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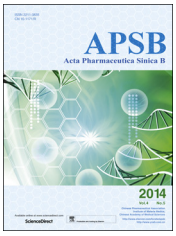

ORIGINAL ARTICLE

Development and *in vitro*/*in vivo* evaluation of controlled release provesicles of a nateglinide–maltodextrin complex

Ranjan Ku. Sahoo, Nikhil Biswas, Arijit Guha, Nityananda Sahoo, Ketousetuo Kuotsu*

Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, India

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Abstract The aim of this study was to characterize the provesicle formulation of nateglinide (NTG) to facilitate the development of a novel controlled release system of NTG with improved efficacy and oral bioavailability compared to the currently marketed NTG formulation (Glinate™ 60). NTG provesicles were prepared by a slurry method using the non-ionic surfactant, Span 60 (SP), and cholesterol (CH) as vesicle forming agents and maltodextrin as a coated carrier. Multilamellar niosomes with narrow size distribution were shown to be successfully prepared by means of dynamic laser scattering (DLS) and field emission scanning electron microscopy (FESEM). The absence of drug-excipient interactions was confirmed by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. *In vitro* release of NTG in different dissolution media was improved compared to pure drug. A goat intestinal permeation study revealed that the provesicular formulation (F4) with an SP:CH ratio of 5:5 gave higher cumulative amount of drug permeated at 48 h compared to Glinate™ 60 and control. A pharmacodynamic study in streptozotocin-induced diabetic rats confirmed that formulation F4 significantly ($P<0.05$) reduced blood glucose levels in comparison to Glinate 60. Overall the results show that controlled release NTG provesicles offer a useful and promising oral delivery system for the treatment of type II diabetes.

*Corresponding author. Tel.: +91 8981099151.
E-mail address: ketousetuoju@yahoo.in (Ketousetuo Kuotsu).

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1. Introduction

Since the 1980s, non-ionic surfactant vesicles (niosomes) have been shown to possess distinct advantages over conventional dosage forms and play an increasingly important role in drug delivery. Compared to phospholipids, nonionic surfactants form vesicles that are more stable, easier to handle and less expensive to produce[1]. In recent years, provesicular (proniosomal) derived niosomes have received considerable attention as an oral dosage form with the potential to improve therapeutic activity, reduce side effects and enhance stability of drugs to chemical degradation or transformation. This is because niosomes themselves have limitations for oral delivery due to poor integrity at the site of absorption, physicochemical instability to hydrolysis, separation of drug and their tendency to sediment and aggregate[1,2].

A proniosomal formulation is a dry formulation of a liquid crystalline niosomal hybrid which converts to niosomes upon hydration with aqueous media. It offers a versatile drug delivery system that is not only capable of encapsulating drug but can also minimize drug degradation after administration, prevent undesirable side effects and increase drug bioavailability[3–5]. In addition, it is convenient to transport, distribute and store and less subject to the high cost and variable purity problems of phospholipid based formualtions[6]. All this makes proniosomes (or 'dry niosomes') a promising, commercially valuable product[2].

Nateglinide [*N*-(*trans*-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, NTG] is a novel non-sulfonylurea oral hypoglycemic agent which has outstanding clinical effectiveness in the treatment of type II diabetes mellitus. Its mechanism of action involves increasing insulin release from pancreatic β-cells through inhibition of potassium-ATP channels. After oral administration, NTG is rapidly absorbed from the gastrointestinal tract and rapidly eliminated from plasma with a half-life of approximately 1.5 h. As a result, a dose of NTG of 20–40 mg must be administered thrice a day. In addition, NTG has low bioavailability and poor dose proportionality probably resulting from its limited absorption through the gastrointestinal tract consequent on its low water solubility (8 mg/L)[7] and/or wettability[8].

Maltodextrins (MLTs) are complex mixtures of high and low molecular weight carbohydrates obtained by acid and/or enzymatic hydrolysis of starch. They contain linear amylose and branched amylopectin degradation products and are considered as D-glucose polymers joined by α-(1,4) and α-(1,6) linkages. MLTs are endowed with the capability to form complexes with various classes of compounds usually of the host–guest type. Complex formation depends on the size of the complexing molecule and is believed to require a conformational change from a flexible coil to a helix form in the presence of the guest molecule[9]. Because NTG probably exhibits dissolution rate limited absorption, we anticipated that its dissolution rate would be improved through the preparation of an MLT complex. The aim of this study was therefore to examine a provesicular system based on the MLT complex of NTG.

MLT-based provesicular powders offer a simple and stable carrier for efficient oral delivery of lipophilic or amphiphilic drugs since they allow the production of provesicles with greater drug loading. Due to its high surface area and porous structure, MLT forms provesicles with high surfactant:carrier mass ratios[10]. MLT-based NTG provesicles prepared with the nonionic surfactant Span 60 (SP) have been previously reported[9,11]. SP with its longer saturated alkyl chains and high phase transition temperature shows higher entrapment efficiency (EE) in comparison with those of other nonionic surfactants[12–16]. Cholesterol (CH) is also commonly included not only to improve the stability and EE of a vesicular formulation but also to impart rigidity and orientational order to the niosomal bilayer[9,16–19].

Many formulation approaches have been investigated to improve the bioavailability of NTG including various solvent systems[20], solid dispersions[21], complexes with β-cyclodextrins[22–24], floating microspheres[25,26], polymeric nanoparticles and solid lipid nanoparticles[27,28]. To date, no study has evaluated an MLT-based provesicular drug delivery system of NTG for diabetic therapy. In this study, controlled release provesicles of NTG–MLT complex were prepared and evaluated with the aim of producing an NTG formulation that would provide decreased dosing frequency, fewer side effects and increased bioavailability.

2. Material and methods

2.1. Materials

NTG (purity 99.87%) was a gift from Alembic Pharmaceutical Ltd. (Vadodara, India). A commercial sample of Glinate™-60 (Glenmark Pharmaceuticals Ltd., Mumbai, India) was procured from a retail pharmacy. MLT and SP were purchased from Loba Chemie (Pvt.) Ltd. (Mumbai, India). CH was obtained from Sigma Chemical Co., India. Potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium chloride and potassium chloride were all of analytical grade from S.D. Fine Chem. Ltd. (Mumbai, India). All other chemicals and solvents were of analytical grade and used as received.

2.2. Preparation of NTG–MLT provesicular powders

Provesicular powders of the NTG–MLT complex were prepared containing different ratios of CH and SP according to a literature method[9] with slight modifications. The compositions of the NTG provesicles are given in Table 1. In brief, 100 mg MLT was placed into a 100 mL round-bottomed flask followed by a solution of NTG (60 mg), SP and CH (total lipid 100 μmol/L) in 10 mL chloroform. The mixture was vortexed for 5–10 min to obtain a slurry with additional chloroform being added in the case of mixtures with lower surfactant loading. Chloroform was then removed by rotary evaporation under reduced pressure at 50–60 °C over 15–20 min. After drying, powders were placed in a desiccator overnight to ensure complete evaporation of solvent. The final "provesicular powders" were stored in sealed glass containers at room temperature until characterization.

2.3. Formation of niosomes from provesicular powders

Niosomes were prepared from provesicular powders by hydration with phosphate buffered saline (PBS) pH 7.4 at 80 °C using a vortex mixer for 2 min. The resultant dispersion was then subjected to determination of particle size, zeta potential, EE and morphology.

2.4. Characterization aspects

2.4.1. Field emission scanning electron microscopy (FESEM)

The morphology of pure NTG, blank and the optimized formulation (F4) was examined by FESEM using a JSM 6360 electron