K15M 15%) HB-3 (HPMC K15M 10%). HC-1 (HPMC K100M 20%) ES-1-(Eudragit RS-100 20%), ES- 2-(Eudragit RS-100 15%), ES-3-(Eudragit RS-100 10%). EL-1-(Eudragit RL-100 20%), EL-2-(Eudragit RL-100 15%), EL-3-(Eudragit RL-100 10%). PO-1 (polyethylene oxide 20%), PO-2 (polyethylene oxide 15%), PO-3 (polyethylene oxide 10%).

Table 3: Pharmacokinetic parameters from the plasma concentration-time curve (results expressed are mean of six rabbits).

| Parameters | Conventional tablet | HA-2 |
|-------------------------------------------------|---------------------|-----------------|
| C _{max} (ng/ml) | 505.20 ± 20.67 | 403.75 ± 28.77 |
| T _{max} (h) | 1.5 ± 0.0 | 4.0 ± 0.0 |
| AUC _{0-t} (ng h/ml) | 3039.1 ± 215.98 | 4895.2 ± 314.66 |
| MRT (h) | 3.5 ± 2.67 | 14.3 ± 3.59 |
| Elimination rate Constant Ke (h ⁻¹) | 0.3649 ± 0.09 | 0.08821 ± 0.01 |

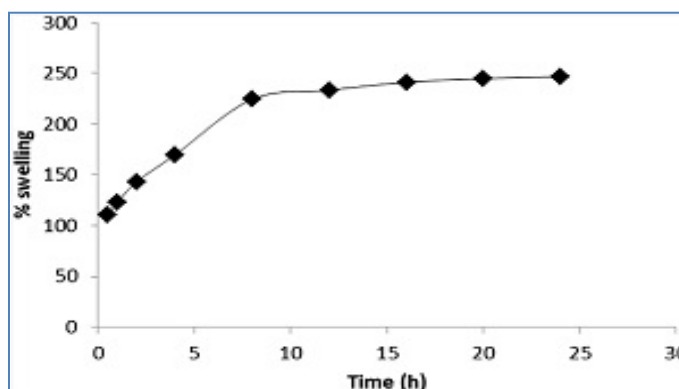


Figure 1: Release profile of formulations containing different polymers.

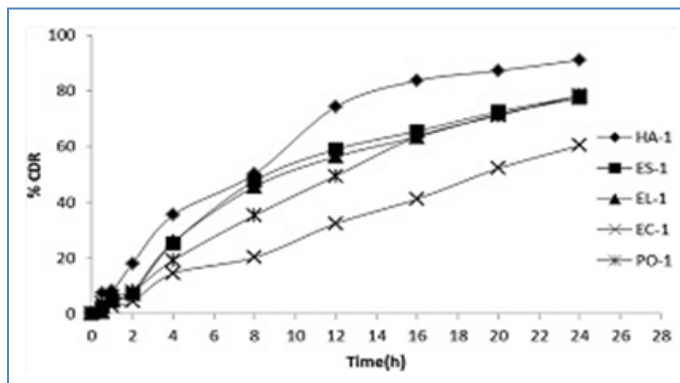


Figure 2: Percentage swelling of optimized formulation HA-2.

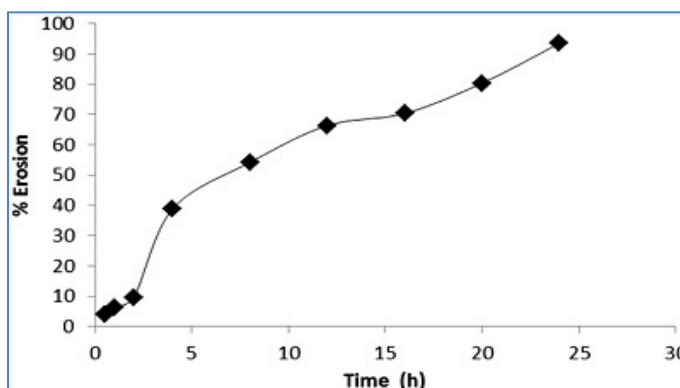


Figure 3: Percentage erosion of optimized formulation HA-2.

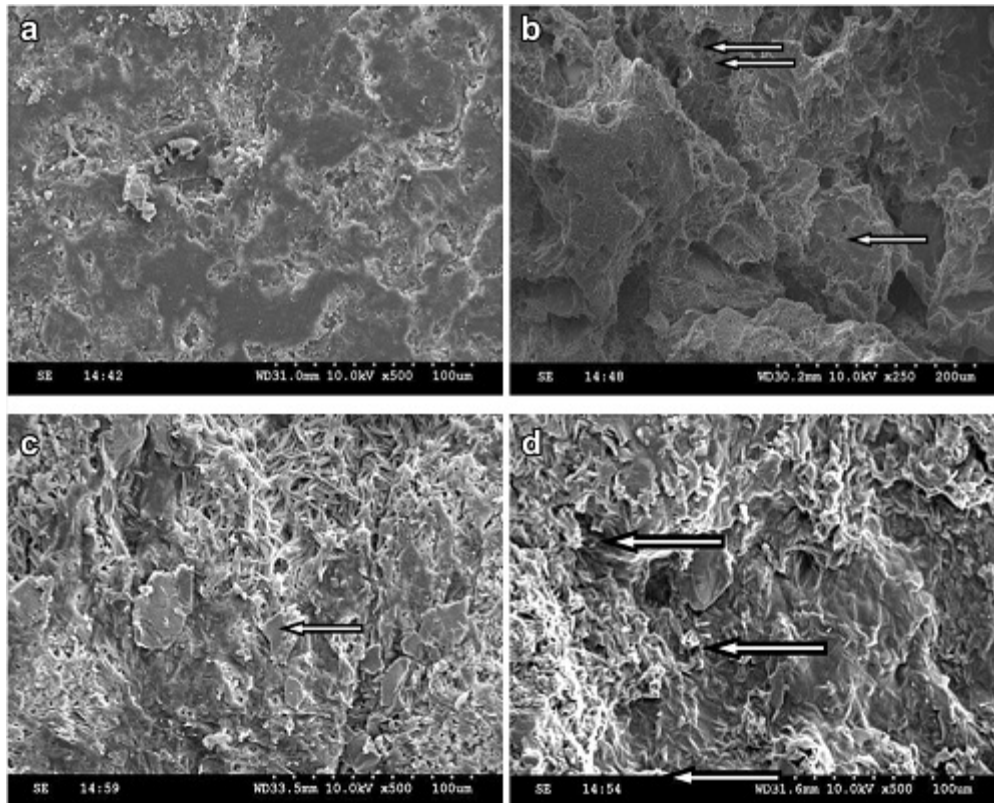


Figure 4: A & B sem images of optimized formulation matrix tablet HA-2 AT 0 & 2 H respectively. C & D sem images of optimized formulation matrix tablet HA-2 AT 12 & 24 H respectively.

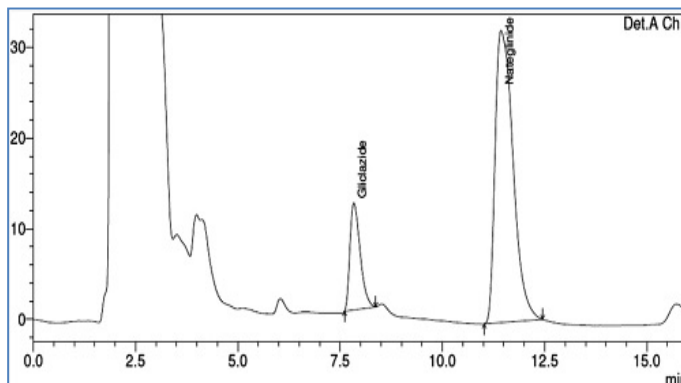


Figure 5: retention time of nateglinide and internal standard gliclazide.

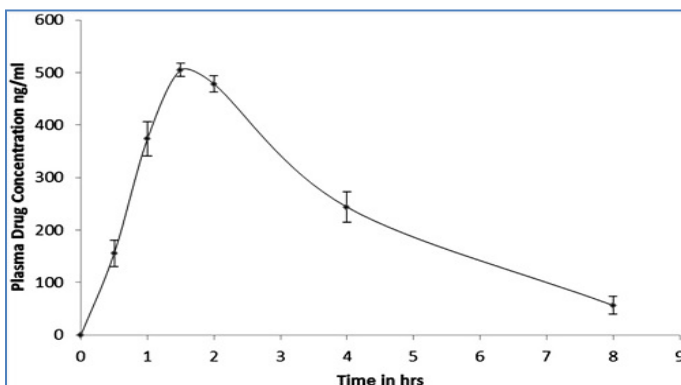


Figure 6: Plasma concentration time curve for conventional tablet.

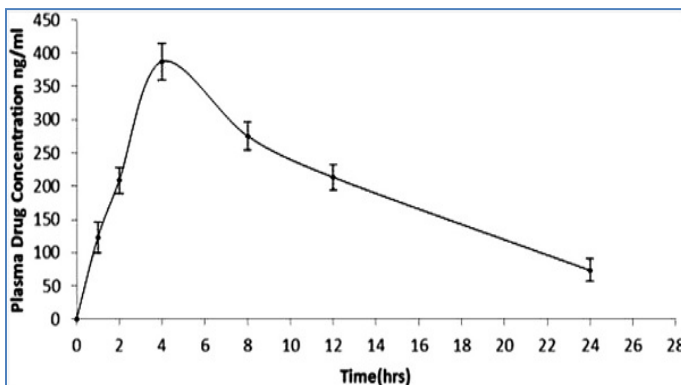


Figure 7: Plasma concentration time curve for extended release tablet.

5. DISCUSSION

The results of dissolution studies indicate that release was influenced by the grade of control release polymer. Polymers ethyl cellulose, HPMC K100M, eudragits and polyethylene oxide had a retarding effect compared to polymers HPMC K4M and HPMC K15M when used in same concentration. Hence further trials were not undertaken with these

polymers. When polymer concentration is high drug release rates are too low. Once there is sufficient polymer concentration in the matrix system a uniform barrier is formed. This barrier protects the drug from releasing immediately into the dissolution medium. Only formulation HA-2 followed the desired release profile up to 24 h. The matrix tablets underwent both swelling and erosion at the same time after placement in the dissolution

media. It has been reported that constant release can be obtained in such type of matrices.¹⁴ Constant release in such situations occurs because the increase in diffusion path length due to swelling is compensated for by continuous erosion of the matrix.¹⁵ SEM further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized formulation (HA-2). Initially, tablet matrix showed swelling with pore formation that is clearly visible from SEM image. At the end of 12 h, the matrix was intact and pores had formed through it. SEM images also show the formation of gel structure indicating swelling and pore formation on the tablet surface. In case of Peppas model¹⁶; n values close to 0.64 indicate diffusion as the mode of release. In case of Higuchi R², the value was close to unity indicating a linear response and clearly supporting the Peppas model. HA-2 showed R² value close to unity when zero order models was applied which indicates good linearity and hence following zero order release. Korsmeyer's plot showed good linearity with regression value of 0.9914 and slope 0.6562 indicating that diffusion is the dominant mechanism of drug release coupled with erosion.¹⁷ In case of conventional tablet, nateglinide was detectable in blood within 30 min after its oral administration in rabbits. The absorption was rapid with conventional tablets as indicated by low t_{max} value (1.5 h) in comparison with HA-2 formulation which exhibited delayed absorption as demonstrated by high t_{max} (4 h) values. C_{max} value of conventional tablet was high compared with HA-2 (Table 3). In comparison, HA-2 formulation exhibited low elimination rate constant and high values of mean residential time (MRT).

The low area under the curve (AUC) was observed with conventional tablets whereas the extended release formulation showed high AUC values indicating increased bioavailability of the drug in the matrix tablet. The results of

the in vivo bioavailability test indicate that drug release from matrix tablet is controlled thereby providing prolonged drug delivery.

6. CONCLUSION

Extended release matrix tablets of nateglinide were prepared by direct compression. Various polymers in varying concentrations were developed and evaluated. The formulation containing 15% HPMC K15M (HA-2) followed the desired release profile and was therefore selected for further studies. SEM studies revealed initial swelling and intact structure of the formulated tablets. Erosion and diffusion mechanisms were responsible for the sustained release of nateglinide from formulated matrix tablet. In vivo pharmacokinetic studies in rabbits confirmed the prolonged release by showing increase in bioavailability for matrix tablet compared to conventional tablet. The formulation (HA-2) was found stable under accelerated conditions for 3 months with respect to physical characteristics and drug content. However clinical studies and extensive stability studies at different conditions are required to confirm these results.

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