Saudi Pharmaceutical Journal (2015) **23**, 528–540

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Design, optimization and evaluation of glipizide solid self-nanoemulsifying drug delivery for enhanced solubility and dissolution

Rajendra Narayan Dash [a], Mohammed Habibuddin [b,*], Touseef Humaira [b], Devi Ramesh [c]

[a] *Alliance Institute of Advanced Pharmaceutical & Health Sciences, Plot No. 64, Survey No. 145, Sardar Patel Nagar, Kukatpally, Hyderabad 500 072, Telangana, India*
[b] *Adept Pharma and Bioscience Excellence Private Limited, Corporate Office: 10-3-561/3/A/102, Vijayanagar Colony, Hyderabad 500057, Telangana, India*
[c] *Government Polytechnic for Women, Gujarathipeta, Srikakulam, Andhra Pradesh, India*

Received 29 December 2014; accepted 28 January 2015
Available online 19 February 2015

KEYWORDS

Central composite design;
SNEDDS;
Nanoemulsion;
Solubility enhancement;
Dissolution enhancement

Abstract A solid self-nanoemulsifying drug-delivery system (solid SNEDDS) has been explored to improve the solubility and dissolution profile of glipizide. SNEDDS preconcentrate was systematically optimized using a circumscribed central composite design by varying Captex 355 (Oil), Solutol HS15 (Surfactant) and Imwitor 988 (Co-surfactant). The optimized SNEDDS preconcentrate consisted of Captex 355 (30% w/w), Solutol HS15 (45% w/w) and Imwitor 988 (25% w/w). The saturation solubility (*SS*) of glipizide in optimized SNEDDS preconcentrate was found to be 45.12 ± 1.36 mg/ml, indicating an improvement (1367 times) of glipizide solubility as compared to its aqueous solubility (0.033 ± 0.0021 mg/ml). At 90% *SS*, glipizide was loaded to the optimized SNEDDS. *In-vitro* dilution of liquid SNEDDS resulted in a nanoemulsion with a mean droplet size of 29.4 nm. TEM studies of diluted liquid SNEDDS confirmed the uniform shape and size of the globules. The liquid SNEDDS was adsorbed onto calcium carbonate and talc to form solid SNEDDS. PXRD, DSC, and SEM results indicated that, the presence of glipizide as an amorphous and as a molecular dispersion state within solid SNEDDS. Glipizide dissolution improved

Abbreviations: solid SNEDDS, solid self-nanoemulsifying drug delivery system; *SS*, saturation solubility; DR_{15min}, percentage drug release in 15 minutes; LCT, long chain triglycerides; MCT, medium chain triglycerides.

* Corresponding author. Tel./fax: +91 4066103388.
E-mail address: drhabib21@gmail.com (H. Mohammed).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2015.01.024

significantly ($p < 0.001$) from the solid SNEDDS (~100% in 15 min) as compared to the pure drug (18.37%) and commercial product (65.82) respectively.

1. Introduction

Glipizide: 1-Cyclohexyl-3-{4-[2-(5-methylpyrazine-2-carboxamido) ethyl] benzene sulphonyl} urea is an antidiabetic. It is given orally for the treatment of type II diabetes mellitus. Glipizide acts to lower blood glucose by stimulating the release of pancreatic β cell (Sweetman, 2009). Glipizide, a weak acid ($pK_a = 5.9$) is practically insoluble in water (Wilson et al., 2004). Owing to its poor solubility, several formulation approaches have been investigated, including cyclodextrin complex (Gan et al., 2002; Huang et al., 2013; Nie et al., 2011; Shivakumar et al., 2007; Zhang et al., 2008), solid dispersion (Isaac et al., 2013), nanosuspension (Mahesh et al., 2014), bionanocomposites (Kushare and Gattani, 2013), co-solvent assisted solubilization (Seedher and Kanojia, 2009) and microparticles (Madhusudhan et al., 2010) to improve solubility of glipizide.

Self-nanoemulsifying drug-delivery systems (SNEDDS) have emerged as an effective delivery system due to their proven ability to enhance bioavailability of lipophilic drugs (Singh et al., 2013). SNEDDS is a thermodynamically stable isotropic mixture of oil, surfactant, co-surfactant and drug that form a spontaneous oil-in-water nanoemulsion with a droplet size less than 100 nm when introduced into an aqueous medium under gentle agitation (Bali et al., 2011).

Several potential advantages of SNEDDS include their ability to present drug in a solubilized form inside the gastrointestinal (GI) lumen, thus providing greater interfacial area for drug absorption, providing greater chemical and enzymatic stability, inhibiting P-glycoprotein (p-gp) mediated drug efflux, enhancing lymphatic transport (Date et al., 2010; Seo et al., 2013).

Components of SNEDDS and their concentrations have profound effect upon droplet size of the formed nanoemulsion which may affect its *in-vitro* and *in-vivo* performance (Hu et al., 2012). However, such formulations often developed and optimized using a trial-and-error approach by varying one-factor-at-a-time keeping rest factors constant. This univariate approach is time-consuming and requires a larger number of experiments to describe the effect of excipients (oil, surfactant and co-surfactant) on the physical properties of the SNEDDS and frequently fails to project the true optimal composition because interactions between factors were not considered (Pund et al., 2014). For understanding the multi-factorial relationship between formulation factors and product quality usually requires the use of multivariate approach, such as statistical design of experiment (DOE) (Wu et al., 2011). Systematic optimization of pharmaceutical product using DOE requires fewer experimental runs and tends to reveal (any) synergism or interaction among factors. Which in turn leads to yield a robust formulation with advantages of economics in terms of time, money and development efforts (Singh et al., 2013).

Moreover, it is worthy to convert conventional liquid SNEDDS to a solid dosage form (solid SNEDDS) having high stability, better transportability, simple and cost effective manufacturing, and above all, the improved therapeutic success owing to better patient compliance (Balakrishnan et al., 2009; Hu et al., 2012). Thus, the present research work aim at developing a solid SNEEDS of glipizide by systematically optimizing the SNEDDS preconcentrate that would generate a nanoemulsion on dilution. The generation of a nanoemulsion could provide a large interfacial surface area for drug solubilization leading to an enhanced solubility and dissolution of glipizide.

2. Materials and methods

2.1. Materials

Pharmaceutical grade of glipizide was a generous gift from Alembic Ltd., Vadodara, India. Abitec Corp., Janesville, USA, supplied EP/NF grade of medium chain tri-glycerides (Captex® 300, and Captex® 355) and medium chain mono-glycerides (Capmul® MCM,). EP grades of poly-glycol mono and di-esters of 12-hydroxy stearic acid (Solutol® HS15) and polyethylene glycol-40 hydrogenated castor oil (Cremophor® RH40); provided by BASF SE, Ludwigshafen, Germany. EP grade of medium chain tri-glycerides (Labrafac lipophile™ WL 1349, Labrafac™ PG) and PEG-8 glyceryl caprylate (Labrasol®) were supplied by Gattefosse Corp., Saint-Priest, France. EP grades of medium chain tri-glycerides (Miglyol® 812 N) and medium chain mono-glycerides (Imwitor® 988) were supplied by Sasol, GmbH Germany. Tween® 80, Coconut oil, Castor oil, Olive oil, and Polyethylene glycol 400 (PEG 400) were purchased from Himedia Lab. Private Ltd., Mumbai, India. Capsugel Health Care Ltd., Mumbai, India, supplied size "1" hard gelatin capsule shell. 18 MΩ Water (HPLC grade) obtained in-house from a Direct Q-3 UV water purification system (Millipore India Pvt. Ltd., Bengaluru, India).

2.2. Analytical methodology

A reversed phase HPLC method was developed in-house to quantify glipizide in samples obtained from solubility and dissolution studies. The analysis was performed on the Perkin Elmer HPLC system (Series 200) at a temperature of 30 ± 2 °C. The column used (Luna C8, 100 × 4.6 mm, 3 µm) was from Phenomenex®, CA, USA, while the mobile phase was acetonitrile–potassium dihydrogen orthophosphate buffer (pH 4.5; 20 mM) (35:65, v/v). Mobile phase flow rate, detection wavelength and injection volume were 0.8 ml/min, 226 nm and 20 µl respectively. The method was linear ($r^2 = 0.999$) in the concentration range of 0.05–70 µg/ml.