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Enhancement of dissolution rate and bioavailability of Paliperidone by Hot Melt Extrusion technique

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The purpose of the study was to increase the dissolution and bioavailability of BCS class II drug, paliperidone by amorphization. The technique that was evaluated for preparing amorphous paliperidone (PAL) was Hot Melt Extrusion (HME). In case of hot melt extrusion process, copovidone was used essentially as a hydrophilic polymer with plasticizers like PEG (6000 and 20000), stearic acid and cetosterayl alcohol. Melt extrusion process was carried out by using different concentrations of drug, polymer, and plasticizers. DSC studies showed that the crystalline nature of PAL was significantly reduced on melt extrude. Incorporation of the plasticizer resulted in faster drug release compared with extrudes without plasticizer. Out of the plasticizers studied extrudes prepared with 25% PEG 6000 showed rapid release, wherein more than 75% of drug release was achieved within 30 minutes. The pharmacokinetics of melt extruded composition (PAL with 25% PEG 6000) and pure PAL was evaluated following oral administration (0.8 mg/kg) in healthy female Sprague Dawley rats. The extent of the mean plasma exposures of PAL was 14-fold higher in animals treated with extruded mixture of PAL, compared to animals treated with PAL. Melt extruded of PAL with PEG, especially PEG 6000, reduced drug crystallinity, increased the rate and extent of dissolution, and improved bioavailability.

Keywords: Paliperidone, Hot Melt Extrusion, Hydrophilic Polymers, bioavailability.

Introduction

Paliperidone (PAL), the major metabolite of risperidone, is a new atypical antipsychotic for the treatment of schizophrenia. PAL is poorly soluble in water. The poor solubility of paliperidone is problematic since bioavailability of a water insoluble active ingredient is usually poor. Hot-melt extrusion (HME), a process used to disperse or dissolve a drug in a molten polymer, has become increasingly important in pharmaceuticals due to the possibility of dissolving poorly soluble drugs in a solid solution. Extrusion can be operated as a continuous process, which is capable of consistent product flow at relatively high throughput rates[1]. HME is an efficient technology and is used for the preparation of solid molecular dispersions with considerable advantages over the solvent based processes such as spray drying and coprecipitation[2]. It helps in the scale-up of solid dispersions for solubility enhancements of poorly soluble drugs since release rate that can be achieved are often much greater[3]. The primary materials in any hot melt extruded formulations are drug, polymers[4-9] and plasticizers[10]. HME technique can provide sustained, modified, targeted and local drug delivery with the use of suitable formulation and process parameters[11].

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Materials and Methods

Materials

PAL was obtained from Dr. Reddy's Laboratories, Hyderabad, India. PVP (Plasdone S630) were gifted by ISP, Wayne, New Jersey, USA. Stearic acid, PEG 6000, PEG 20000 and Cetosterayl alcohol was purchased from Signet (Mumbai, India). All other chemicals used were of analytical grade.

Methods

Preparation of Physical Mixture

Physical mixtures of polymer S-630 and each of the four plasticizers mentioned were prepared with four different (Stearic acid, Cetyl Stearyl alcohol, PEG 6000 and PEG 20000 plasticizers in the concentration range of 5%, 10%, 15%, 20%, and 25%.

Preparation of melt mixtures

The Solid dispersions will be prepared by blending of plasdone S-630 and different plasticizers with different concentrations of plasticizers as mentioned.

These blends were melted on the water bath and mixed thoroughly. Blends were thoroughly mixed in the molten stage. After mixing in the molten stage, mixtures were cooled, scratched and sieved by 30 mesh.

Assay of Hot melts Extrudes (HPLC)

PAL content in the HME compositions were performed with HPLC (Waters, Milford, USA) using 5-µm, 250 X 4.6mm i.d Kromasil C8 column (GL Sciences Inc., Japan) by a gradient elution method. The gradient elution utilized Mobile phase A contained a mixture of 20mM $KH_2PO_4.H_2O$ and 1.5mL of triethylamine buffer (pH adjusted to 6.5, by using trifluoroacetic acid). Mobile phase B contained a mixture of water and acetonitrile in a ratio of 10:90 (v/v), respectively. Mobile phase A (buffer) and Mobile phase B were mixed in the ratio of 65:35. The flow rate of the mobile phase was 0.5mL/min. PAL was monitored using a UV detector at a wave length of 237 nm.

Differential Scanning Calorimetry

Thermal curves of each sample (approximately 2.5 mg) were recorded by simultaneous Differential scanning Calorimeter (TA Instruments Q 1000).

X-Ray Diffraction (XRD)

Powder X-ray diffraction patterns were traced employing X-ray diffractometer (Model No. 3000, Seifert, Germany) for the samples; using Ni filtered Cu-K radiation, a voltage of 40 kV, a current of 30 mA radiation.

In-Vitro Dissolution Studies

In-vitro dissolution testing employed the USP Apparatus II (VK 7010 Varian, USA) at 50 rpm with 900 ml of degassed water (DosaprepX[8], DOSA TECH) at 37 °C ± 0.5 °C. Six capsules of each batch containing powder sample equivalent to 6 mg Paliperidone were tested. Sink condition was maintained in degassed water, Sample of the dissolution media were removed via an automated sampling system at predetermined time interval (0, 5, 10, 15,30,45,60 min) and simultaneously analyzed spectrophotometrically at λ_{max} of 237 nm (Carry 50 UV-Spectrophotometer attached with Dissolution Apparatus). In vitro release studies of Pure PAL , PAL HMT samples were carried out data of dissolution study is shown as Mean ± SD (n=6). Time taken to achieve 50% ($t_{50\%}$) and 80% ($t_{80\%}$) drug release in dissolution medium were used for comparing the dissolution of drug from the various HMT samples with the pure drug.The $T_{50\%}$ was determined by fitting the dissolution data to a four parametric logistic model using the Marquardt-Levenberg algorithm (Sigmaplot 9.0 SPSS Inc., Chicago, IL). (Balasubramaniam *et al*. 2008)[12]

$$y = \min + \frac{\max - \min}{1 + 10^{[log\ EC_{50} - x] \times hillslope}}$$

In this equation, y, represents the cumulative % drug released; x, the time in min; min, the baseline of % drug released at time 0 minute; max, the plateau of % drug released at time 60 minutes and hill slope, the slope of the curve at transition center EC_{50}.

Pharmacokinetic study in rats

The study was conducted at Advinus Therapeutics Pvt. Ltd., Bangalore, India after getting the Ethical Committee Approval. In total 12 (6 per group) female Sprague Dawley rats (6-7 weeks old) weighing between 180-230 g were used for the study. All rats had free access to tap water and pelleted diet (Sniff rats pellet food, Ssniff Spezialdiaten, Germany). The rats were housed in a cage and maintained on a 12h light/dark at room temperature (21 °C to 24 °C) and relative humidity of 50 to 70% and acclimatized to study area conditions for atleast 5 days before dosing. General and environmental conditions were strictly monitored. The room underwent 10 fresh air change cycles per hour. Rats were implanted with canula in the jugular vein for blood sampling. The surgery was performed two days before dosing under anesthesia. The animals were fasted at least 10 h prior to dose administration and for 4 hours post dose with free access to water. Individual oral doses of the test and reference samples were prepared (0.8 mg/kg free base) and accurately weighed drug material was carefully transferred into the dosing syringe containing aliquot of gelatin gel. Transfer the sample into the syringe barrel was accomplished either using a butter-paper funnel/with a spatula; the funnel was weighed before and after transferring drug to account for any loss by sticking to funnel. Separate funnels were used to prepare each dose. After transfer of the drug material into the syringe, an aliquot of gelatin was placed on top of the drug powder, thus effectively sandwiching it between 2 layers of gelatin. The sample was attached to an oral feeding needle and administered into the stomach. After dosing, syringe was rinsed with 1mL of water and dosed again. Serial blood samples (250µL) were withdrawn from the cannulated jugular vein at: Pre dose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12 and 24 h post-dosing and

collected in labeled tubes containing 20 µL of EDTA dipotassium dehydrate solution (200mM) per ml of blood as anticoagulant. Blood samples were held on ice until centrifuged at 10000 rpm; 4 °C for 10min. plasma was transferred to individual Eppendorf tubes and stored below -70 °C until bioanalysis.

Bioanalysis

The samples were analyzed by combined reversed phase liquid chromatography tandem mass spectrometry (LC-MS/MS Model no: API 4000, Applied Biosystems, Foster city, USA) by multiple reaction monitoring (MRM) and Positive ionization mode. The samples were prepared for analysis by liquid – liquid extraction using a TBME. Chromatography was performed on a 250 mm X 4.6mm Kromasil C_{18} Column (Thermo) using isocratic elution with 85:15 0.05M ammonium acetate and methanol. Paliperidone pure drug was used as the internal standard. Under these conditions, no interference was observed for both samples and pure drug. The standard curve was linear from 1ng/ml to 1000 mg/ml.

Pharmacokinetic data analysis

The area under the drug concentration-time curve from zero to 24 h ($AUC_{0\rightarrow 24h}$) and mean residence time (MRT) were calculated using non compartmental analysis (WinNonlin 2.1, Pharsight Corp., Mountain View, CA). The maximal Plasma concentration of drug (C_{max}) and the time to reach maximum Plasma concentration (T_{max}) were directly obtained from Plasma data. One-way *ANOVA* and Bonferroni's multiple pair comparison tests. The differences in T_{max} among the groups were tested by *Kruskal-wallis* test and Dunn's multiple pair comparison tests.

Results and Discussion

Selection of polymer

Polymer selection plays a crucial role in the stabilization of hot melt extruded formulations. Polymer selected in the present work is plasdone S-630. The objective in the present study was to show that plasdone S-630 works as a polymeric carrier in the melt extrusion technique to enhance the solubility of the poorly soluble drugs. Plasdone S-630 is PVP co-polymerised with vinyl acetate. It is preferred over the conventional PVP in the melt extrusion technique because of its lower glass transition temperature (Tg) compared to the conventional PVP and also because it has higher Tg which is required for amorphous stabilization. It has amorphizing and solubilising properties through solid dispersions lowering the percent crystallinity of the drugs. The glass transition temperature of plasdone S-630 is around 106 °C. But it should be further lowered to facilitate the melt extrusion technique.

Selection of plasticizer

The Tg of plasdone S-630 should be reduced to appropriate temperature by the aid of plasticizers. Four different plasticizers taken for the trials in the present work were: Stearic acid, PEG 20000, Ceto sterayl alcohol and PEG 6000. Plasticizers were selected by studying the reduction in the Tg onset of the polymer S-630 by each plasticizer.

Characterization of prepared melt mixtures and physical mixtures

The physical mixtures and the melt mixtures prepared above were analyzed by DSC for the reduction the Tg onset of S-630. From the Tables [Table 1, Table 2] and Figures [Figure 1, Figure 2], it can be concluded that the Tg onset of S-630 decreases with the addition of plasticizers. PEG 6000 in the

Table 1—Reduction in the Tg onset of Plasdone S-630 in Physical Mixtures With Different Plasticizers

%of plasticizer	Tg onset with CSA	Tg onset with PEG 20000	Tg onset with PEG 6000	Tg onset with Stearic acid
0	181.98	180.98	180.28	181.22
5	178.56	176.42	174.53	168.37
10	179.37	173.84	170.98	162.12
15	174.44	172.18	168.56	156.98
20	172.42	168.15	166.67	156.45
25	168.35	165.08	165.17	156.34

Table 2—Reduction in the Tg onset of Plasdone S-630 in Melt Mixtures With Different Plasticizers

%of plasticizer	Tg onset with CSA	Tg onset with PEG 20000	Tg onset with PEG 6000	Tg onset with Stearic acid
0	181.98	180.98	180.28	181.22
5	176.12	173.22	171.27	173.34
10	172.45	169.97	162.56	158.28
15	168.26	167.36	159.37	157.37
20	165.09	165.32	157.28	156.96
25	164.97	164.26	155.27	154.87

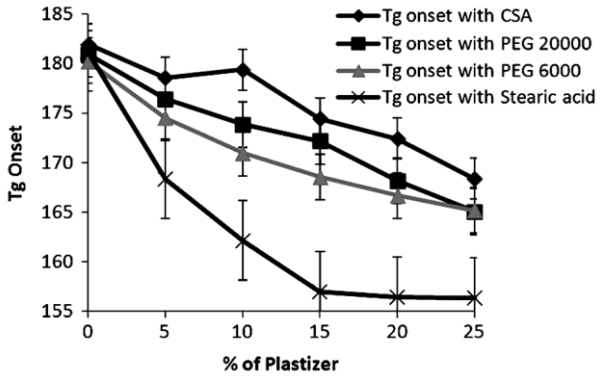

Fig. 1—Tg of PAL Physical Mixtures

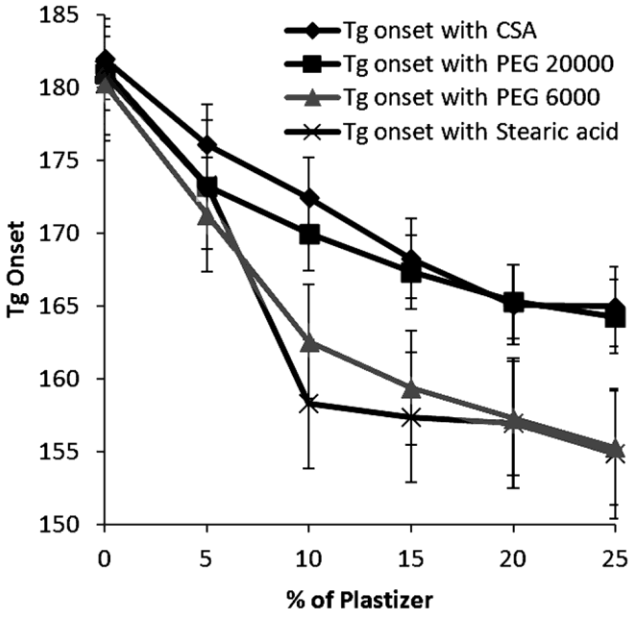

Fig. 2—Tg of PAL Melt Mixtures

concentration of 25% and Stearic acid in the concentration of 25% were found to reduce the Tg of S-630 to a considerable extent in both the physical mixtures and the melt mixtures, therefore they were selected. Release Profile of Solid dispersion was carried out for PEG 6000 and Stearic acid. The Hot melt extruded compositions had showed drug content of 98.0 to 102.0% of PAL, suggesting that the process was successful in achieving good encapsulation of the drug. The melt extruded compositions had drug content of 98.0 to 102.0% of PAL, suggesting that the HME process was successful in achieving good encapsulation of the drug. % dissolved is increased with the increase in the concentration of plasticizer. PEG 6000 at 25% level concentration shown faster drug release compared with other concentrations. Stearic acid at 25% level concentration also showed good release but % dissolved was less when compared to 25% PEG 6000. This may be attributed to the hydrophobic nature of stearic acid. Based on the above results, 25% PEG 6000 and 25% Stearic acid concentration were selected for melt extrusion study.The prepared melt extrudes were evaluated for DSC, *In-Vitro* drug release, XRD studies.

Differential Scanning Calorimetry (DSC)

DSC studies were performed on the individual components and on the freshly prepared melt extrude mixtures in order to study the interaction between PAL and the carriers in the solid state. PAL exhibited a single sharp melting endothermic peak at 181 °C. The DSC thermograms of different Plasdone S630 showed a broad endothermic peak in the range of 50-130 °C, which may be attributed to the endothermic relaxation (Garg *et al*. 2009).[13] The DSC thermograms further indicated that all the carriers are amorphous and hydrated compounds. The thermograms of the melt extruded compositions containing PEG 6000 and Stearic acid showed the absence of the characteristic melting endothermic peak of PAL, suggesting the amorphous nature of PAL in these compositions.

***In vitro* release studies**

The dissolution of PAL increased significantly (t-test; $P<0.05$) from all the melt extruded compositions. Amorphous forms of pharmaceuticals are markedly more soluble than their crystalline counterparts (Hancock and Parks 2000)[14] and improve the dissolution rate (Ahuja et. al. 2007; Friedrich *et al*. 2005)[15, 16]. PAL with 25% PEG 6000 gave 50% drug release in 13.23 min. and 80% drug release in 14.32 min whereas 25% Concentration level stearic acid gave 50% drug release in 42.1 min. and 80% drug

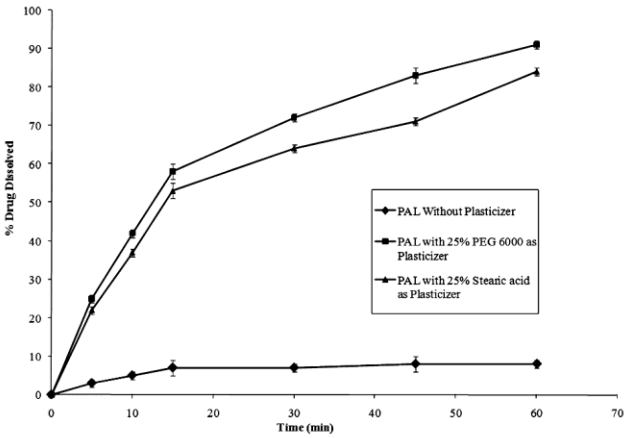

Fig. 3—Dissolution Profile of Melt Extrudes

Table 3—Pharmacokinetic parameters of PAL with 90% confidence intervals (CI) in female Sprague Dawley rats following oral administration of melt extruded sample and Paliperidone Pure drug in 1% gelatin gel sandwich (Dose: 0.8 mg/kg free base)

Sample	T_{max} (h)	Cmax (ng/mL)	AUC0-last (ng.h/mL)	AUC0-inf (ng.h/mL)	MRT0-t	T1/2 (h)
PAL with 25% PEG 6000	1.6 (1.2 -4.1)	282 ± 51	1324 ± 273	1456 ± 382	4.9 ± 1.2	3.4 ± 1.5
Pure Paliperidone	7.3 (4.6 - 8.5)	15.7 ± 3.4	108 ± 22.1	184 ± 21.5	9.3 ± 2.1	8.3 ± 2.8

release in 56.61%. PEG 6000 shown faster drug release compared with Stearic acid as plasticizer. Drug release was not achieved with pure PAL. [Figure 3].

X-Ray Diffraction (XRD)

XRD studies were undertaken to consolidate the DSC data indicating the reduction of the crystallinity of PAL with Plasdone S630 as polymer and PEG as plasticizer. Therefore, the XRD patterns of PAL, Plasdone S630 and the melt extrude with drug and Plasdone S630 with 25% PEG plasticizer were observed. The diffraction spectrum of PAL showed that the drug was crystalline in nature, as demonstrated by numerous distinct peaks observed at 2θ of 8.3, 10.4, 14.7, 15.1, 16.3, 18.8, 20.2, 20.8, 22.2, 24.8, 25.2 and 28.1. XRD pattern of Plasdone S630 and the Hot melt extruded composition showed no sharp peaks, indicating its amorphous nature. Further, no new peaks could be observed, suggesting the absence of interaction between the drug and the carrier (Hancock & Zografi, 1997; Ahuja *et al*. 2007; Williams *et al*. 2005).[14, 15, 17] This suggests that the crystal quality of PAL is reduced in the melt extruded mixture (Betageri & Makarla, 1995; Valizadeh *et al*. 2004; Vippangunta *et al*. 2002)[18, 19, 20]. These results are similar to DSC results.

Pharmacokinetic study

The pharmacokinetic parameters of PAL were determined after oral administration of PAL and melt mixture of PAL with Plasdone S630 and 25% PEG as plasticizer. It was selected on the basis of in-vitro dissolution studies as discussed above. The pharmacokinetic parameters are shown in Table 3. The extent of the mean plasma exposures of PAL was 14 fold higher in animals treated with Hot melt extruded PAL compared to animals treated with pure PAL. Thus, the mean Plasma $AUC_{0\text{-last}}$ in animals that received the melt extrudes of PAL and pure PAL was 1374 ± 273 ng.h/mL and 108 ± 22.1 ng.h/mL respectively, and they were significantly different ($p = 0.0001$ by *ANOVA*). Bonferroni's multiple pair comparison tests also showed significant increase with smelt extruded PAL with PEG 6000 as plasticizer as compared to PAL.The corresponding mean C_{max} values for these treatment groups were 282 ± 51 ng/ml, and 15.7± 3.4 ng/ml and these were significantly different ($p = 0.0052$ by *ANOVA*). Bonferroni's multiple pair comparison tests showed significant increase with the HME composition compared to PAL. The median T_{max} of PAL in animals that received the HME mixture and pure drug was 4 and 8 hours, respectively, and these were significantly different ($p=0.0211$ by Kruskal-Wallis test). Dunn's multiple pair comparison tests also showed significant difference between the groups administered with the HME mixture to the group administered with the pure drug. The mean elimination half-life calculated from the pure drug administered animals was not reliable as there was insufficient number of time points on the terminal declining phase.

Melt extruded of PAL with Plasdone S630 as polymer and different plasticizer, especially PEG 6000, not only reduced the drug crystallinity but also significantly improved both the dissolution and the rate and extent of plasma exposure of the drug in female Sprague Dawley rats. Thus, the study showed that PEG 6000 was found to be a better carrier for PAL.

Conclusion

Melt extruded of PAL with PEG, especially PEG 6000, reduced drug crystallinity, increased the rate and extent of dissolution, and improved bioavailability. The results of the present study demonstrated enhancement of dissolution and bioavailability of paliperidone in rats and can be valuable for preparing the formulation in developing bioavailable dosage forms.

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