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Research paper

Optimization of solid-self nanoemulsifying drug delivery system for solubility and release profile of clonazepam using simplex lattice design

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ABSTRACT

The objective of the present work was to improve solubility and dissolution release properties of clonazepam (CNZ) from solid-self nanoemulsifying drug delivery system (S-SNEDDS). Liquid SNEDDS (L-SNEDDS) of CNZ was a system consisted of sunflower oil, Tween 80 and PEG 600 as vehicle, surfactant and co-surfactant, respectively. The L-SNEDDS were systematically optimized using simplex lattice design. The selected independent variables were % of sunflower oil (X_1), % of PEG 600 (X_2) and % of Tween 80 (X_3) and dependent variables were droplet size (Y_{DS}) and polydispersity index (Y_{PDI}). S-SNEDDS were prepared by simple adsorption technique using Aerosil® 200 as inert solid carrier. Both L-SNEDDS and S-SNEDDS showed significantly improved *in vitro* drug release and ex-vivo permeation than pure drug. Solid state characterization (DSC, X-RD and SEM) studies revealed that complete conversion of crystalline CNZ to amorphous form in optimized SNEDDS formulation. FT-IR studies revealed that there was no chemical interaction between drug and excipients. Accelerated stability studies revealed that there was no significant changes in physical appearance, emulsification time, droplet size, PDI, assay and dissolution release profile before and after storage. The obtained results illustrate the perspective use of S-SNEDDS for the oral delivery of poorly water soluble drugs.

1. Introduction

Over recent years, large population of new chemical entities and many of existing drug molecules are characterized by being poorly water soluble and highly lipophilic. Due to this fact these drugs though they exhibit potential pharmacodynamic activity present a serious challenge for their formulation development, industrial applicability and marketing and also clinical efficacy, leading to increase toxicity with increased dose. The Dissolution rate in the gastrointestinal tract (GIT) is the rate-limiting step in most of the cases. Various formulation strategies including solid dispersions [1], surface modification [2], micronization [3], complexation with cyclodextrins [4], salt formation [5,6], supercritical fluid process [7] and use of cosolvents [8] have been adopted to improve the solubility, dissolution release profile and thus improve the oral bioavailability. Although, the formulation strategies presently employed were capable to tackle formulation challenges of poorly water-soluble drugs, limits the physicochemical stability [5]. Among several approaches the use of lipid and surfactant based formulations found to be potential approach for improving oral bioavailability of poorly water soluble drugs by presenting and maintaining the drug in solution form throughout its period in GIT [6].

Self-emulsifying drug delivery system (SEDDS) is one of the lipid formulations and is an isotropic mixture of natural or synthetic oils, surfactants and co-surfactants. SEDDS are capable of forming fine oil-in-water emulsion upon gentle agitation in the GIT. Thereby maintains the drug in dissolved state, in small droplets of oil all over its transit through GIT, prevents dissolution related problems which is rate-limiting factor and hence facilitates faster onset of action. SNEDDS are the systems which form nanoemulsion of droplet size less than 200 nm upon dispersion in aqueous media. The characteristics of SNEDDS depend on the nature of oil, surfactant and co-surfactants and their mixing proportions [9,10]. When compared to emulsion formulations, SNEDDS is the most efficient and convenient method and also has patient compliance [11].

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SNEDDS are also capable of eliminating the food effect and have excellent stability. The drug can be protected from enzymatic action and inhibition of *p*-glycoprotein mediated drug efflux pumping. The drug was directly delivered to lymphatic transport system preventing the first pass metabolism and also to reduce the hepatic clearance of drug [12].

Traditional SNEDDS, administered as liquid dosage forms or included in a soft gelatin capsule, however, had few limitations such as drug stability, drug leakage, manufacturing methods, capsule ageing, excipient-capsule incompatibility and the storage temperature, as it results in precipitation of active ingredients or excipients when the product is kept at low temperature [13,14]. So combining the advantages of lipid based drug delivery systems with those of solid dosage forms, liquids SNEDDS were incorporated into solid dosage form overcoming these problems [15]. Among many techniques available for converting the liquid SNEDDS to solid dosage forms, adsorption of liquids on to solid carriers is simple and involves only addition of the liquid formulation on to suitable carriers by mixing in a blender. The resulting powder shows good content uniformity and could be filled into capsules or mixed with suitable excipients before compression into tablets [16].

Clonazepam (CNZ) is a widely used anticonvulsant benzodiazepine having also anxiolytic, muscle relaxant, sedative and hypnotic properties and is efficient for the treatment of panic disorder [17]. According to Biopharmaceutic classification system (BCS), CNZ belongs to class II. Though having drawbacks due to adverse drug reaction, CNZ is advantageous due to high effectiveness rate and low toxicity in overdose. CNZ show low water solubility (0.14 mg/mL) and thus limits dissolution on which the onset of absorption strongly depends on [18]. Onset of absorption depends on dissolution and absorption which in-turn was effected by administered formulation [19,20]. Hence, CNZ was formulated by a novel approach such as SNEDDS to improve the dissolution rate, resulting in faster onset of action.

2. Materials and methods

2.1. Materials

Clonazepam was obtained as a gift sample from Centaur Pharmaceuticals Pvt. Ltd., Mumbai, India. PEG-400, PEG-600, propylene glycol, tween 80 and tween 20 were purchased from S.D fine chemicals, Mumbai, India. Arachis oil, cottonseed oil, olive oil, soyabean oil, sunflower oil, brij 30 and Aerosil® 200 were purchased from Sigma life sciences, Hyderabad, India. Acetonitrile and methanol of HPLC grade were also obtained from Merck specialities Pvt Ltd, Mumbai, India. HPLC grade triethanolamine and orthophosphoric acid were purchased from Fischer scientific qualigens, Mumbai, India.

2.2. Determination of clonazepam

The method of evaluation of CNZ was established using high-pressure liquid chromatography (HPLC) on a Shimadzu HPLC system with a PDA detector set at a wavelength of 320 nm and an injector with injection volume 20 μL. The mobile phase (Acetonitrile/0.1% TEA buffer (pH 5.5), 60/40 v/v) was filtered through 0.45 μm membrane filter (Axiva Nylon 66, 170047X) and was eluted at a flow rate of 1.0 mL/min. CNZ was separated by a ODS C18 column (Chemsil ODS C18 column 4.6 × 250 mm, 5 μ) and retention time was 4.4 min [21,22].

2.3. Selection of oil, surfactant and co-surfactant

Equilibrium solubility of CNZ was determined employing various oils viz. soyabean oil, Arachis oil, cottonseed oil, olive oil, sunflower oil, Surfactants viz. tween 20, tween 80, brij 30 and co-surfactants-propylene glycol, PEG-400, PEG-600. An excess amount of CNZ was added to each of vehicle and the mixture was vortexed by vortex mixer (Remi 101C, Hyderabad, India) to ensure mixing. The mixtures were shaken at 25 °C for 48 h in a temperature controlled orbital shaking incubator (Remi CIS-2413L, Hyderabad, India). After attaining equilibrium, the samples were centrifuged at 5000 rpm for 10 min to separate undissolved drug. The supernatant was taken and diluted with methanol for quantification of CNZ in all samples by HPLC system. Oil suitable for the formulation was selected based on the solubility [23,24].

The selected oily phase was further used for screening of different surfactants having high solubility of CNZ for their emulsification ability. For this 20 μL of surfactant (Tween 20, Tween 80, Brij 30) were added to each 20 μL of oily phase. The mixtures were vortexed for homogenization of components. From each mixture 25 μL was diluted with 25 mL of distilled water in a volumetric flask. Ease of emulsification was judged by the number of flask inversion to yield homogenous emulsion. Emulsions were allowed to stand for 2 h and their % transmittance was evaluated at 638.2 nm by using UV–visible double beam spectrophotometer (UV-3200, LABINDIA, India) with distilled water as blank [20].

Different co-surfactants (PEG-400, PEG-600, Propylene glycol) were screened for emulsification ability using the selected oily phase and surfactant. Mixtures of 40 μL surfactant and 20 μL co-surfactant were prepared and 60 μL of oily phase was added to this mixture. Prepared mixtures were evaluated in a similar fashion as described above [20].

2.4. Construction of ternary phase diagram

From the ternary phase diagram, the self-emulsifying formulation that could self emulsifies under dilution and gentle agitation can be identified. Sunflower oil, Tween 80, PEG 600 were selected as oil phase, surfactant and co-surfactant, respectively. Surfactant and co-surfactant were mixed in different weight ratios (1:1, 1:2, 1:3 and1:4). Further for each surfactant and co-surfactant ratio, oil and specific surfactant: co-surfactant were mixed in 17 ratios ranging from 1:9 to 9:1. From the mixtures, formulation of 0.1 mL was taken in a beaker to which 100 mL of water was added and the contents were gently mixed with a magnetic stirrer. % transmittance of the formed emulsion was checked at 638.2 nm by using UV–visible double beam spectrophotometer (UV-3200, LABINDIA, India). The resultant emulsion was checked for clarity, phase separation and coalescence of oil droplets. Emulsions showing phase separation and coalescence were judged as unstable emulsions. Ternary phase diagram was drowned by identifying the good self-emulsifying region with oil, surfactant and co-surfactant each of them representing apices of the triangle [25].

2.5. Experimental design

Sipmlex lattice design (Design expert, version 8.0.4, Stat-Ease Inc., Minneapolis, MN) was used for the optimization of CNZ loaded SNEDDS. Three factors were evaluated at three levels and the L-SNEDDS optimization was carried with seven experimental runs. The selected independent variables were % of oil (X_1), % of co-surfactant (X_2) and % of surfactant (X_3). The dependent variables were droplet size (Y_{DS}) and polydispersity index (Y_{PDI}) (Table 1). The non-linear quadratic expression by this design is given as $Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3$