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Polymeric solid self-nanoemulsifying drug delivery system of glibenclamide using coffee husk as a low cost biosorbent

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ABSTRACT

Surface adsorbed chitosan-loaded solid self-nanoemulsifying drug delivery system (S-SNEDDS) of glibenclamide (GBN) was developed. Low cost coffee husk was investigated as a biosorbent for solidification of liquid SNEDDS. Different liquid and S-SNEDDS of GBN were developed by aqueous phase titration method. Developed formulations were characterized in terms of thermodynamic stability, self-nanoemulsification efficiency, droplet size, viscosity, % transmittance, drug content and droplet morphology. Finally, selected liquid and surface adsorbed S-SNEDDS were subjected to in vitro dissolution. In vitro drug release studies showed 98.91% release of GBN from optimized formulation. The release pattern of GBN from S-SNEDDS was found to be sustained release type as compared to immediate release pattern of liquid SNEDDS. The results of solubility studies showed 1492 fold enhancement in GBN solubility in optimized SNEDDS. These results indicate that developed surface adsorbed chitosan loaded S-SNEDDS could be successfully used as a unit dosage form of GBN.

1. Introduction

Glibenclamide (GBN) is a potent hypoglycemic agent which has been recommended for the treatment of type 2 diabetes [1–3]. According to the biopharmaceutical classification system (BCS) of drugs, it belongs to BCS class II drug that means it shows poor aqueous solubility and good permeability through gastrointestinal (GI) mucosa [4]. Due to poor aqueous solubility (24 μg/ml) and extensive hepatic first pass metabolism, its oral administration shows variable and poor absorption/bioavailability (only 45% after oral administration) [1,5]. In recent years, liquid self-nanoemulsifying drug delivery systems (SNEDDS) as well as solid SNEDDS (S-SNEDDS) have been investigated as potential drug delivery vehicles for various poorly water-soluble drugs [5–13]. Developed SNEDDS could enhance the bioavailability of GBN by maintaining the drug at solubilized molecular state and avoiding the first pass metabolism [6]. Recently, some drug delivery carriers such as surface solid dispersion, liquid self-microemulsifying drug delivery system (SMEDDS), solid SMEDDS and liquid SNEDDS have been used to enhance solubility and bioavailability of GBN [1,2,5]. Although, liquid SNEDDS have great potential for drug delivery to enhance solubility/bioavailability of poorly soluble drugs due to their solubilization potential but they are difficult to administer as a unit dosage form due to their liquid nature [11,12]. Moreover, liquid dosage forms are also associated with several problems like handling problems, transportation issues, palatability issues, stability issues and dose variations [2]. To solve all these issues, many attempts have been made to convert liquid SNEDDS into S-SNEDDS [11–13]. Chitosan is a well known cationic biodegradable biopolymer which is obtained by full or partial N-deacetylation of chitin [14,15]. Chitosan has been investigated extensively in various kinds of drug delivery systems and moreover it offers several advantages like biodegradability, compatibility, inexpensive, nontoxic, sustainability and renewability etc [16–19]. Chitosan is reported to be insoluble in an aqueous media (water). But, it was found to be soluble in acetic acid solution [19]. Therefore, various concentrations of chitosan (0.25–2% w/v) were prepared in 1% w/v solution of acetic acid and used as an aqueous phase for the development of chitosan loaded SNEDDS in a present study. Recently, tremendous work has been carried out towards the development of effective and low cost biosorbents for removal of toxic dyes from aqueous solutions and wastewater [20]. Coffee husk is one of the effective and low cost biosorbent. Coffee husks are generally known as “solid waste” discarded from the extraction of instant coffee which originated from cafeterias [21]. Coffee husk has been investigated as an effective and low cost biosorbent for the removal of some toxic metals and dyes from aqueous solutions [22–25]. Nevertheless, its low cost, efficiency and biodegradability [26,27] has never been applied for drug delivery/pharmaceutical applications. To the best of our knowledge, acid treated coffee husk has never been investigated as a biosorbent for solidification of liquid

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SNEEDS into S-SNEDDS in the literature. Most recently, surface-adsorbed liquid SNEDDS were developed and converted into S-SNEDDS using silicon dioxide (SiO_2) as a biosorbent to enhance in vitro dissolution of olmesartan medoxomil [11]. However, SiO_2 is not a biodegradable biosorbent, SiO_2-adsorbed S-SNEDDS could not be utilized as an efficient capsular dosage form. Despite the extensive application of silica nanomaterials in various area of research like biosensors, biomarkers, drug delivery, gene delivery, DNA delivery and enzyme immobilization, the results of their potential toxicity are still controversial [28,29]. Exposure of silica nanoparticles even at microscale level developed various autoimmune disorders such as lupus, rheumatoid arthritis, systemic sclerosis, renal failure, silicosis and lung cancer [29]. Therefore, silica was avoided to use as a biosorbent for conversion of liquid SNEDDS into S-SNEDDS in the present study as it is associated with several toxicity issues. The aim of this study was to develop surface adsorbed chitosan loaded SNEDDS of GBN as unit dosage form to extend its drug release and to enhance its in vitro dissolution and solubility which in turn enhance therapeutic efficacy and bioavailability using acid treated coffee husk as a low cost biodegradable biosorbent.

2. Materials and methods

GBN (purity 99%) was procured as a gift sample from Alfa Aesar, A Johnson Matthey Company (Ward Hill, MA). Caprylocaproyl macrogol-8-glyceride (Labrasol) (purity 99.2%) and diethylene glycol monoethyl ether (Transcutol-HP) (purity 99.98%) were kind gift samples from Gattefossé (Cedex, France). Polyoxyethylene (20) sorbitan monooleate (Tween-80) (purity 99.3%), low molecular weight chitosan (purity 99.6%) and ethanol (purity 99%) were purchased from Sigma Aldrich (St. Louis, MO). Propylene glycol monocaprylate (Sefsol-218) (purity 99.5%) and polyoxy-35-castor oil (Cremophor-EL) (purity 99.5%) were purchased from Nikko Chemicals (Tokyo, Japan) and BASF (Cheshire, UK) respectively. Coffee husk was procured from the central cafeteria of King Saud University (Riyadh, Saudi Arabia). Deionized water was obtained from ELGA water purification unit (Wycombe, UK).

2.1. Screening of components for liquid SNEDDS preparation

Model monoglyceride oil Sefsol-218 and deionized water were selected as oil phase and aqueous phase, respectively for the development of SNEDDS formulations of GBN. The criterion for selection of surfactant and cosurfactant was based on maximum SNEDDS zones in pseudo-ternary phase diagrams. The mass ratio of surfactant to cosurfactant (S_{mix} ratio) was kept constant at 1:1 for this purpose. Various combinations of surfactants and cosurfactants such as Tween-80/Transcutol-HP, Cremophor-EL/Transcutol-HP, Tween-80/ethanol, Cremophor-EL/ethanol, Tween-80/Labrasol and Cremophor-EL/Labrasol were investigated for SNEDDS zones in pseudo-ternary phase diagrams.

2.2. Nanophasic map construction and optimization of liquid SNEDDS

Pseudo-ternary phase diagrams for various combinations of surfactants and cosurfactants were constructed using aqueous phase titration method as reported previously [8,9]. Each surfactant and co-surfactant were premixed at a mass ratio of 1:1. For the construction of each phase diagram, oil phase (Sefsol-218) and specific S_{mix} were mixed thoroughly in different mass ratios (1:9 to 9:1) to delineate the phase boundaries formed precisely in the phase diagrams. The mixture of oil phase and specific S_{mix} was titrated with slow addition of aqueous phase and visual observations were made after each addition of water [9]. The clear/transparent and easily flowable systems were considered as SNEDDS. The physical state of each formulation was marked on a pseudo-ternary phase diagram.

2.3. Formulation development

Combination of Cremophor-EL and Labrasol was selected as surfactant and cosurfactant respectively, for the development of GBN encapsulated SNEDDS based on the maximum zones in pseudo-ternary phase diagrams. From the pseudo-ternary phase diagram, SNEDDS zones were pointed out and different formulations were selected. Almost the entire range of SNEDDS zones in the phase diagram were taken into account and varied oil compositions with minimum surfactant and cosurfactant concentrations were selected. 5 mg of GBN was solubilized in the required amount of S_{mix} and oil was added to this solution. Finally, aqueous phase was added in drop-wise manner till an apparent and clear solution was obtained.

2.4. Thermodynamic stability tests

In the search of robust formulations, developed liquid SNEDDS (G1–G5) were subjected to different thermodynamic stability tests such as centrifugation, heating & cooling cycle and freeze–pump–thaw cycles as reported previously [8,9]. For centrifugation test, developed SNEDDS were centrifuged at 5000 rpm for 30 min and observed for any phase separation or coalescence. For heating & cooling cycle test, three cycles were performed between 4 and 50 °C for the period of 48 h and formulations were observed for cracking, coalescence, phase separation or phase inversion. However, for freeze–pump–thaw cycles, three cycles were performed between −21 and 25 °C for 24 h. Only thermodynamically stable formulations were selected for self-nanoemulsification tests.

2.5. Self-nanoemulsification efficiency test

Self-nanoemulsification test was carried out visually to evaluate any drug precipitation or phase separation upon dilution with an aqueous media. Diluent deionized water was used as an aqueous medium. The self-nanoemulsification performance of each SNEDDS (G1–G5) was assessed visually using following grading systems [1,8,9]:

Grade A: Rapid forming clear o/w nanoemulsion (emulsify within 1 min)
Grade B: Rapid forming bluish white o/w nanoemulsion (emulsify within 2 min)
Grade C: Milky o/w emulsions (take more than 2 min to emulsify)
Grade D: Dull, grayish milky o/w emulsions (take more than 3 min to emulsify)
Grade E: Formulations with large oil globules at the surface

Formulations those passed this test in grade A or B were selected for further evaluation.

2.6. Entrapment of chitosan into liquid SNEDDS

Chitosan is reported to be insoluble in aqueous media. Therefore, different concentrations of chitosan were prepared in 1% v/v solution of acetic acid, because chitosan is reported to be soluble in acidic aqueous solutions [19]. 0.25–2% w/v solutions of chitosan were prepared in 1% w/v solution of acetic acid. These chitosan solutions were used as aqueous phase instead of deionized water now for entrapment of chitosan into SNEDDS. Pseudo-ternary phase diagrams were repeated again by replacing deionized water by chitosan solutions (0.25–2% w/v) using the same procedure as described in Section 2.2.

2.7. Physicochemical characterization and optimization of SNEDDS

Mean droplet size and polydispersity index (PI) of liquid SNEDDS (G1–G5) and chitosan-loaded SNEDDS (G6–G30) were determined