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Development of aprepitant loaded orally disintegrating films for enhanced pharmacokinetic performance

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ABSTRACT

The present investigation was aimed to prepare orally disintegrating films (ODFs) containing aprepitant (APT), an antiemetic drug employing pullulan as film forming agent, tamarind pectin as wetting agent and liquid glucose as plasticizer and solubiliser. The ODFs were prepared using solvent casting method. The method was optimized employing 3^2 full factorial design considering proportion of pullulan: tamarind pectin and concentration of liquid glucose as independent variables and disintegration time, wetting time, folding endurance, tensile strength and extensibility as dependent variables. The optimized ODF was evaluated for various physicochemical, mechanical, drug release kinetics and bioavailability studies. The results suggested prepared film has uniform film surface, non-sticky and disintegrated within 18 s. The *in-vitro* release kinetics revealed more than 87% aprepitant was released from optimized ODF as compared to 85%, 49%, and 12% aprepitant release from marketed formulation Aprecap, micronized aprepitant and non micronized aprepitant, respectively. The results of animal preference study indicated that developed aprepitant loaded ODFs are accepted by rabbits as food material. Animal pharmacokinetic (PK) study showed 1.80, 1.56 and 1.36 fold enhancement in relative bioavailability for aprepitant loaded ODF, Aprecap and micronized aprepitant respectively, in comparison with non-micronized aprepitant. Overall, the solubilised aprepitant when incorporated in the form of aprepitant loaded ODF showed enhanced bioavailability as compared to micronized/non-micronized aprepitant based oral formulations. These findings suggested that aprepitant loaded ODF could be effective for antiemesis during cancer chemotherapy.

1. Introduction

Orally disintegrating films (ODFs) are one of the most popular dosage forms. The key advantage of such dosage forms is its quick disintegration, when placed on the tongue without the need of water, releasing the drug which dissolves in saliva. This usually results in enhanced bioavailability with faster onset of action compared to conventional oral dosage forms (Puttalingaiah et al., 2011). The presence of larger surface area of ODF is the cause of quick disintegration and dissolution in the oral cavity. ODFs are flexible so they are not as fragile as tablet and need not any kind of special package for protection during transportation and storage as compared to ODT (Siddiqui et al., 2011). In addition, the orally disintegrating tablets are prepared at higher crushing strength for preventing breakage during transportation. The increase in hardness leads to compromise with disintegration time even with enhanced concentration of superdisintegrants (Fukami et al., 2005). Because of convenience and ease of use over other dosage forms, ODFs have been introduced in the market (Bhyan et al., 2011). ODF formulations containing cetirizine hydrochloride (Mishra and Amin, 2011), ropinirole (Panchal et al., 2012), anastrozole (Satyanarayana and Keshavarao, 2012), or miconazole (Murata et al., 2013) were developed that disintegrate in less than 30 s and showed more than 90% of *in-vitro* drug release. However, no attempts have been made so far to load water insoluble drugs like aprepitant (APT). This may be associated with blockage of aqueous channels and interference in disintegration of films (Goel et al., 2009).

Aprepitant (APT); is selected due to its selective high affinity neurokinin-1 receptor (NK-1R) antagonist activity against chemotherapy induced nausea and vomiting (Olver et al., 2007). However, the limiting factor for the use of APT is its low solubility in water (about 3–7 μg/ml over the pH range 2–10), weak basic and lipophilic nature (log P at pH 7 = 4.8). This is the reason that APT is categorized into BCS class IV, being "low permeable" and "low soluble" (Kesisoglou and Wu, 2008; 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; Kesisoglou et al., 2007; Shono et al., 2010). Thus, the development of APT formulation with enhanced bioavailability potentially reduces its required dose (Ren et al., 2014; Shono et al., 2010). Presently APT capsules in different doses (40 mg, 80 mg and 125 mg) are manufactured by Merck & Co., Inc., and are commercially available in the USA (Ren et al., 2014). Further, the

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unformulated APT exhibit limited oral bioavailability in fasted state and showed marked enhanced food effects (Angi et al., 2014; Wu et al., 2004). Interestingly, an enhanced oral bioavailability was observed following oral administration of APT solution indicating negligible first pass metabolism effect (Angi et al., 2014). Therefore, entrapment of APT in solubilised form in ODF formulation is expected to enhance oral bioavailability of APT.

Various attempts have been made to enhance bioavailability of APT. The Merck & Co., Inc. utilized size reduction principle to develop micronized/nanosized APT that was found to enhance the solubilisation rate of drug (Ren et al., 2014). The studies on beagle dogs conducted under fed and fasted conditions showed that administration of micronized APT and nanosized (milled) crystals of APT results in increased bioavailability in the fasted state as well as reduced the food effect, both in animal models and clinical studies (Majumdar et al., 2006; Shono et al., 2010; Wu et al., 2004). Wu et al. (2004) investigated APT bioavailability in humans that exhibit 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 a decrease in particle size from 5.49 μm to 0.12 μm. Based on these findings a nanosized APT in capsule form is available in market. Although, Emend® provides APT with enhanced bioavailability, but the efforts to enhance the solubility and dissolution rate of APT have never been stopped, probably due to the high cost of this drug.

Several methods have been introduced to enhance the solubility of APT. These include the use of surfactants (Niederquell and Kuentz, 2013), solid dispersion (Liu et al., 2006), hot melt extrusion technique (Breitenbach, 2002) and cyclodextrin complexes (Hiremath and Godge, 2013; Torne and Vavia, 2006). Angi et al. (2014) attempted novel continuous flow technology for the development of nanostructured APT formulations in which the generation of the nanosized particles takes place at the molecular level. The method produces a stable amorphous solid form comprising nanostructured particles (less than 100 nm) with improved apparent solubility and permeability. This leads to improved pharmacokinetic properties (Huskey et al., 2003). Thus, suggested reduction in particle size enhances solubility as well as permeability of APT. Another feasible and commercially viable approach is cyclodextrin inclusion complexation. This approach has been extensively used to enhance drug solubility, convert liquid drugs in microcrystalline powders, prevent drug–drug or drug–additive interactions, reduce or eliminate unpleasant taste and odour in most of the formulations (Loftsson and Brewster, 1996; Ren et al., 2014). These benefits were utilized to develop APT-sulphobutyl ether-β-cyclodextrin complex to enhance solubility of APT (Ren et al., 2014). The results suggested enhancement in dissolution rates and magnitude of release of the test formulation as compared to Emend®. However, no significant effect on permeability of APT was evident from these investigations. Shono et al. (2010) investigated *in silico* simulation technology to forecast *in-vivo* oral absorption of micronized and nanonized APT formulations in pre- and postprandial states. They suggested dissolution is the primary limitation to the rate of absorption for micronized APT. However, permeability issue was still evident for nanonized formulation.

The present investigation is intended to formulate and evaluate aprepitant (APT) loaded orally disintegrating films that could enhance its oral bioavailability as compared to micronized APT, non-micronized APT and marketed formulation (Aprecap).

2. Materials and methods

2.1. Materials

Aprepitant (non-micronized) and aprepitant (micronized) were gifted by Ranbaxy Laboratories Ltd. Gurgaon, India and Dr. Reddy's Pvt. Ltd., Hyderabad, India, respectively. Commercially available aprepitant capsules (Aprecap 80 mg, Glenmark Pharmaceuticals Ltd., India) were procured from the local market. Pullulan was obtained as gift sample from Gangwal Chemicals Ltd., Mumbai, India. Liquid glucose (DE = 38–44, Gujarat Ambuja Exports Ltd.) was kindly gifted by Nayan Pharmaceuticals Pvt. Ltd., Patiala, India. Tamarind fruits were procured from the local market, Patiala, India. HPLC grade acetonitrile and orthophosphoric acid were purchased from Thermo Fischer Scientific Pvt. Ltd., Mumbai, India. All other materials and chemical used were of analytical grade.

2.2. Methods

2.2.1. Extraction of tamarind pectin (TP)

The extraction of tamarind pectin (TP) was carried out as per the method reported by Sharma et al. (2015).

2.2.2. Analytical method

The analytical profile of aprepitant (APT) was validated for its quantification on a high-performance liquid chromatography (HPLC) system. The samples obtained from *in-vitro* drug release and pharmacokinetic studies were quantitatively analysed for APT concentration using an isocratic HPLC system. For analysing blood plasma samples obtained during animal pharmacokinetic study, the method was validated in presence of blood plasma. 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-Aldrich, UK). The mobile phase was a mixture of acetonitrile and 0.1% orthophosphoric acid (60:40) at a flow rate of 1 ml min^{-1}. The injection volume was 20 μl. 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. Preparation of blank ODFs

The blank ODFs were prepared by dissolving pullulan (PU; 10–90%), tamarind pectin, (TP; 90–10%) and different plasticizers sorbitol (0.1–1%), glycerine (0.1–1%) or liquid glucose (LG) (0.01–0.1%) in water, while maintaining total polymer concentration to 2.5% *w/v*. For the preparation of film formulation, PU was dissolved in a minimum amount of purified water. Separately, TP was dissolved in purified water containing a plasticizer. This TP–plasticizer solution was added dropwise to the PU solution with stirring and makes up the volume to 25 ml. A clear homogenous solution obtained was poured onto a polypropylene petriplate (7 cm diameter) and dried at 50 °C for 24 h. The dried films were stored in polyethylene bags till further use. The different films prepared were physically examined for their integrity, surface behaviour, smoothness, *etc*. Table 1 summarizes different film combinations.

2.2.4. Preparation of APT loaded ODFs

For the preparation of APT loaded ODF, solution was prepared by dissolving APT (92.4 mg) in 0.5 ml of 0.1 M NaOH followed by addition of plasticizer LG (0.1% *v/v* of total polymer). This LG–APT solution was mixed with PU solution. Separately, TP was dissolved in purified water, added dropwise to a PU–APT–LG mixture with stirring and makes up the volume up to 25 ml. The clear homogenous solution obtained was poured onto the polypropylene petriplate (7 cm diameter) and dried at 50 °C for 24 h. The dried films were stored in polyethylene bags till further use.

2.2.5. Experimental design

A 3^2 full factorial design was employed for optimization of ODF formulation. The two factors, each at three levels (−1, 0 and +1) were taken as independent variables (proportion of PU:TP (X_1) and