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Aprepitant loaded solid preconcentrated microemulsion for enhanced bioavailability: A comparison with micronized Aprepitant

Sunil Kamboj, Radhika Sharma, Kuldeep Singh, Vikas Rana *

Pharmaceutics Division, Dept. of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, India

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ABSTRACT

Aprepitant (APT) is a lipophilic, poorly water soluble drug with moderate permeability characteristic. Therefore, we aimed to improve solubility as well as permeability that could possibly improve oral bioavailability of APT. For this purpose, Quality by design (QbD) approach employing simplex lattice mixture design was used to prepare solid preconcentrated microemulsion (S-PCM). Further, the software generated numerically optimized S-PCM formulations were developed by utilizing desirability function. The spectral attributes (powder X-ray diffraction, ATR-FTIR, and differential scanning calorimetry) of S-PCM formulations suggested that APT was present in amorphous form. The results of droplet size (150–180 nm), zeta potential (−13 to −15 mV), poly dispersity index (PDI) (0.211–0.238) and emulsification time (<1 min), of these S-PCM formulations (SP_1, SP_2 and SP_3) suggested spherical shape morphology (Transmission electron microscopy) with thermodynamic stability. The comparison of *in vitro/ex vivo* behavior of S-PCM (SP_1) with micronized and non-micronized formulations of APT suggested 2-fold and 5-fold enhancement in solubility and permeability, respectively. This was further evident from pharmacokinetic studies in rabbits that showed 1.5-fold enhancement in bioavailability of S-PCM with respect to micronized APT. Thus, it could be envisaged that development of S-PCM formulation of APT is the best alternative to micronization technology based APT formulations reported earlier.

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1. Introduction

Aprepitant (APT) is an antiemetic agent that mediates its effect by blocking neurokinin 1 (NK1) receptors Olver et al., 2007. Previous studies have shown that the projected efficacious human dose for APT is relatively high due to low solubility of nanoformulated APT in simulated intestinal fluids (Kesisoglou and Mitra, 2012; Shono et al., 2010; Kesisoglou et al., 2007). Thus, the development of enhanced bioavailability formulation of APT could potentially reduced the required dose (Shono et al., 2010; Ren et al., 2014). Currently, APT is available in capsule formulation with different dose (40 mg, 80 mg and 125 mg) manufactured by Merck and Company, Inc., and commercially marketed in the United States of America (Ren et al., 2014).

APT is a lipophilic compound [log P (pH 7) = 4.8], weakly basic in nature with a low water solubility (3–7 μg/mL, pH 2–10) (Olver et al., 2007; Kesisoglou and Wu, 2008). The first pass metabolism by CYP3A4 leads to low pharmacokinetic profile (Nago et al., 2009; Sanchez et al., 2004). Further, an intermediate permeability of APT (7.85×10^{-6} cm/s) across Caco2 model indicated that APT did not have "high permeability". Therefore APT was categorized as a BCS class IV drug, being "low soluble" and "low permeable" (Kesisoglou and Mitra, 2012; Shono et al., 2010).

Various attempts have been made to enhance bioavailability of APT. The Merck and Company, Inc. utilized size reduction principle to developed micronized/nanosized APT, that was found to enhance solubilization rate of the drug (Ren et al., 2014). Wu et al. (2004) investigated APT bioavailability in beagle dogs that exhibited dependency on solubility as well as on particle size. An increase in bioavailability (AUC 5.88 ± 1.86 μg/mL to 25.3 ± 3.29 μg/mL) was evident with decrease in particle size from 5.49 μm to 0.12 μm. Although, the Emend® (nanoparticulate formulation of APT available in market) improved bioavailability of APT, but the efforts to enhance the solubility and dissolution rate of APT are still on pursuit, probably due to high cost of this drug.

Several methods have been introduced to enhance the solubility of APT, which include, the use of surfactants (Niederquell and Kuentz, 2013), solid dispersion (Liu et al., 2006; Goddeeris and Van den Mooter, 2008), hot melt extrusion technique (Breitenbach, 2002), cyclodextrin complexes (Ren et al., 2014; Hiremath and Godge, 2012; Torne and Vavia, 2006) and nanoparticles (Angi et al., 2014). But, a most effective alternative approach to increase solubility as well as permeability of BCS class IV drugs

* Corresponding author.
E-mail addresses: vikas_pbi@rediffmail.com, vikas@pbi.ac.in (V. Rana).

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could be the development of microemulsion based drug delivery systems (Singh and Singh, 2013). In this system, the drug exists in lipid phase that is dispersed in highly solubilized form which has a capability to easily cross permeability barriers and transport the drug via lymphatic route (Dahan and Hoffman, 2008). Thus, solubility as well as permeability problem of APT could be resolved. In addition, Emulsion-based delivery systems are convenient means of delivering poorly water soluble drugs *via* the oral route, protecting and encapsulating drugs for pharmaceutical applications (Li and McClements, 2011; Chakraborty et al., 2009). Microemulsion are considered to be an ideal liquid vehicles for drug delivery as they possess additional merits like very low interfacial tension with spontaneous formation, high solubilization, thermodynamic stability (long shelf-life), low viscosity (with Newtonian behavior) and high surface area (high solubilization capacity), droplet size (5–200 nm) Chen et al., 2012; Kogan and Garti, 2006; Pawar and Vavia, 2012. Preconcentrated microemulsion (PCM) formulation design approach has been used for many poorly water soluble and poorly permeable drugs like talinolol (Ghai and Sinha, 2011), amphotericin B (Singh et al., 2013), carvidilol (Singh and Singh, 2013), ezetimibe (Bandyopadhyay et al., 2012), etc. to improve their solubility as well as permeability that leads to enhanced oral bioavailability.

Solid preconcentrated microemulsion delivery system (S-PCM) is one of the lipid-based drug delivery systems prepared by incorporation of liquid excipients into powders by using various solidification techniques (Shanmugam et al., 2011). It is a beneficial drug delivery system for low water-soluble drugs as it possesses the advantages of solid dosage forms (high stability with various dosage form options) with those of liquid preconcentrated microemulsion drug delivery system (L-PCM) (solubility and bioavailability enhancement). S-PCM produce oil-in-water microemulsion upon mild agitation in aqueous media (such as gastrointestinal fluids) (Kang et al., 2012; Wang et al., 2010). The micro/nano sized droplets generated in this process bears the advantage of carrying the drug in a solubilized form with a high interfacial surface area for an enhanced, more uniform and reproducible bioavailability (Rao et al., 2008).

In the present study, an attempt was made to enhance the solubility, *in vitro* dissolution and permeability that could possibly enhance the oral bioavailability of APT. For this purpose L-PCM formulations of APT were prepared using a medium chain oil, surfactant and co-surfactant combination as per simplex lattice mixture design and evaluated using surface response methodology. The L-PCM formulations developed were characterized for its ability to form microemulsion based on droplet size, dissolution characteristics and zeta potential. These L-PCM formulations were then converted into S-PCM using Aerosil 200 employing spray drying technique. The S-PCM formulations were then evaluated for *in vitro, ex vivo and in vivo* performance in comparison to micronized form of APT. Therefore, the present investigation could be an effective alternative to enhance oral bioavailability of APT as compare to already available techniques.

2. Materials and methods

2.1. Materials

Micronized Aprepitant (particle size 3.21 ± 0.9 μm) and non-micronized Aprepitant (particle size 25.91 ± 3.2 μm) were provided *ex gratia* by Dr. Reddy's Laboratories Ltd., Andhra Pradesh, India and Ranbaxy laboratory, Gurgaon, India, respectively. Labrafil M 1944CS (Oleoyl macrogol-6 glycerides), Labrafil M 2125CS (Linoleoyl macrogol glycerides), Lauroglycol 90 (Propylene glycol monolaurate), Plurol olique (Polyglyceryl-3 dioleate) and Transcutol (Diethylene glycol monoethyl etherol) were received as gift samples from M/s Gattefosse, Saint-Priest, France. Capmul MCM C10 (Glyceryl mono and dicaprate), Captex 200 (Propylene glycol dicaprylate/dicaprate), Captex 355 (Caprylic/Capric triglyceride) were received as gift samples from M/s Abitec Corp., Wisconsin, USA. Aerosil 200 *ex-gratia* was a gift by Panacea Biotech Pvt. Ltd., Derabassi, Punjab, India. The HPLC grade solvents like methanol, acetonitrile etc. were used for liquid chromatographic studies. All the reagents were of analytical grade and used as received.

2.2. Methods

2.2.1. Equilibrium solubility studies for Aprepitant

Solubility of APT was determined in various oils (Labrafil M1944CS, Labrafil M212CS, Captex 355, Lauroglycol 90, Capmul MCM C10, Labrafac lipophile, Captex 200, Plurol oleique), surfactants (Tween 80) and co-surfactant (Transcutol). For this purpose, an excess amount of APT was transferred to each of the glass vial previously containing 1 mL of oil phase and/or surfactant phase and/or co-surfactant phase and vortexed for 5 min after every 2 h for 24 h. In between these intervals, these vials were kept at a constant temperature in shaking incubator at 50 rpm and 25 ± 0.5 °C. All the vials were centrifuged (3000 rpm for 10 min) after keeping them aside for 24 h to attain equilibrium. The obtained supernatant was filtered through a membrane filter having pore size of 0.45 μm (Millipore, Darmstadt, Germany), 0.1 mL of solution was taken after filtration and diluted with mobile phase and analyzed employing HPLC method. Based upon solubility studies Capmul MCM C10, Tween 80 and Transcutol were selected as oil, surfactant and co-surfactant, respectively.

2.2.2. Analytical method

The analytical profile of APT was validated for its quantification on high-performance liquid chromatography (HPLC) system. The samples obtained from solubility, dissolution tests, *ex vivo* permeation and *in vivo* pharmacokinetic analysis were quantitatively analyzed for APT concentration using an isocratic HPLC system. The HPLC system consists of 515 HPLC pump and 2489 UV detector (Waters Ges.m.b.H. Wien/Austria). The chromatograms were evaluated with Empower 3 Software (Waters Ges.m.b.H. Wien/Austria). The analytical column used was a Discovery® C8 column 15 cm × 4.6 mm, 5 μm particles (Supelco, Sigma-Adlrich, UK). The mobile phase was a mixture of acetonitrile and 0.1% orthophosphoric acid (60:40) at 1 mL min^{-1} flow rate and 20 μL sample volume. The detection wavelength was set at 210 nm. The limit of detection and limit of quantification were found to be 0.035 μg/mL and 0.113 μg/mL, respectively. The method was found to be linear in the range of 0.1–50 μg/mL with regression coefficient (r^2 = 0.999). The analysis was performed under ambient conditions.

2.2.3. Construction of ternary phase diagrams

The ternary phase diagrams of the system Tween 80, Transcutol and Capmul MCM C10 in the absence and presence of model drug APT (80 mg/mL), were constructed by carefully measuring each component mixture (total 10 mL) into a glass vial. Various compositions of Capmul MCM C10 (10–90%), Tween 80 (10–90%) and Transcutol (10–40%) were used to prepare ternary mixtures. After complete solubilization of all the ternary components, a clear and transparent solution was obtained. These clear mixtures were then diluted 100 times with distilled water at room temperature (25 ± 1 °C) for the evaluation of droplet size, PDI and self-emulsification time.

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