**In vitro** Evaluation of Nateglinide-Loaded Microspheres Formulated with Biodegradable Polymers

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**Abstract**

**Purpose:** To formulate and evaluate sustained release microspheres of nateglinide (NTG) for enhanced patient compliance.

**Methods:** Nateglinide microspheres were prepared with varying proportions of biodegradable polymers (olibanum gum and guar gum) by calcium chloride/sodium alginate ionic gelation method. The microspheres were characterized by micromeritic analysis, particle size analysis, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and in vitro drug release studies. Yield and encapsulation efficiency were also evaluated while drug release data were subjected to various kinetic models.

**Results:** Micrometric analysis showed good flow properties of the microspheres while yield and microsphere size were in the range of 70 to 80 % and 781 to 842 µm, respectively. FTIR and DSC results indicate the absence of drug-polymer interactions while SEM revealed that microspheres were almost spherical shape and porous in nature. Drug release was sustained in simulated intestinal fluid (pH 7.2), extending up to 10 to 12 h with greater release retardation in microspheres containing olibanum gum. The release pattern followed Higuchi kinetics model with non-Fickian diffusion.

**Conclusion:** Suitable microspheres for sustained release of nateglinide can be formulated by ionic gelation method.

**Keywords:** Nateglinide, Microspheres, Micromeritics, Drug release, Ionic gelation, Olibanum gum, Guar gum

INTRODUCTION

Oral route is the most convenient, predominant, acceptable and preferable route for solid drug administration. Oral drug delivery systems (DDS) are commonly divided into immediate release and modified release systems. Modified DDS are designed for control or target release of the drug, to achieve a desired pharmacokinetic profile, to enhance patient compliance and to minimize adverse drug reactions. Microencapsulation is the application of a thin coating to individual core materials of active substance that have an arbitrary particle size range from 1 - 1000 µm \(^1\). Microencapsulation can be used to convert the liquids to solids, alter the colloidal and surface properties, provide environmental protection and control drug release characteristics by using the coating materials.
A large number of natural as well as synthetic polymers, gums and waxes are available or used in the formation of matrix for holding drug in microspheres. These may include xanthine gum, guar gum, gum arabic, gum karaya, olibanum gum, methyl cellulose, etc depending upon the nature of the drug as well as technique employed for preparing microspheres [2]. Microspheres are used as carriers with dispersed drug particles to allow for sustained action and also minimize the adverse effects. The most significant feature of microspheres is their microscopic size that allows for a huge surface area. This large surface area is available for sites of adsorption and desorption, chemical reactions, light scattering, etc [3,4].

Nateglinide belongs to meglitinides, a class of oral anti-diabetic drugs, for controlling blood glucose level. It acts by binding to the sulfonyl urea receptors for its action with a short half life of 1.5 to 2 hrs. It is administered before meal so in order to prolong its effect, controlled release microspheres of nateglinide are formulated for better control and improve patient compliance [7].

The objective of the present work was to determine the effect of nature and concentration of biodegradable polymers i.e. olibanum and guar gums as well as sodium alginate on release retardation of nateglinide from microspheres. Sodium alginate also acts as gelating agent.

**EXPERIMENTAL**

**Material**

Nateglinide was purchased from Sigma Chemicals Company, USA. Sodium alginate, olibanum gum, guar gum and chloroform were purchased from Riedel-deHaen, China. Sodium hydroxide, monobasic potassium phosphate, hydrochloric acid and calcium chloride (CaCl\(_2\)) were purchased from Merck, Germany. All chemicals and reagents used were of analytical grade, and were used as received.

**Preparation of microspheres**

Five formulations of nateglinide loaded microspheres were prepared by blending drug, sodium alginate and olibanum gum with concentration 1:1:0.5 and 1:1:1 and named as NTG2 and NTG3 while the remaining two formulations were made by the use of drug, sodium alginate and guar gum at ratios 1:1:0.5 and 1:1:1 and were named as NTG4 and NTG5, respectively. Sodium alginate (1.0 gm) and polymer were dissolved in 100 mL of distilled water in a reagent bottle by using magnetic stirrer. Nateglinide (1.0 g) was dissolved in 100 mL of chloroform in a well-closed volumetric flask. Solution of drug was added to 100 mL sodium alginate solution in reagent bottle and was closed with lid. Solutions were mixed with a magnetic stirrer at a speed of 1000 rpm for 1 h in order to form a homogenous blend.

Then this solution was dropped manually from a hypodermic syringe (22G) into 10 % w/v aqueous solution of CaCl\(_2\) in distilled water, resulting in production of microspheres. They were allowed to harden in gelling bath for 30 min and were filtered with Whatman filter paper no. 4. The microspheres were washed with distilled water, allowed to dry in air at room temperature for 30 min and then transferred to Petri dishes for drying in hot air oven at 37 °C until a constant weight was obtained [8].

**Determination of yield**

The dried microspheres were weighed and their percentage yield (WW) was determined using Eq 1 [9].

\[
\text{Yield (\%)} = \frac{W}{D+P} \times 100 \quad (1)
\]

where W is the weight of the dried microspheres recovered, D is the weight of drug and P is the weight of polymer used in forming the microspheres.

**Particle size analysis**

The prepared formulations of microspheres were subjected to particle size analysis by most widely used Sieving method [10]. Microspheres were placed on a set of sieves ranging from sieve No. 10# to 40# which were shaken mechanically using an electromagnetic sieve shaker (Electro Lab, EMS-8). After completion of shaking, the amount retained on each sieve was weighed and expressed as percentages. Average size of microspheres was determined using Eq 2.

\[
\text{Average particle size} = \frac{\sum RP}{100} \quad (2)
\]
where $R$ is the percent retained microspheres on each sieve and $P$ is the mean aperture size of the sieve.

**Evaluation of micromeritic properties of microspheres**

**Angle of repose**

A weighed quantity of microspheres was passed through a funnel fixed on a stand at a specific height upon a graph paper [11]. A static heap of powder with only gravity acting upon it was tending to form a conical mound. The height of the heap ($h$) and radius ($r$) of lower part of cone were measured and calculated as in Eq 4.

$$\theta = \tan^{-1}\frac{h}{r} \quad \cdots \quad (4)$$

where $\theta$ = angle of repose, $h$ = height of cone and $r$ = radius of cone base.

**Carr’s index**

The Carr’s index was evaluated for the flow ability of the powder by comparing the pour density and tapped density of microspheres [11] and was calculated using Eq 5.

$$\text{Carr’s index} = \frac{(\rho_t - \rho_b) \times 100}{\rho_t} \quad \cdots \quad (5)$$

where $\rho_b$ is bulk density and $\rho_t$ is tapped density which was measured in a 10ml graduated cylinder and the number of tapings was 100 as it was sufficient to bring about a plateau condition. Carr’s index less than 15 % gives good flow characteristics and above 25 % indicates poor flow characteristics.

**Hausner’s ratio**

Hausner’s ratio ($H$), another index of flow ability, was calculated using Eq 6.

$$H = \frac{\rho_t}{\rho_b} \quad \cdots \quad (6)$$

A value < 1.2 is preferred for free flow; however, a value close to 1 indicates good flow properties.

**Shape and surface morphology**

The external morphology of microspheres was analyzed by a scanning electron microscope (Hitachi S3400N, Japan). Samples were prepared by lightly sprinkling microspheres on a double adhesive tape which was stuck to an aluminium stub. The stubs were then coated with gold to a thickness of 150–200 Å using a fine coat ion sputter. The microspheres were examined under scanning electron microscope and pictures were taken.

**Fourier transform infrared spectroscopy (FTIR)**

Drug–polymer interactions were studied by FTIR spectroscopy (JIR-Prestige-21, Shimadzu, Japan). The spectra were recorded for pure drug, polymers (Olibanum gum and Guar gum) and drug-loaded microspheres. The pellets were prepared in KBr press (2 mg sample in 200 mg KBr) under a hydraulic pressure of 150 kg/cm². The scanning range was 4,000 – 400 cm⁻¹ and the resolution was 2 cm⁻¹ [12].

**Differential scanning calorimetry (DSC)**

DSC analysis of pure Nateglinide, polymers and drug-loaded microspheres were carried out using Mettler Toledo DSC-823e to determine if there were any drug-polymer interactions. Nateglinide, polymers and drug-loaded microspheres were triturated separately to get a finely divided powder and DSC thermograms were obtained at a heating rate of 50 °C/min from 0 to 300 °C temperature range under a nitrogen flow of 40 ml/min. Reproducibility was checked by running the sample in triplicate [12].

**Determination of encapsulation efficiency**

Dried microspheres (100 mg) were crushed in a mortar, placed in 100 mL of phosphate buffer (pH 7.2) and vortexed for 5 min in an ultrasonic bath for complete removal of nateglinide from microspheres then samples was filtered through 0.45 um filter paper. After filtration, the absorbance of nateglinide at 210 nm was measured using a UV–VIS spectrophotometer (IRMECO U2020). The measured absorbance was then converted to the amount of nateglinide using a standard calibration curve. Encapsulation efficiency (EE) was calculated using Eq 7.

$$\text{EE} = \frac{(D_a/D_t) \times 100}{\text{100}} \quad \cdots \quad (7)$$

where $D_a$ is the actual amount of drug the microspheres while $D_t$ is the theoretical drug content.

**In vitro drug release studies**

In vitro release of nateglinide from microspheres was carried out by enclosing the microspheres in hard gelatin capsule in a quantity equivalent to 120 mg dose of drug. USP dissolution paddle apparatus (Pharmatest) was used in order to study the release behavior of microspheres. The dissolution study was carried out for 2 h in 900
ml of 0.1 N HCl. The microspheres were transferred to 900 ml of pH 7.2 buffer medium at 37 ± 0.5 °C and release studies continued for 10 h. An aliquot of 5 ml of the dissolution medium was withdrawn at definite time intervals and an equal volume of fresh dissolution medium, which was pre-warmed at 37 °C was replaced. The collected samples were suitably diluted and analyzed by UV–VIS spectrophotometer for nateglinide contents at 210 nm. The concentration of nateglinide in test samples was calculated using calibration curve. Three samples were run for each formulation in solutions of pH 1.2 and 7.2.

Drug release kinetic analysis

Data obtained from in vitro release studies were fitted to various release kinetic models i.e., Zero order, First order, Higuchi square root model, Hixson Crowell model and Korsmeyer-Peppas model to find out the mechanism of drug release from the microspheres [13].

Statistical analysis

The quantitative data were expressed as mean ± standard deviation (SD). The regression coefficients (R²) were calculated by linear regression analysis using Microsoft Excel 2003 software [14].

Table 1: Physical and micromeritic properties of microspheres

| Formulation | Mean particle size (μm) | Yield (%) | Entrapment (%) | Angle of repose | Carr’s index | Hausner’s ratio |
|-------------|-------------------------|-----------|----------------|----------------|-------------|----------------|
| NTG1        | 781.75±2.08             | 72.23±0.74| 52.57± 0.17   | 29.54±1.21     | 7.80± 1.64  | 1.08           |
| NTG2        | 811.43±1.73             | 77.16± 0.16| 69.81± 0.09   | 28.25±0.88     | 5.78± 0.34  | 1.06           |
| NTG3        | 823.19±1.52             | 78.64± 0.51| 73.96± 0.15   | 27.55±0.57     | 8.06± 1.16  | 1.08           |
| NTG4        | 835.68±1.53             | 75.47± 0.44| 57.57± 0.10   | 28.75±1.07     | 9.03± 1.53  | 1.09           |
| NTG5        | 842.36±1.15             | 77.52± 0.88| 63.42± 0.21   | 29.20±0.30     | 8.20± 2.13  | 1.07           |

RESULTS

Particle size, yield and entrapment efficiency data are presented in Table 1. Free flowing white colored nateglinide microspheres were successfully prepared by ionic gelation technique. The particle size of microspheres was in the range of 781 ± 2.08 to 842 ± 1.15 μm, while yield varied from 72 to 78 % for the formulations. Entrapment efficiency of the microspheres was in the range of 52 - 73 %, with entrapment highest (73 %) for NTG3. Hausner’s ratio for all microspheres formulations was < 1.25 and angle of repose ranged from 27.55 to 29.27 (Table 1).

A typical morphological appearance of microspheres by scanning electron microscope is shown in Fig 1. The microspheres prepared with NTG1 formulations produced almost spherical microspheres with the presence of cracks on the surface as shown in Fig 1(A). The microspheres obtained from blend of olibanum gum along with sodium alginate (NTG3) produced smooth and spherical microspheres as shown in Fig 1 (B) while Guar gum plus sodium alginate (NTG5) were smooth but lack spherical shape as shown in Fig 1 (C).

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Fig 1: SEM photographs of nateglinide loaded microspheres. Note: A = NTG1, B = NTG3, C = NTG5
The FTIR spectra of nateglinide showed principal peaks at the wave number range of 1280 - 1431 cm\(^{-1}\), indicating the presence of carboxyl, carboxylate and carbonyl at 1651 cm\(^{-1}\), C-H stretching between 2866 - 3047 cm\(^{-1}\), C=O vibration at 1714 cm\(^{-1}\) and N-H stretching appeared at 3298 cm\(^{-1}\) as shown in Figure 2. C=O stretching, C-O stretching and C-O-H stretching in acidic group were prominent at 1643, 1296, and 1446 cm\(^{-1}\), respectively, indicating the presence of carboxylic group. A more intense peak was found between 3296 and 3311 cm\(^{-1}\) because of N-H stretching indicating the presence of amino group in the structure. The peak at 1384 cm\(^{-1}\) wave number indicates the presence of C-N stretching, as shown in Fig 2.

![FTIR Spectra](image1)

![DSC Thermograms](image2)

**Fig 2:** FTIR spectra and DSC thermograms; **Note:** A = nateglinide, B = sodium alginate, C = olibanum gum, D = guar gum, E = nateglinide + sodium alginate, F = nateglinide + sodium alginate + olibanum gum, G = nateglinide + sodium alginate + guar gum

The thermal curves of the pure components and of the drug-polymer microspheres are presented in Fig 2. A sharp exothermic peak was observed for nateglinide at a temperature of 142 °C. For sodium alginate, olibanum gum and guar gum, exothermic peaks were observed at > 300, 77 - 78 and 93 - 98 °C, respectively.

Dissolution studies revealed that microspheres made with sodium alginate (NTG1) produced the fastest release in 10 h than the other formulations. There was a decrease in drug release as we increased the ratio of olibanum gum or guar gum to sodium alginate. All the formulations showed a sustained release pattern of nateglinide release at pH 7.2 as shown in Fig 3. In order to study the drug release kinetics from the microspheres, five equations were applied on the release profiles of all nateglinide loaded microspheres and the results are presented in Table 2. In most of the formulated microspheres, R\(^2\) values were higher for Higuchi model, indicating that drug release was diffusion-controlled.

![Nateglinide release from formulations of microspheres](image3)

**Fig 3:** Nateglinide release from formulations of microspheres. **Key:** NTG1 (□), NTG2 (○), NTG3 (△), NTG4 (×) and NTG5 (■)

| Formulation | Zero order | First order | Higuchi | Korsmeyer-Peppas | Hixon-Crowell |
|-------------|------------|-------------|---------|------------------|--------------|
|             | \(R^2\)    | \(R^2\)    | \(R^2\) | \(R^2\) \(n^*\) | \(R^2\)      |
| NTG1        | 0.994      | 0.830       | 0.987   | 0.998            | 0.74         |
| NTG2        | 0.988      | 0.942       | 0.996   | 0.997            | 0.79         |
| NTG3        | 0.985      | 0.963       | 0.993   | 0.996            | 0.82         |
| NTG4        | 0.990      | 0.926       | 0.991   | 0.998            | 0.83         |
| NTG5        | 0.989      | 0.933       | 0.992   | 0.982            | 0.87         |

**Table 2:** Correlation coefficient \((R^2)\) data for microspheres derived from various kinetic models

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DISCUSSION

Particle size and yield of microspheres increased significantly with increasing polymer concentration. It was also observed that olibanum gum was more effective in encapsulating nateglinide than guar gum as described in Table 1; furthermore, entrapment efficiency increased with the amount of polymer used due to the availability of more polymeric binding sites for drug. Similar findings regarding encapsulation efficiency have also been reported previously for alginate microspheres [15].

Hausner's ratio for all the formulations, which was < 1.10, indicates good flow property of microspheres. The results were further confirmed by angle of repose and Carr’s index data which were < 30° and < 10 %, respectively. Aulton and Wells had also reported a similar behavior previously [16].

Scanning electron microscopy of drug loaded microspheres revealed that microspheres possess almost smooth surface and spherical shape while cracks were also present on the surface of microspheres of NTG1 which was further confirmed from the fast release of nateglinide from this formulation. Gowda and Shivakummar also described that presence of cracks on microspheres surface increased the release rate of encapsulated drug from polymers [17]. SEM photographs revealed the absence of crystals of drug on the surface of the microspheres made with Olibanum gum indicating uniform distribution of drug within these microspheres.

FTIR analyses of the drug, polymers and their physical mixtures showed that polymers used were also compatible with each other. The characteristic peaks of nateglinide were not altered after successful encapsulation which confirmed the absence of any chemical interactions between the drug and polymers. The principle peaks corresponding to nateglinide appeared with less intensity in the microsphere formulations. The decrease in peak intensity may be attributed to a fine dispersion of the drug in the polymers and increasing drug to polymer ratio [18].

The characteristic, well recognizable thermal profile of the drug at the temperature corresponding to its melting point was also observed in nateglinide loaded microspheres indicating absence of any possible drug-polymer interaction. It appeared that there was a significant reduction of drug crystallinity in the microspheres because thermal peak of drug loss its sharp appearance in microspheres [19].

Drug release from NTG1 was 97 % in 10 h due probably to the presence of cracks on the surface of microspheres but a decrease in the drug release occurred with increasing proportion of the gum in the mixture with sodium alginate due to more effective encapsulation of the drug. Drug release was greatly dependent on the type of polymer used. Greater retardation in drug release from microspheres was offered by olibanum gum than guar gum and this seems to correlate with the SEM photographs of the microspheres.

For most of the microspheres, higher R² values were using the Higuchi model, indicating the drug release from the microspheres was by a diffusion mechanism. The Korsmeyer–Peppas diffusion exponent (n) values was between 0.847 and 0.889, indicating non-Fickian diffusion, thus confirming the findings of Nazar et al [20].

CONCLUSION

Sustained-release microspheres of nateglinide have been prepared successfully by ionic gelation method, and this could prove helpful in developing formulations with improved patient compliance as a result of reduced dosing frequency. Olibanum gum was considered the better encapsulating material of the two gums evaluated. The drug release mechanism was both diffusion-controlled. Release retardation depended not only on the proportion of the encapsulating material used but also on the type of polymer.

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