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Dissolution Rate Enhancement of BCS class II drug, Paliperidone by Spray Drying

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ABSTRACT

The purpose of the study was to increase the dissolution of BCS class II drug, paliperidone by Spray Drying. The technique adopted is very well used industrially for preparing amorphous composition of poorly soluble crystalline drugs. In case of spray drying effect of spray drying PAL with different classes of hydrophilic carriers (different grades of polyvinyl pyrrolidones [PVPs, Plasdones] and cellulosic polymers) were taken. Pre-formulation studies were conducted to select the appropriate carriers and drug: carrier ratio for preparing the spray dried compositions. The dissolution studies of the prepared spray-dried compositions were carried out in USP Type II apparatus. The solid state interactions of the spray dried mixtures were evaluated by DSC & XRD. Preformulation studies revealed that amorphous compositions of PAL could be obtained only with Plasdones (K12, K29/32 and S630). DSC studies showed that the crystalline nature of PAL was significantly reduced on spray drying. Significant enhancement in dissolution rate was observed with the prepared spray dried compositions and out of the three grades of Plasdone, Plasdone K12 demonstrated the maximum enhancement in rate of release of PAL. Spray drying of PAL with Plasdones, especially Plasdone K12, reduced drug crystallinity, increased the rate and extent of dissolution.

Keywords: Paliperidone, Hydrophilic Carriers, Amorphous, Dissolution

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INTRODUCTION

Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development [1,2]. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability active agents include: Enhancing solubility and dissolution rate of poorly water- soluble drugs and enhancing permeability of poorly permeable drugs. These two areas form the basis of the biopharmaceutical Classification system (BCS) which is incorporated in the guidelines of the Food and Drug Administration (FDA). Drugs can be categorized into four Biopharmaceutical classes based on solubility, permeability and invitro dissolution. Role of correlation or non correlation with in-vivo process also can be explained from this classification system. Paliperidone, a major metabolite of risperidone (9-hydroxyrisperidone), has been approved by the FDA for the treatment of schizophrenia since 2006. Paliperidone is a BCS class II drug.

The development of new pharmaceutical agents is often confounded by their poor water solubility which impacts a number of derivative properties including poor dissolution rate[3,4]. Inadequate solubility or dissolution rate can significantly reduce both the rate and extent of drug absorption deleteriously affecting oral bioavailability. Several factors rooted in contemporary drug pipelines are thought to contribute to this overall decrease in drug ability including the manner in which drugs are discovered and the chemically allowed space of the drug target. Solid amorphous dispersions provide a unique opportunity in this regard [5,6].

An amorphous material can be substantially more soluble than the corresponding crystalline material, as much as 1600 times more soluble [7].

There is a growing interest in the amorphous state in the field of pharmaceutics. The amorphous state is a high energy state and thus, it offers one possible solution to overcome the poor water solubility problem related to many drug molecules. Amorphous material can be created during several pharmaceutical processing steps both unintentionally as well as intentionally. Therefore, there is a need for techniques that can be used to obtain more information about the amorphous state as well as to monitor process induced changes associated with it. Spray drying unit operations are used for the production of dried powder across a wide range of material processing applications from food to fertilizer to pharmaceuticals [8]. This one step, continuous process converts a bulk liquid into powder and has been shown to be both robust and scalable, with the appropriate hardware and process modifications. Spray drying applications in the pharmaceutical industry date to almost 50 years ago. It was first applied as an intermediate processing step in the production of solid dosage forms. Spray dried lactose was used as an excipient for direct compression [9], for compression ready granulation [10], solid dispersion [11,12] and more recently to manufacture dry powders for inhalation [13-20].

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MATERIALS AND METHODS

Materials

Paliperidone was obtained from Dr. Reddy's Laboratories, Hyderabad, India. PVP (Plasdone K-12, 29/32 and Plasdone S630) were gifted by ISP, Wayne, New Jersey, USA. Hydroxypropyl methyl cellulose (Pharmacoat 606), Hydroxypropyl cellulose (Klucel EF) and Hydroxypropyl methyl cellulose acetate succinate (HPMC AS, LF, MF and HF) was purchased from Signet (Mumbai, India). All other chemicals used were of analytical grade.

Pre-Formulation Studies

Solubility of Paliperidone (PAL)

The solubility of PAL in various solvents and in solvent mixtures was determined using a gravimetric method. 10 ml of the various solvents and the solvent mixture were taken in a stoppered glass bottle, to which accurately weighed graded amount of the drug was added and after each addition the bottles were shaken using a shaker. Addition of drug was stopped, when no further drug goes into solution and the bottles were shaken for a period of 24 hours. The point where no further drug goes into solution was taken as the 'saturation point' for that particular solvent and the weight of the drug added up to that point was considered for calculating the solubility in that particular solvent system.

Film Studies of Paliperidone With Polymers

Film studies were carried out with different drug: polymer ratios (1:1, 1:3 and 3:1). Polymers used include Plasdone K12, K 29/32 and S 630, HPMC (Pharmacoat 606), HPC (Klucel EF), HPMC acetate succinate (HPMC AS – LF, MF, HF). The drug polymer mixtures were dissolved in a mixture of ethanol and DMF. The solution was then poured on glass slides using a dropper and allowed to dry under vacuum for 3 hours at 60°C. The dried films were then subjected to DSC at a heating rate of 10°C / min.

Preparation of PAL Spray-Dried Compositions

Polymeric solution of the different PVP grades (Plasdone K12, K29/32 and S630) was prepared by dissolving the polymer in ethanol (0.5 or 1.5% w/v according to the ratio desired). PAL was dissolved in dimethyl foramamide (DMF) (0.5% w/v) and the solution of the drug was added to the polymeric solution. The prepared drug/polymer solution, in the desired ratio, was spray dried using Buchi (B-290, Flawil, Switzerland) with 0.5 mm nozzle. The PAL: PVP solutions were fed to the nozzle via peristaltic pump (flow rate of 8 ml/min). The volume of solution sprayed was 200 ml. The solutions were sprayed as atomized droplets by the force of compressed nitrogen (nitrogen flow rate of 42 kg/cm^2). The solvents in the droplets were evaporated in the drying chamber by the blown hot nitrogen (inlet nitrogen temperature of

180°C and outlet nitrogen temperature of 120°C). The dried products were collected in the collection vessel and weighed.

Assay of Spray-Dried Compositions (HPLC)

PAL content in the spray dried 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. 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.

Estimation of Methanol and DMF in Spray Dried Compositions Using HSS-GC

Organic volatile impurities (ethanol and DMF) were estimated using headspace Gas chromatography (Agilent 6890N) using capillary column DB-624 30 meters, 530 µm internal diameter and 3µm film thickness. The initial oven temperature was held at 40°C for 20 minutes and increased at the rate of 10°C per minute up to 240°C and held for further 20 minutes. Injector and detector temperatures were maintained at 140 and 250°C, respectively and column flow was maintained 4.9 ml/minute.

Differential Scanning Calorimetry

Thermal curves of each sample were recorded by simultaneous Differential scanning Calorimeter (TA Instruments Q 1000). Each sample (approximately 2.5 mg) were scanned in hermetic pan made of aluminium at heating rate of 10 °C/min over the range of 50 °C-220 °C with an empty aluminium pan used as reference. Samples were heated under nitrogen atmosphere (flow rate of N_2 - 50 ml/min).

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 scattered in the crystalline regions of the sample was measured with a vertical goniometer. Patterns were obtained by using a step width of 0.04 °C with a detector resolution in 2θ (diffraction angle) between 10° and 50° at ambient temperature.

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 6mg Paliperidone were tested. Sink condition was maintained in degassed water, Sample of the dissolution media were removed

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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 Paliperidone , PAL Spray dried sample , Spray dried with polymer 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 spray dried 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) [21].

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

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}.

RESULTS AND DISCUSSION

Pre-Formulation Studies

The solubility of PAL in various solvents was determined so as to select an appropriate solvent or solvent system for dissolving both the drug and the polymer and is shown in Table 1. Out of the solvent studied, both Dimethyl formamide (DMF) and Dimethyl sulfoxide (DMSO) were found to be suitable for dissolving PAL.

Table 1: Solubility of Paliperidone in different solvents

Solvent	Solubility(mg/ml)
Dichloromethane (DCM)	< 5
Ethyl Acetate	< 5
Acetone	< 5
n-Butanol	< 5
Methanol	5
n-Hexane	< 5
Cyclohexane	< 5
Acetonitrile	< 5
n-Heptane	< 5
Ethylene Chloride	< 5
Ethanol	< 5
Water	< 5
n-Propanol	< 5
IPA	< 5
DMF	160

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DMSO	415
DMF + Ethanol	90
DMF + DCM	10
DMF + Acetone	10

Film studies with various carriers at different drug to carrier ratios were done in order to screen for polymers that could convert the drug into a less crystalline or an amorphous form. The results of the film studies are summarized in Table 2. Out of the polymers screened PVP (Plasdone) K12, K29/32 (in ratio of 1:1) and S630 (ratio of 1:3) converted the drug to the amorphous form.

Table 2: Film studies of Paliperidone with different Polymers

Drug: Polymer	Ratios		
	1:1	1:3	3:1
PAL:K29	Amorphous	Amorphous	Amorphous
PAL:K12	Amorphous	Amorphous	Endothermic transition at 178.35 °C
PAL: S 630	Endothermic transition at 181.80 °C	Amorphous	Endothermic transition at 179.20 °C
PAL:HPMC	Endothermic transition at 178.6°C	Endothermic transition at 179.1°C	Endothermic transition at 179.5°C
PAL:HPC	Endothermic transition at 181.4°C	Endothermic transition at 180.3°C	Endothermic transition at 181.7°C
PAL:HPMC AS LF	Endothermic transition at 178.4°C	Endothermic transition at 179.1°C	Endothermic transition at 179.8°C
PAL:HPMC AS MF	Endothermic transition at 177.9°C	Endothermic transition at 176.5°C	Endothermic transition at 181.3°C
PAL:HPMC AS HF	Endothermic transition at 180.8°C	Endothermic transition at 179.3°C	Endothermic transition at 180.2°C

Spray Dried Compositions

The prepared spray dried compositions were evaluated for their volatile content since a combination of ethanol and DMF was used as the solvent system for spray drying, by a head space GC. Ethanol was selected as one of the solvent because of the soluble nature of all the polymers, used in the study, in it and out of DMF and DMSO, DMF was preferred because of its relatively lower boiling point than DMSO. The Ethanol and DMF eluted at 2.8 and 27.5 minutes, respectively, owing to their obvious difference in their boiling points. The amount of the respective solvents, present in the spray dried compositions, were calculated relative to the area count of their respective standards (3000 µg/ml of pure methanol and 880 µg/ml of DMF, as recommended by ICH guidelines). The level of ethanol in the spray dried compositions was in the range of 475 to 512 µg/ml of ethanol and the level of DMF was in the range of 60 to 75µg/ml. A representative chromatogram is shown in Fig. 1. This suggests that spray dried compositions contained very less amounts of both the solvents since it is significantly lower than the ICH recommended levels. This low level of solvent present in the spray dried compositions could also aid in lowering of the re-crystallization rate of the drug from the spray

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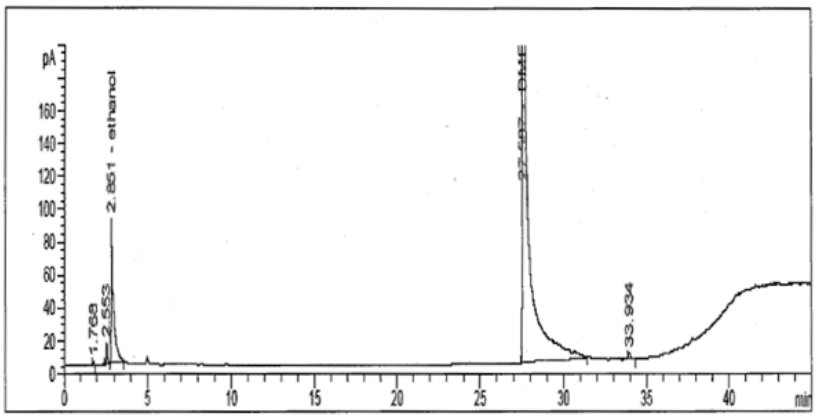
dried compositions. The spray dried compositions had drug content of 98.0 to 102.0% of PAL, suggesting that the spray drying process was successful in achieving good encapsulation of the drug.

Fig 1: Representative GC chromatogram of PAL spray dried mixture showing elution of methanol and DMF



DSC of Spray Dried Compositions

DSC studies were performed on the individual components and on the freshly prepared spray dried mixtures in order to study the interaction between PAL and the carriers in the solid state (Fig. 2). PAL exhibited a single sharp melting endothermic peak at 181^0C. The DSC thermograms of different Plasdone grades showed a broad endothermic peak in the range of 50-130^0C, which may be attributed to the endothermic relaxation [22]. The DSC thermograms further indicated that all the carriers are amorphous and hydrated compounds. The thermograms of the spray dried compositions containing Plasdone K12 and K29/32 showed the absence of the characteristic melting endothermic peak of PAL, suggesting the amorphous nature of PAL in these compositions. However, a slight shift of the endothermic melting peak and broadening was observed in thermogram of the spray dried mixture prepared using Plasdone S 630. This suggests that the crystalline nature of the drug was greatly reduced by Plasdone K12.

X-Ray Diffraction (XRD)

XRD studies were undertaken to consolidate the DSC data indicating the reduction of the crystallinity of PAL with Plasdone. Therefore, the XRD patterns of PAL, Plasdone K12 and the spray dried mixture with drug and Plasdone K12 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 (Fig. 3). XRD pattern of Plasdone K12 and the spray dried composition showed no sharp peaks, indicating its amorphous nature (Fig. 4 and Fig. 5). Further, no new peaks could be observed, suggesting the absence of interaction between the drug and the carrier [23,24,25]. This

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suggests that the crystal quality of PAL is reduced in the spray dried mixture [26,27,28]. These results are similar to DSC results.

Fig 2: DSC of PAL, Plasdone grades and Spray dried compositions

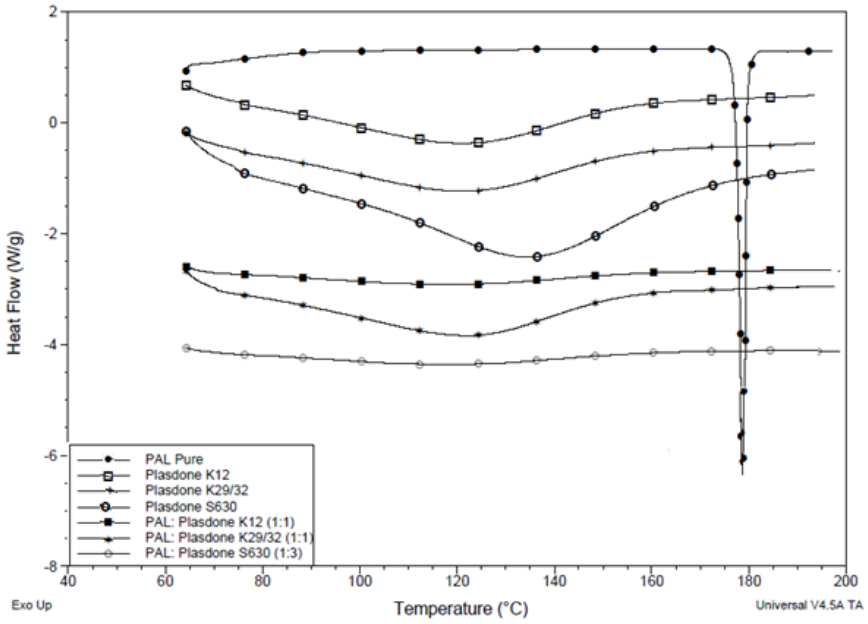

Fig 3: XRD Spectra of PAL

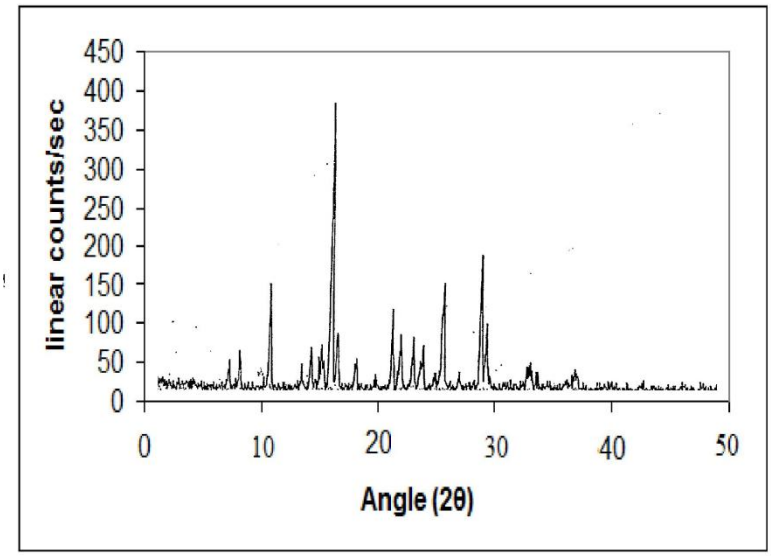

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Fig 4: XRD spectra of Plasdone K12

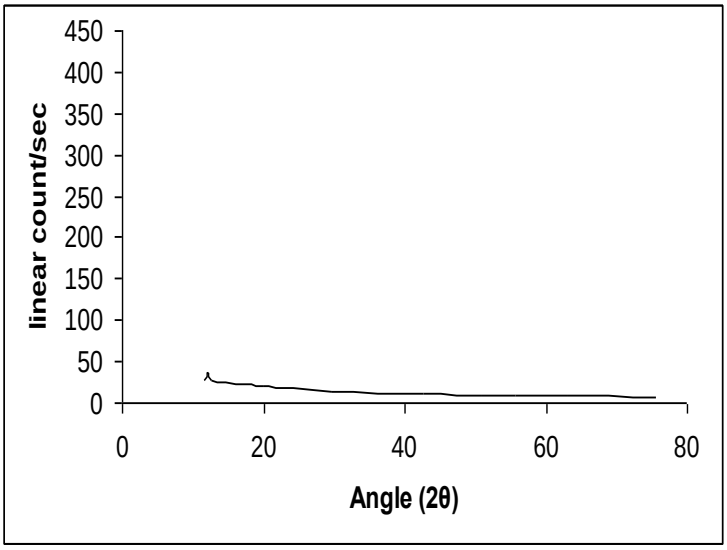

Fig 5: XRD spectra of Spray dried PAL: Plasdone K12 1:1

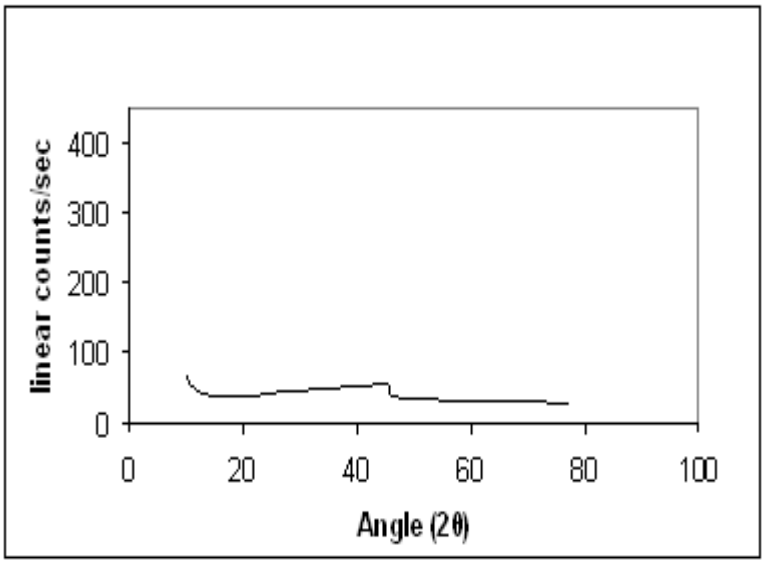

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Fig 6: Dissolution Profile of spray dried PAL compositions in water

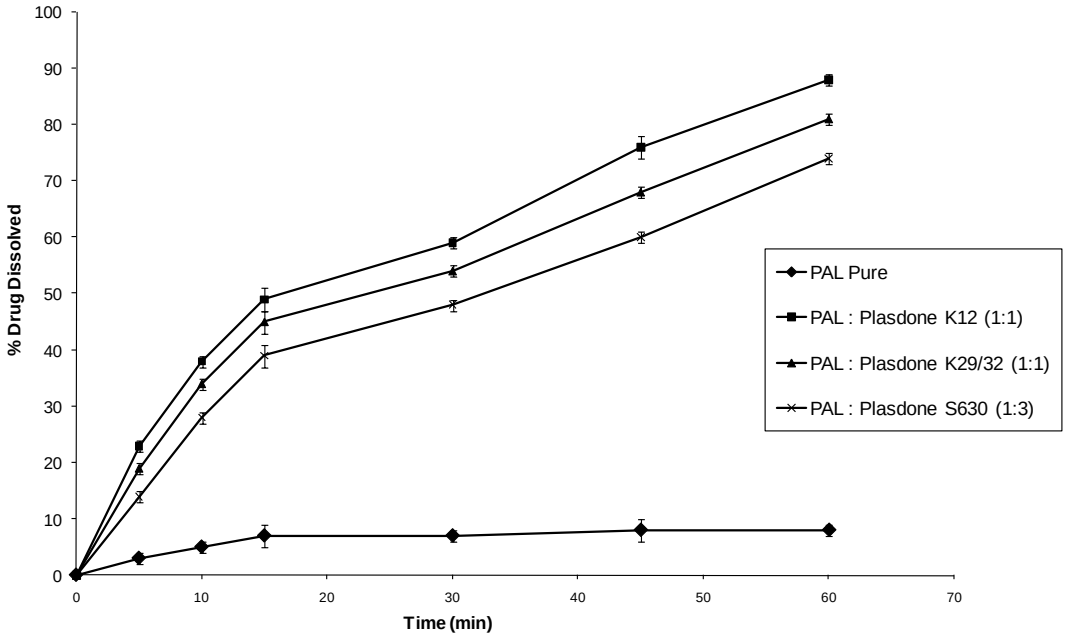

Table 3: Dissolution parameters of PAL and Spray dried mixtures

Batch	$T_{50\%}$ (min.)[a]	$T_{80\%}$ (min.)[a]
Pure PAL	NA	NA
PAL: K12 1:1	16.32	53.21
PAL: K29/32 1:1	24.36	58.26
PAL: S630 1:3	36.24	NA

a- time in min. to achieve 50% drug release and 80% drug release respectively.
NA – Not achieved.

Invitro Release Studies

Table 3 shows the T_{50}% and T_{80}% of PAL, and the different spray dried compositions and Fig. 6 shows the dissolution profile of pure PAL and the different spray dried compositions. The dissolution of PAL increased significantly (t-test; $P<0.05$) from all the spray dried compositions. Amorphous forms of pharmaceuticals are markedly more soluble than their crystalline counterparts [29] and improve the dissolution rate [23,30]. Out of the three grades of PVP, Plasdone K12 gave the maximum enhancement in rate of drug release as evidenced by the $T_{80\%}$ values. This could be due to the relative lower molecular weight of Plasdone K12.

CONCLUSION

Spray drying of PAL with different grades of Plasdone, especially Plasdone K12, not only reduced the drug crystallinity but also significantly improved the dissolution. Thus, the study showed that Plasdone K12 was found to be a better carrier for PAL.

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