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Research paper

Development of oral solid self-emulsifying lipid formulations of risperidone with improved *in vitro* dissolution and digestion

Mohsin Kazi *, Hassan Al-Qarni, Fars K. Alanazi

Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

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ABSTRACT

Liquid adsorption on solid adsorbent carriers is an emerging technique for oral lipid-based drug delivery systems. The purpose of the current study is to convert liquid into solid self-emulsifying lipid formulations (SELFs) using an inorganic adsorbent Neusilin® grade US2 (NUS2) and investigate *in vitro* dissolution and digestion performance of the model antipsychotic compound risperidone.

Methods: The liquid SELFs were designed using various oils, nonionic surfactants and converted into solid at various SELF: NUS2 (%m/m) mixing ratios. The characterization of solid SELF powder was performed by using SEM, XRD, FT-IR & DSC to investigate the physical nature of the drug. The *in vitro* dissolution experiments were conducted to compare the representative formulations with marketed product risperdal®. *In vitro* digestion experiments were performed using a pH-stat at pH 6.8 for 30 mins to predict the fate of risperidone in the GI tract after exposure of the solid SELF to pancreatic enzymes and bile.

Results: The results from the characterization studies showed that NUS2 with SELF at 1:1 (%m/m) yield superior flowability of the powder. The SEM revealed that pure risperidone was in irregular crystal shape whereas the drug loaded solid SELFs were in smooth regular shape. The XRD and DSC analyses of pure risperidone also confirmed the intense peaks due to the native crystalline form of the drug. However, the absence of sharp peaks in solid SELFs indicated the amorphous form of the drug. From the dissolution studies it was found that solid SELFs provided significant release profiles (>95%) compared to marketed product risperdal®. The digestion experiments suggested that risperidone was in a supersaturated state which could be maintained in the presence of mixed bile salt micelles.

Conclusions: Solid SELF of risperidone with improved dissolution and digestion profile was successfully prepared using Neusilin® US2 as an adsorbent carrier.

1. Introduction

Since most drugs at market and New Chemical Entities (NCEs, approx. 75%) from the discovery pipeline are poorly water-soluble, it has never been so important for formulation scientists from academia and pharmaceutical industries to work on improving solubility. A large number of new poorly water-soluble compounds require significant formulation design in order to maximize bioavailability and exposure [1]. Within the available formulation techniques to enhance solubility, lipid-based drug delivery systems (LBDDS) have the most advances attributes and high level considerations [2,3]. Among LBDDS, a simple approach of self-emulsifying lipid formulations (SELFs) systems have attracted both scientific and commercial interests which can provide acceptable shelf life and flexibility for different dosage forms design [4,5]. The designed SELFs are composed of a mixture of medium and/or long chain glyceride oils, non-ionic surfactants and possibly water-soluble cosolvents with the unique property that they are able to undergo rapid self-emulsification in gastrointestinal (GI) fluids, forming fine oil-in-water (O/W) emulsions under the GI motility [6–8].

Lipid carriers like SELFs are usually liquid in nature and generally encapsulated into soft/hard gelatin capsules as final oral delivery product. In capsulated form, the interaction between liquid SELFs and capsule shell could make a major issue as it may result in either brittleness or softness of the shell [9]. In addition, several water-insoluble blockbuster drugs (e.g., anticancer drugs, antipsychotic drugs, cholesterol lowering drugs, and HIV protease inhibitors) might suffer significant chemical instability in both aqueous and oily formulations [10,11]. These limitations could cause significant challenges for the delivery of poorly soluble drugs using liquid SELFs.

* Corresponding author.
E-mail address: mkazi@ksu.edu.sa (M. Kazi).

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The model drug risperidone (RSD) is highly unstable (likely to be oxidized) in liquid SELFs that require significant delivery improvement [12]. RSD is a water-insoluble (weak base) second-generation antipsychotic drug, which leads to erratic bioavailability thus require frequent dosing. It is widely used in the clinical management of schizophrenia, bipolar disorder, and irritability in children. Novel formulations of some antipsychotic drugs currently have become popular due to the convenience in dosage form [13,14]. Therefore it has been remained a high demand for finding effective oral formulations of these hydrophobic therapeutic compounds due to the safety, stability, and patient compliance. This demand has created a window of opportunity for research on the solidification of liquid SELF dosage forms, which eventually can provide a safe and effective delivery system for the model drug.

Given the advantages of solid dosage forms, previously the available solid dosage forms were usually self-emulsifying (SE) capsules, SE solid dispersions, dry emulsions, SE pellets/tablets, SE beads, microspheres/nanoparticles and SE suppositories/implants [15,16]. However, adsorption onto solid carriers such as using Neusilin® grade inorganic material is a very recent approach, and a limited number works has been done till now, particularly with weak base like RSD using this technique [17].

Neusilin®'s high specific area, increased surface adsorption, porosity, anticaking, flow enhancing properties and its ability to keep the drug stable under amorphous state make it one of the best choice among adsorbents available today [14]. After conversion of liquid SELFs into solids, free flowing powders have flexibility (ease of processing) in designing and developing solid dosage forms (easy to encapsulate the powder) as well as the reduction of intra- and inter-subject variability of drug dissolution and plasma profiles, thus lead to improvements in drug safety and efficacy [18].

Within the scope of the current study, Lipid Formulation Classification System (LFCS) was used as a guideline to design, identify and compare SELFs each other without making any trial and errors [3]. Among four Types of LFCS, Type I system represented 100% oils (triglycerides or mixed glycerides), where digestion is required for drug to release. Type II formulations were self-emulsifying drug delivery systems encapsulating drug in 40–80% oils and 20–60% water-insoluble surfactants. Type III formulations were the most efficient systems produce self-microemulsifying and or self-nanoemulsifying drug delivery systems (droplet size ranged 0–250 nm) sub-divided into IIIA & IIIB systems. Type IIIA formulations contained 40–80% oils and 20–40% water-soluble surfactants as well as 0–40% hydrophilic cosolvents if necessary. Type IIIB formulations contained a greater proportion of water-soluble components (50–80% hydrophilic surfactants/cosolvents) and a lesser proportion of oils (<20%). Type IV formulations were the most hydrophilic systems which did not contain any oils. Type IV formulations encapsulated drug in 30–80% water-soluble surfactants and 0–20% water-insoluble surfactants as well 0–50% hydrophilic cosolvents [19].

Thus, the present work aimed to solidify SELFs using inorganic adsorbent Neusilin® US2 (NUS2) and improve the current practices of RSD bioavailability by increasing aqueous solubility, dissolution profiles as the solid dosage form [20]. By understanding the differences in lipolysis of different lipid formulations an *in vitro* lipolysis model was also used in this study to investigate the distribution of solubilized drug in the post lipid digestion products.

2. Materials and methods

2.1. Materials

RSD (3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2a] pyrimidin-4-one, purity > 99.5%) was generously donated by Riyadh Pharma Medical and Cosmetic Products Co. LTD, Riyadh, Saudi Arabia. Cremercoor® MCT 70/30 (caprylic/capric acid triglycerides (70% caprylic C8, 30% capric C10) was purchased from Cremor Oleo, GmbH, Germany. Coconut oil (CO, Medium chain fatty acids, 92% saturated, melting point 24 °C) was obtained from Winlab, Gemini-house, England. Capmul MCM (Mix of mono-80% & diglycerides C_{8-10}) was obtained from Abitec Corporation, Germany. Imwitor 988 (I988, equal amount of medium chain mono- and diglycerides), and Imwitor 308 (I308, 90% monocaprylate) were supplied by Sasol Germany GmbH, Werk Witten, Germany.

The nonionic surfactants HCO-30 (Polyoxyethylene hydrogenated castor oil, HLB-11) and TO-106V (PEG-6 sorbitan oleate, HLB-10) were gift from Nikko Chemicals Co. (Tokyo, Japan). Transcutol P (2-(2-Ethoxyethoxy) ethanol), a highly purified powerful solvent was donated by Gattefosse, France.

Porcine pancreatin (8_USP specifications activity) was purchased from Sigma Chemical Co. St Louis, MO, USA. Lipolysis inhibitor, 4 bromophenylboronic acid (4-BPB) was obtained from Aldrich Chemicals Co. St Louis, MO, USA. 1 M sodium hydroxide (Titrisol) was purchased from Merck, Darmstadt, Germany. High purity Milli-Q water was obtained through a Milli-Q pure lab flex (Veolia water). Neusilin® as adsorbent (US2 grade fine powder of Magnesium Alumino Metasilicate) was obtained from Fuji Chemical Industry, Japan. All other chemicals and solvents were of analytical purity and or HPLC grade, respectively.

2.2. Methods

2.2.1. SELF design technique

A smart excipient selection is crucial for the successful formulation design in lipid-based drug delivery systems [21]. In the current study, several excipients from oils to surfactants were used to develop a series of SELFs by a simple technique. Different concentrations of oil and surfactant with water-soluble cosolvent were mixed together that represented various types of formulation and alternative systems within LFCS. The "Formulation" (F) and its "Alternative formulation" (AF) were designed based on the similarities of their structural/chemical compositions, but F represented glycerides form and AF as fatty acid form respectively. All the formulations and their alternative systems from the most lipophilic Type I, through to Type II, Type IIIA, Type IIIB to Type IV, were developed using just pure triglycerides, mixed mono- & diglycerides and the nonionic surfactants of sorbitan oleate and hydrogenated castor oil. The formulations were prepared by simply changing one excipient at a time.

2.2.1.1. Assessment of self-emulsification systems. A visual assessment is very common and already been recognized as a standard method to evaluate the self-emulsification properties of the formulation. For sample preparation, a 100 µl of each formulation was dispersed into 50 ml water in a volumetric flask and vortexed (model K-550-G, VWR, scientific industries Inc. USA) slowly for 1 min at room temperature. The miscibility, homogeneity and the appearance were examined by maintaining the same conditions accordingly.

2.2.2. Determination of average particle size and polydispersity (PDI)

The average droplet size and polydispersity index (PDI) of the dispersed liquid SELFs were determined for the efficiency of the self-emulsification systems. The droplet size measurement was achieved by photon correlation spectroscopy (ZEN3600, Malvern Zetasizer nano series, UK) at 90° scattering angle. All the SELFs for particle size analysis were diluted 1 in 1000 (100 mg in 100 ml) with milliQ water to maintain the similar experimental condition and mixed for 1 min before measuring at 25 °C