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Solid supersaturatable self-nanoemulsifying drug delivery systems for improved dissolution, absorption and pharmacodynamic effects of glipizide

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ABSTRACT

The objective of this study was to prepare a solid supersaturatable self-nanoemulsifying drug delivery system (solid S-SNEDDS) to improve the dissolution, absorption and pharmacodynamic effects of a poorly water-soluble drug: glipizide. The liquid supersaturatable formulation (liquid S-SNEDDS) was prepared by adding a polymeric precipitation inhibitor (HPMC-E5 at 5% w/w) to a liquid SNEDDS. Dilution of the liquid S-SNEDDS generated a nanoemulsion with a mean droplet size of 28.0 nm. The liquid S-SNEDDS was transformed into a free-flowing powder (solid S-SNEDDS) by adsorption onto calcium carbonate and talc. The solid S-SNEDDS generated a higher glipizide concentration in comparison with the solid SNEDDS (without HPMC-E5) during an in-vitro supersaturation test. Moreover, glipizide precipitated in an amorphous form from the solid S-SNEDDS. SEM studies of solid S-SNEDDS indicated the existence of molecularly dissolved glipizide. The solid S-SNEDDS was found to be stable during accelerated stability studies. In-vivo pharmacokinetic studies showed a significant ($p < 0.001$) increase in C_{max} (3.4-fold) and AUC_{0-12h} (2.7-fold) of glipizide from solid S-SNEDDS as compared with the pure drug. Solid S-SNEDDS showed a significant ($p < 0.001$) decrease in the plasma glucose level by 1.3, 1.3, and 2.9-fold as compared with solid SNEDDS, the commercially available drug product and the pure drug, respectively.

1. Introduction

Glipizide, a sulfonyl urea oral hypoglycemic agent, used to decrease the blood-glucose level in individuals with Type II diabetes mellitus. Glipizide lowers blood glucose by stimulating insulin release from the functioning pancreatic beta cells [1]. Glipizide is a weakly acidic drug (pKa = 5.9), practically insoluble in water, and exhibits better solubility at basic pH [2]. Owing to its poor water solubility, several formulation approaches have been explored to improve the solubility of glipizide, including solid dispersion [3], nanosuspension [4], cyclodextrin complex [5–7], bionanocomposites [8], micro particles [9], co-solvent assisted solubilization [10], self-emulsifying drug-delivery system [11], and solid self-nanoemulsifying drug-delivery system [12].

Self-nanoemulsifying drug-delivery system (SNEDDS) is the technological advances of the self-emulsifying drug-delivery system that attracted significant attention to improve oral bioavailability of lipophilic drugs [13]. SNEDDS is a transparent, thermodynamically stable, anhydrous isotropic mixture of oil, surfactant, co-surfactant, and drug that forms oil-in-water nanoemulsion (usually droplet size less than 200 nm) when exposed to the aqueous media upon gentle agitation or digestive motility of gastrointestinal (GI) tract [14,15]. The large surface area that arises from the nano-range droplet size facilitates pancreatic lipase to hydrolyze more effectively forming mixed micelles, which promotes solubilization of the lipophilic drug in the intestinal aqueous environment [16]. As a dosage form, SNEDDS offers distinctive advantages for enhanced drug absorption by various mechanisms

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such as (i) improving intra-luminal drug solubilization, (ii) inhibiting P-glycoprotein (P-gp) mediated drug efflux, (iii) enhancing lymphatic transport of drug, (iv) avoiding hepatic first-pass metabolism, and (v) increasing GI membrane permeability [16–18]. Additional benefits of SNEDDS include, reduction in inter- and intra-subject variability, quick onset of action, reduction in drug's dose and ease of manufacturing along with scale-up [14].

However, low drug loading and risk of drug precipitation following dilution, neutralizes the advantage of formulating lipophilic drug candidate as SNEDDS [19]. In-vivo drug precipitation might pose a risk for drug absorption. To overcome such difficulties there has been an increasing focus on the application of supersaturatable SNEDDS (S-SNEDDS) [20,21]. S-SNEDDS contains a water-soluble polymeric precipitation inhibitor (PPI) in addition to the typical composition of SNEDDS. The PPI retards excessive drug precipitation following dilution and maintain a temporary supersaturated state [22]. Consequently, the generation and stabilization of intraluminal supersaturation can provide an efficient solution for the oral bioavailability enhancement of lipophilic drugs [23].

Further, it is important to have these liquid supersaturatable formulations as a solid dosage form having higher stability, better transportability, simple and cost effective manufacturing, and improved therapeutic success owing to the better patient compliance [12,24,25]. Thus, the present research work aims at developing a stable, solid S-SNEDDS of glipizide that could generate a supersaturated state by retarding the precipitation of solubilized drug. Simultaneously, it was hypothesized that the developed formulation would generate a nanoemulsion upon dilution, thereby providing a larger interfacial area for enhanced drug solubilization and dissolution. Hence, this combined approach would enhance the oral bioavailability and glucose lowering efficacy of glipizide due to its precipitation resistant as well as nanosized nature.

2. Material and methods

2.1. Materials

Pharmaceutical grade of glipizide was a generous gift from Alembic Ltd. (Vadodara, India). Medium chain tri-glycerides (Captex 355®) was supplied by Abitec Corp. (Janesville, USA). Poly-glycol mono and di-esters of 12-hydroxy stearic acid (Solutol HS15®) was provided by BASF SE (Ludwigshafen, Germany). Medium chain mono glycerides (Imwitor 988®) was obtained from Sasol (GmbH Germany). Five centipoise viscosity grade hydroxypropyl methylcellulose (HPMC-E5) was provided by Colorcon Asia Ltd. (Mumbai, India). Size "1" hard gelatin capsules were kindly gifted by Capsugel Health Care Ltd. (Mumbai, India). Acetonitrile (HPLC), Methanol (HPLC), Potassium dihydrogen phosphate (Chromatography), Hydrochloric acid (AR), and Sodium chloride (AR) were purchased from Merck Specialties Pvt. Ltd. (Mumbai, India). 18 MΩ Water (HPLC grade) was obtained in-house from a Direct Q-3 UV water purification system (Millipore India Pvt. Ltd., Bengaluru, India). Drug-excipients compatibility studies were carried out (data not shown) before selecting the excipients for subsequent studies.

2.2. Analytical methodology

Chromatographic estimation of glipizide was achieved on a HPLC system (series 200, Perkin Elmer, USA) at a temperature of 30 ± 2 °C. The analytical column used was Luna C8, 100 × 4.6 mm, 3 μm (Phenomenex, CA, USA). The mobile phase was a mixture of acetonitrile and potassium dihydrogen phosphate buffer (pH 4.5; 20 mM) (35:65 v/v). The injection volume, mobile phase flow rate, and detection wavelength were selected as 20 μl, 0.8 ml/min, and 226 nm, respectively. The method was stability-indicating and was validated in-house. The method was linear (r^2 = 0.999) over the concentration range of 0.05–70 μg/ml. The relative standard deviations for inter-day and intra-day precision were less than 2%.

2.3. Preparation of liquid S-SNEDDS

For the present study, a previously developed and characterized liquid SNEDDS was used for the preparation of liquid S-SNEDDS [12]. The liquid SNEDDS was an isotropic mixture of glipizide, and SNEDDS preconcentrate [Captex 355: Solutol HS15: Imwitor 988 (30:45:25% w/w)]. The concentration of glipizide in liquid SNEDDS was 4% w/v.

For preparing liquid S-SNEDDS, variable amounts (0.5, 1, 3, 5, 7.5, and 10% w/w) of PPI (HPMC-E5) were added to a series of liquid SNEDDS (10 g) kept in dust-free glass vials. The mixtures were mixed for five minutes using a Cyclo-mixer (CM101, Remi, Mumbai, India) to obtain uniform suspensions.

2.4. Characterization of liquid S-SNEDDS

2.4.1. Measurement of droplet size and zeta potential

Liquid S-SNEDDS (0.1 g) or liquid SNEDDS (0.1 g) were diluted to 50 ml with water (HPLC) in volumetric flasks and were gently mixed by inverting the flask. The flasks were allowed to stand for 12 h at room temperature [24]. The droplet size and zeta potential of the diluted liquid S-SNEDDS and diluted liquid SNEDDS were measured using dynamic light scattering techniques (at a 90° scattering angle). Measurement was done at 25 °C using a Zeta potential/Particle sizer (Nanopartica SZ100, Horiba instrument, UK).

2.5. Preparation of solid S-SNEDDS

Adsorption studies were carried out to prepare solid S-SNEDDS with an extensively employed porous adsorbent such as calcium carbonate [26]. Briefly, 10 g of each liquid S-SNEDDS was poured onto calcium carbonate (15 g) placed in a mortar, mixed for 5 min to obtain a homogenous mass. Talc (2 g) (used as a lubricant) was added to the above mass, mixed gently, and passed through a mesh (250-μm). Correspondingly, solid SNEDDS was prepared by adsorbing the liquid SNEDDS onto above-mentioned excipients. Respective blank formulations of solid S-SNEDDS and solid SNEDDS were prepared using above excipients in the same proportion but without using glipizide.

The drug contents in each formulation were determined by HPLC. Briefly, 100 mg of solid S-SNEDDS or solid SNEDDS were transferred to 10-ml volumetric flasks containing methanol (HPLC) and sonicated for 10 min to solubilize glipizide. The resulting solutions were filtered through a 0.22-μm nylon filter. The filtrate (2 ml) was diluted to 10 ml with mobile phase, mixed and injected six times into the HPLC system. Similarly, blank injections were made in the same way by using blank formulations. Powder of solid S-SNEDDS or solid SNEDDS equivalent to 5 mg of glipizide were filled into size "1" hard gelatin capsules (Capsugel, Mumbai, India) and stored in glass bottles at 25 °C until used for the subsequent studies.

2.6. Characterization of solid S-SNEDDS

2.6.1. Micromeritic properties

The micromeritic properties of solid S-SNEDDS were evaluated in terms of angle of repose, Carr's index and Hausner's ratio [27].