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Spray drying as an approach for enhancement of dissolution and bioavailability of Raloxifene hydrochloride.

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Abstract

The present study investigated the effect of spray drying raloxifene HCl (RHCL) with different classes of hydrophilic carriers (different grades of polyvinyl pyrrolidones) and cellulosic polymers) in order to determine the potential effect on dissolution rate and bioavailability of RHCL. Pre-formulation studies were conducted to select the appropriate carriers and drug:carrier ratio for preparing the spray dried compositions.The solid state interactions of the spray dried mixtures were evaluated by DSC & XRD. Preformulation studies revealed that amorphous compositions of RHCL could be obtained only with Plasdones (K12, K29/32 and S630). DSC studies showed that the crystalline nature of RHCL 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 RHCL. The pharmacokinetics of spray dried composition (1:1 RHCL: K12) and pure RHCL was evaluated following oral administration (25 mg/kg) in healthy female Sprague Dawley rats. The extent of the mean plasma exposures of RHCL was 7-fold higher in animals treated with spray dried mixture of RHCL, K12 (1:1) compared to animals treated with RHCL. Spray drying of RHCL with Plasdones, especially Plasdone K12, reduced drug crystallinity, increased the rate and extent of dissolution, and improved bioavailability..

Keywords: : Dissolution enhancement, Bioavailability, Spray drying, roloxifene, poorly soluble drug.

Introduction

Raloxifene hydrochloride (RHCL) is a selective estrogen receptor modulator (SERM) shown to be effective in the prevention of osteoporosis, with potential utility as a substitute for long-term female hormone replacement therapy [1-3]. However, it is a drug with low water solubility and high membrane permeability included in class II of Biopharmaceutical drug classification system. It has an absolute bioavailability of approximately 2% in humans and its bioavailability could consequently be increased by improving its solubility [4]

Poorly soluble drugs may benefit from formulation approaches that overcome poor solubility and dissolution rate limited bioavailability. The solubility of a compound in the amorphous form is higher than in the more stable crystalline form because the Gibb's free energy is higher [5]. The dissolution rate of an amorphous compound is improved relative to the crystalline form and it can be further improved if the amorphous compound is dispersed in a hydrophilic polymer [6].

Solubility can be enhanced by using several methods. Techniques such as micronization [7,8], co-grinding [9-11], solid dispersions [12], complexation, spray drying, super critical fluid technology and lipid –based drug delivery system have commonly been used to improve the dissolution and bioavailability of poorly water soluble drugs.

Spray drying is a particle processing technology that transforms a liquid feedstock into a powder product by first spraying the feedstock to create droplets, and then evaporating the feedstock liquid through the use of a heated drying medium, typically air. The liquid feedstock can take the form of a solution, suspension, liquid-paste, or emulsion, and must be pumpable and capable of droplet formation [13]. Spray drying has gained more importance as a method of microencapsulation. This method has already been used to prepare micro particles with polyesters, polymethacrylates, cellulose derivatives and biopolymers containing both hydrophilic

and lipophilic drugs and macromolecules. Compared with other techniques, like solvent evaporation, it has many advantages, including shorter duration, reliability and reproducibility, cost effectiveness of process preparation, particle size control, good yield of production and the possibility of being free of organic solvent [14,15]. Examples of successfully tested drugs which improved their dissolution by spray drying technique are indomethacin [16], tolbutamide [17], carbamazepine [18], ketoprofen [19] and Albendazole [20].

In an earlier study [4], we had investigated the effect of co-grinding of RHCL with different hydrophilic carriers such as PVP, HPMC, HPC and sodium alginate and found that significant enhancement in dissolution of RHCL was observed with co-ground mixtures of PVPs. The aim of the present study was to investigate the feasibility of improving the rate of dissolution and bioavailability of RHCL using hydrophilic polymers like PVP (different grades), Hydroxy propyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC) and Hydroxypropyl methyl cellulose Acetate succinate (HPMC AS).

Experimental

Materials

Raloxifene (Glochem Industries Ltd., Hyderabad, India) was purchased from the source indicated. HPMC (Pharmacoat 603), Hydroxypropyl cellulose (HPC, Klucel EF) and Hydroxypropyl methyl cellulose acetate succinate (HPMC AS, LF, MF and HF) were purchased from Signet (Mumbai, India). Polyvinyl pyrrolidones (Plasdone K12, K29/32 and S-630) were in-house materials (International Specialty Products, New Jersey, US). All other reagents used were of analytical grade.

Solubility of Raloxifene

The solubility of RHCL 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 Raloxifene 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 and S 630, HPMC (Pharmacoat 603 and 606), HPC (Klucel EF), HPMC acetate succinate (HPMC AS – LF, MF, HF). The drug polymer mixtures were dissolved in a mixture of methanol and DMF. The solution was then poured on glass slides using a dropper and allowed to dry under vacuum for 3 hours at 60℃. The dried films were then subjected to DSC at a heating rate of 10℃ / min.

Preparation of RHCL spray-dried compositions

Polymeric solution of the different PVP grades (Plasdone K12, K29/32 and S630) was prepared by dissolving the polymer in methanol (0.5 or 1.5% w/v according to the ratio desired). RHCL 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 RHCL: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℃ and outlet nitrogen temperature of 120℃). The dried products were collected in the collection vessel and weighed.

Assay of spray-dried compositions (HPLC)

RHCL content in the spray dried compositions were performed with HPLC (Waters, Milford,USA) using 5-µm, 250 X 4.6mm i.d Inertsil C8 column (GL Sciences Inc., Japan) by a gradient elution method reported earlier (Kerry et al. 2000). The gradient elution utilized acetonitrile and a 75 mM phosphate buffer adjusted to pH 3.0 with 85% phosphoric acid. The initial mobile phase composition of 25% acetonitrile was maintained for 5 min, and then increased by 0.8%/min to final composition of 50% acetonitrile. RHCL was monitored using a UV detector at a wave length of 280 nm.

Estimation of Methanol and DMF in spray dried compositions using HSS-GC

Organic volatile impurities (methanol 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℃ for 20 minutes and increased at the rate of 10℃ per minute up to 240℃ and held for further 20 minutes. Injector and detector temperatures were maintained at 140 and 250℃, respectively and column flow was maintained 4.9 ml/minute.

Differential Scanning Calorimetry

Thermal curves of each spray fried sample was recorded by simultaneous Differential Scanning Calorimeter (TA Instruments Q 1000, Bangalore, India). Each Sample (~ 2-3 mg) was scanned in aluminum pan at a heating rate of 10C/min over the range of 50-300^{0}C with an empty aluminum pan used as reference. Samples were heated under nitrogen atmosphere (flow rate of N_2-50mL/min).

X-Ray Diffraction (XRD)

Powder XRD patterns were traced employing X-ray diffractometer (Model No. 3000, Seifert, Germany) for the samples, using Ni-filtered Cu-K radiation, a voltage of 40kV, a current of 30mA radiation scattered in the crystalline regions of the sample, which 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 80° at ambient temperature.

FT-IR Spectroscopy

FT-IR spectra were obtained using FT-IR spectrometer (Nicolet 5700, Thermo Scientific, Madison, WI, USA) by the conventional KBr pellet method. The samples were ground gently with anhydrous KBr and compressed to form pellet. The scanning range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1}.

In-Vitro Dissolution Studies

In-Vitro dissolution testing employed the United States Pharmacopeia (USP) Apparatus II (VK 7010 Varian, Cary, NC, USA) at 50 rpm with 1000 mL of water with 0.1% Tween 80 at 37 ± 0.5^{0}C. Six capsules of each batch containing powder sample equivalent to 50mg RHCL were tested. The sample of the dissolution media was removed using an automated sampling system at a predetermined time interval (0, 5, 10, 15, 30, 45 and 60 min) and was simultaneously analyzed spectrophotometrically at λ_{max} of 285nm (Cary 50 UV- Spectrophotometer attached with dissolution Apparatus; Cary, NC, USA). The time required for 80% of drug to be released ($T_{80\%}$) was considered for comparing the dissolution results. The $T_{30\%}$ 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) [20].

$Y=min+max-min / 1+10^{[log\ ec_{50}-x]}x\ hillslope$

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 (Ssniff rats pellet food, Ssniff Spezialdiaten, Germany). The rats were housed in a cage and maintained on a 12h light/dark at room temperature (21^{0}C to 24^{0}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 (25mg/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^{0}C for 10min. Plasma was transferred to individual Eppendorf tubes and stored below -70^{0}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 150mm X 4.6mm Kromasil C_{18} Column (Thermo) using isocratic elution with 80:20 methanol and aqueous 10mM ammonium acetate (pH 5.0). Raloxifene 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 2000 mg/ml.

Pharmacokinetic data analysis

The area under the drug concentration-time curve from zero to 24 h (AUC_{0-24h}) and mean residence time (MRT) were calculated using noncompartmental 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

Pre-formulation studies

The solubility of RHCL 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 RHCL.
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 (DSC thermograms not shown).

Spray dried compositions

The prepared spray dried compositions were evaluated for their volatile content since a combination of methanol and DMF was used as the solvent system for spray drying, by a head space GC. Methanol 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 methanol 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 methanol in the spray dried compositions was in the range of 475 to 512 µg/ml of methanol and the level of DMF was in the range of 60 to 75µg/ml. A representative chromatogram is shown in Figure 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 dried compositions. The spray dried compositions had drug content of 98.0 to 102.0% of RHCL, suggesting that the spray drying process was successful in achieving good encapsulation of the drug.

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 RHCL and the carriers in the solid state (Figure 2). RHCL exhibited a single sharp melting endothermic peak at 267^0C. 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 [4]. 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 RHCL, suggesting the amorphous nature of RHCL 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 S630.

X-Ray Diffraction (XRD)

XRD studies were undertaken to consolidate the DSC data indicating the reduction of the crystallinity of RHCL with Crospovidone. Therefore, the XRD patterns of RHCL, Plasdone K12 and the spray dried mixture with drug and Palsdone K12 were observed. The diffraction spectrum of RHCL showed that the drug was crystalline in nature, as demonstrated by numerous distinct peaks observed at 2θ of 13.4, 14.4, 15.7, 19.0, 20.9, 21.1, 22.6 and 25.9 (Figure 3A). XRD pattern of Plasdone K12 and the spray dried composition showed no sharp peaks, indicating its amorphous nature (Figures 3 B and C).
Further, no new peaks could be observed, suggesting the absence of interaction between the drug and the carrier [12, 22, 23]. This suggests that the crystal quality of RHCL is reduced in the spray dried mixture [24-26]. These results are similar to DSC results.

FT-IR Spectroscopy

FT-IR studies showed that there was no significant changes in the spectrum of spray dried mixture with Plasdone K12 when compared with drug alone. The absence of shifts in the wave numbers of the FT-IR peaks (Figure 4) of the spray dried mixture indicates the lack of significant interaction between the drug and the carrier in the mixture [25,26].
Thus these results ratify the absence of any well-defined interaction between RHCL and the grade of Plasdone used.

Table 1. Solubility of raloxifene 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	260
DMSO	715
DMF + Methanol	110
DMF + DCM	10
DMF + Acetone	10

In vitro release studies

Table 3 shows the T_{80}% of RHCL, and the different spray dried compositions and Figure 5 shows the dissolution profile of pure RHCL and the different spray dried compositions.

The dissolution of RHCL 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 [27] and improve the dissolution rate [9,12]. 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.

Pharmacokinetic study

The pharmacokinetic parameters of RHCL were determined after oral administration of RHCL and spray dried mixture of RHCL with Plasdone K12 in the ratio of 1:1. It was selected on the basis of in-vitro dissolution studies as discussed above. The plasma concentration time data of RHCL are shown in Figure 6 and their mean pharmacokinetic parameters are shown in Table 4.

Table 2. Film studies of Raloxifene with different Polymers

Drug: Polymer	Ratios		
	1:1	1:3	3:1
RAL:K29	Amorphous	Amorphous	Amorphous
RAL:K12	Amorphous	Amorphous	Endothermic transition at 225.35 deg C
RAL: S 630	Endothermic transition at 245.80 deg C	Amorphous	Endothermic transition at 252 deg C
RAL:HPMC	Endothermic transition at 252.87 deg C	Endothermic transition at 260.88 deg C	Endothermic transition at 258.54 deg
RAL:HPC	Endothermic transition at 255.07 deg C	Endothermic transition at 254.98 deg C	Endothermic transition at 261.77 deg C
RAL:HPMC AS LF	Endothermic transition at 257.35 deg C	Endothermic transition at 252.55 deg C	Endothermic transition at 261.44 deg C
RAL:HPMC AS MF	Endothermic transition at 257.22 deg C	Endothermic transition at 252.90 deg C	Endothermic transition at 263.06 deg C
RAL:HPMC AS HF	Endothermic transition at 261.02 deg C	Endothermic transition at 257.20 deg C	Endothermic transition at 278.16 deg C

Table 3. $T_{80\%}$ data of Spray dried compositions of raloxifene

Sample	$T_{80\%}$
RHCL	Not achieved
RHCL: K12 1:1	22.32
RHCL: K29 1:1	35.94
RHCL: S630 1:3	35.24

Table 4. Pharmacokinetic parameters of raloxifene with 90% confidence intervals (CI) in female Sprague Dawley rats following oral administration of co ground mixture and Raloxifene Pure drug in 1% gelatin gel sandwich (Dose: 25 mg/kg free base)

Sample	T_{max} (h)	C_{max} ng/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ ng.h/mL)	$MRT_{0\text{-t}}$	T1/2 (h)
R HCl : K12 1: 1	4 (2.0 -12.0)	116 ± 44.6	931 ± 72.2	1006 ± 66.6	7.9 ± 2.0	4.5 ± 1.9
RHCL	8 (4.0 - 8.0)	16.9 ± 7.30	138 ± 26.7	184 ± 13.5	9.8 ± 2.1	8.8 ± 2.8

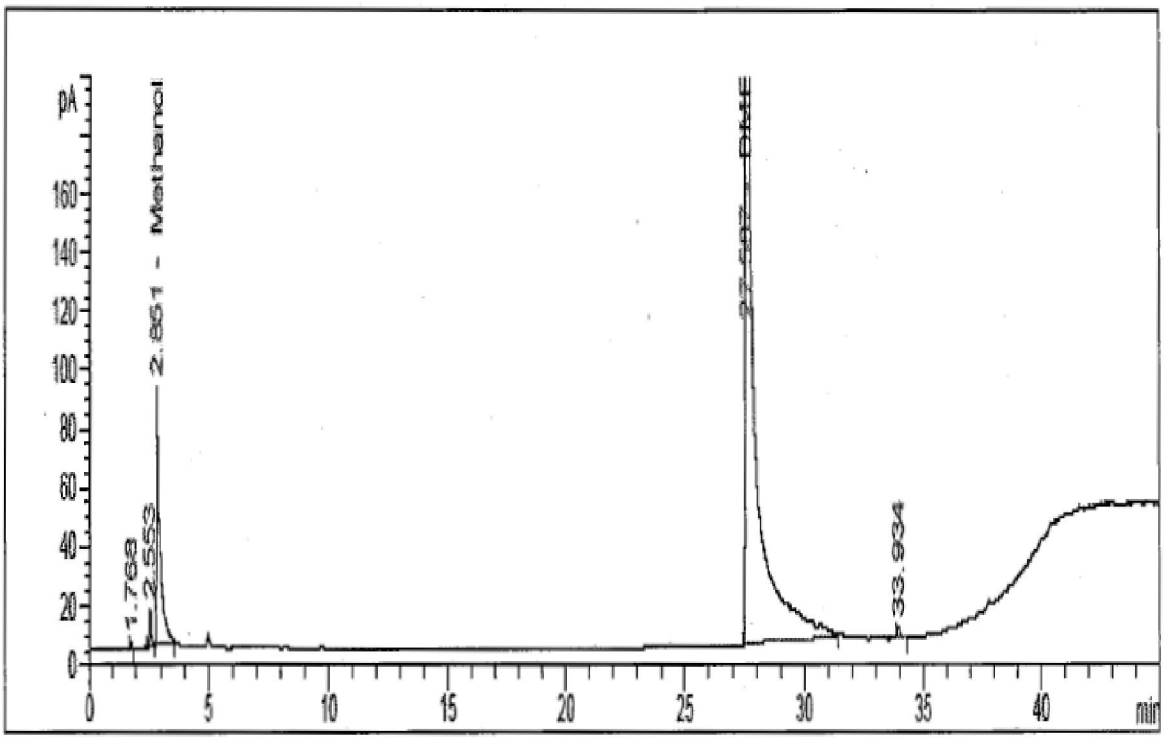

Figure 1. Representative GC chromatogram of RHCL spray dried mixture showing elution of methanol and DMF

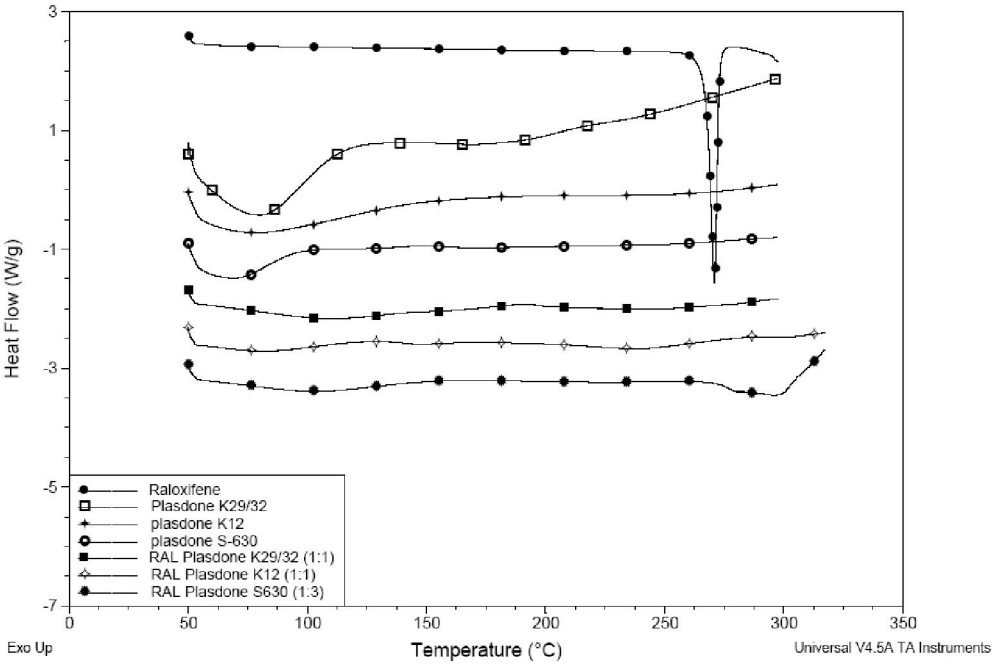

Figure 2. DSC of RHCL, Plasdone grades and Spray dried compositions

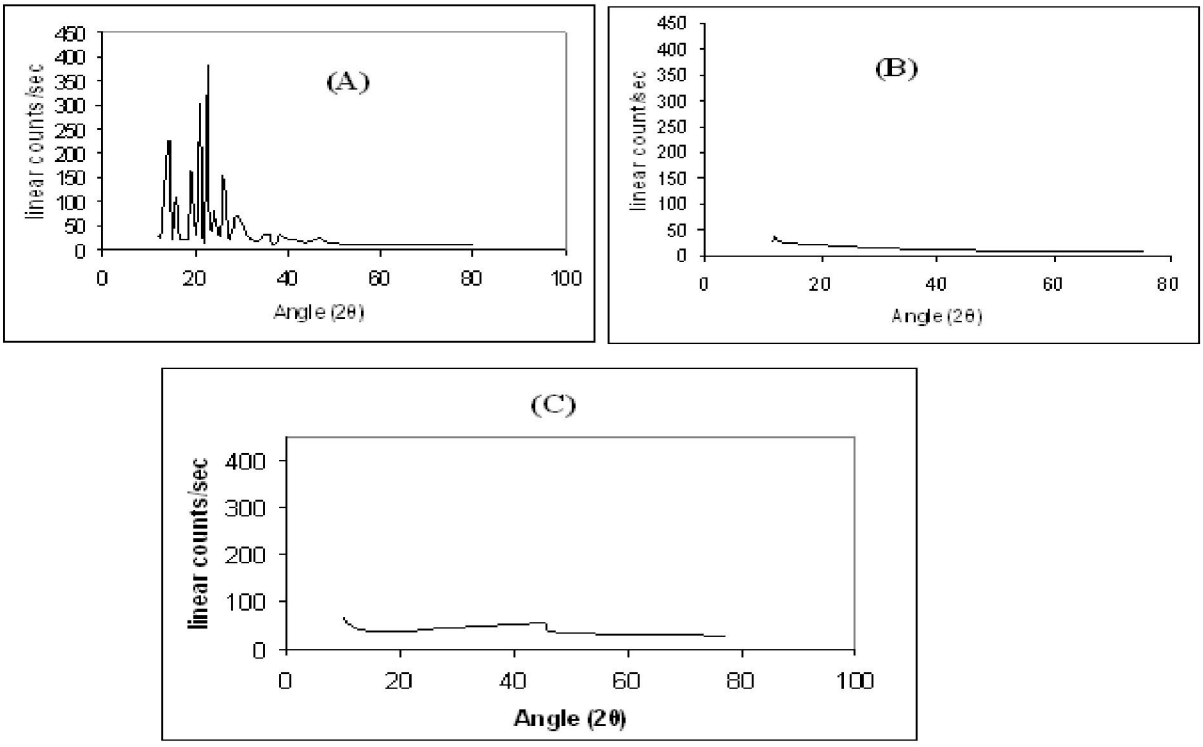

Figure 3.XRD Spectra of (A) RHCL; (B) PVP K12; (C) Spray dried RHCL : K12 1:1

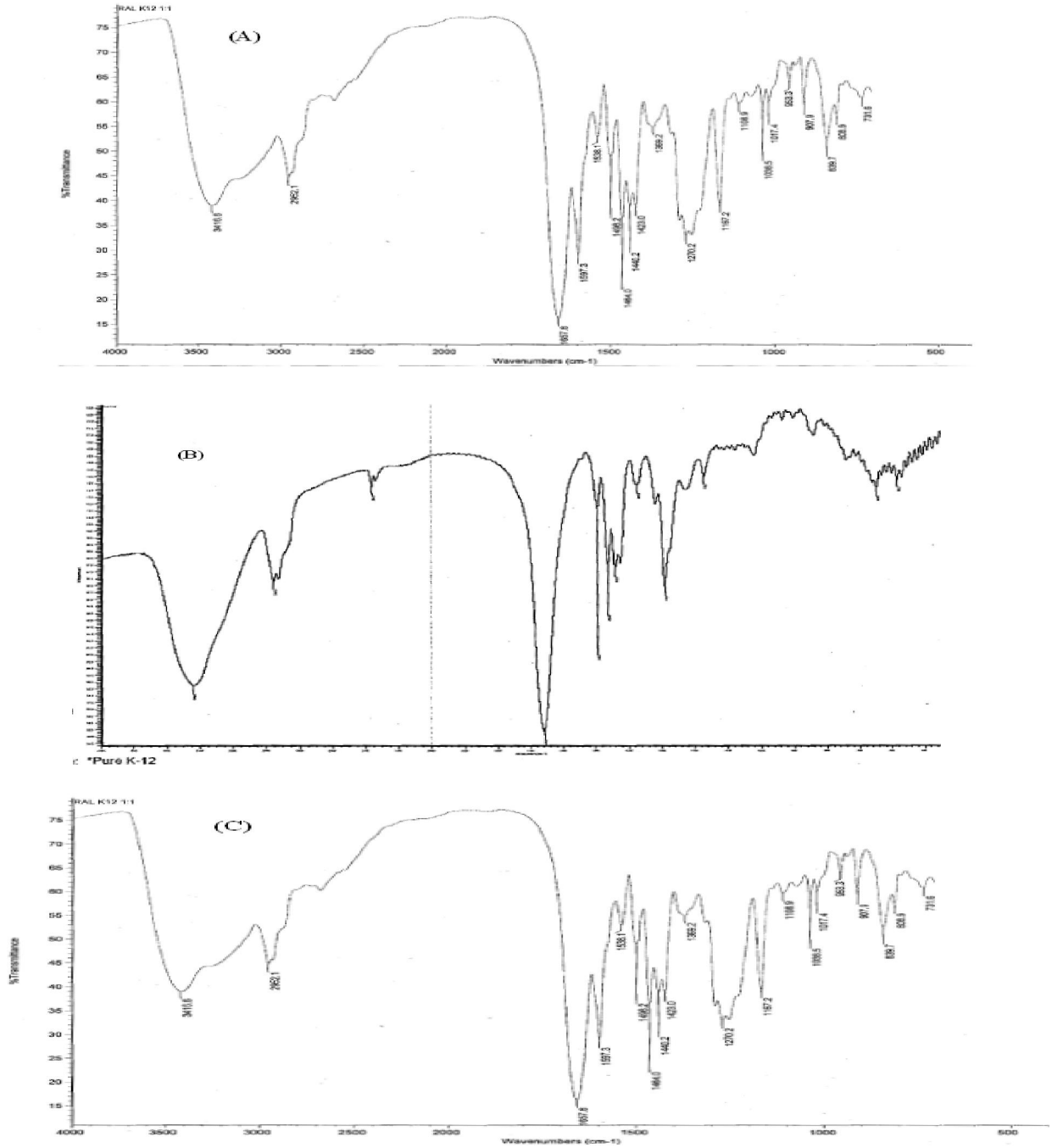

Figure 4. FTIR spectra of (A) RHCL; (B) PVP K12; (C) Spray dried RHCL : K12 1:1

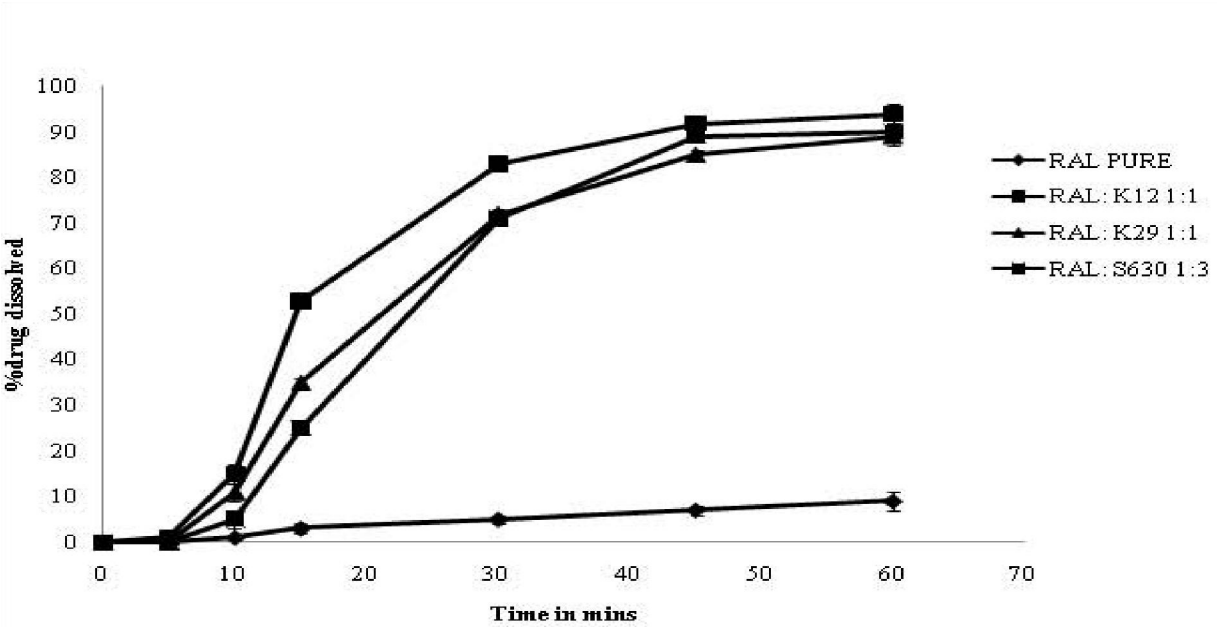

Figure 5. Dissolution of spray dried RHCL compositions in 1000 ml water

RHCL

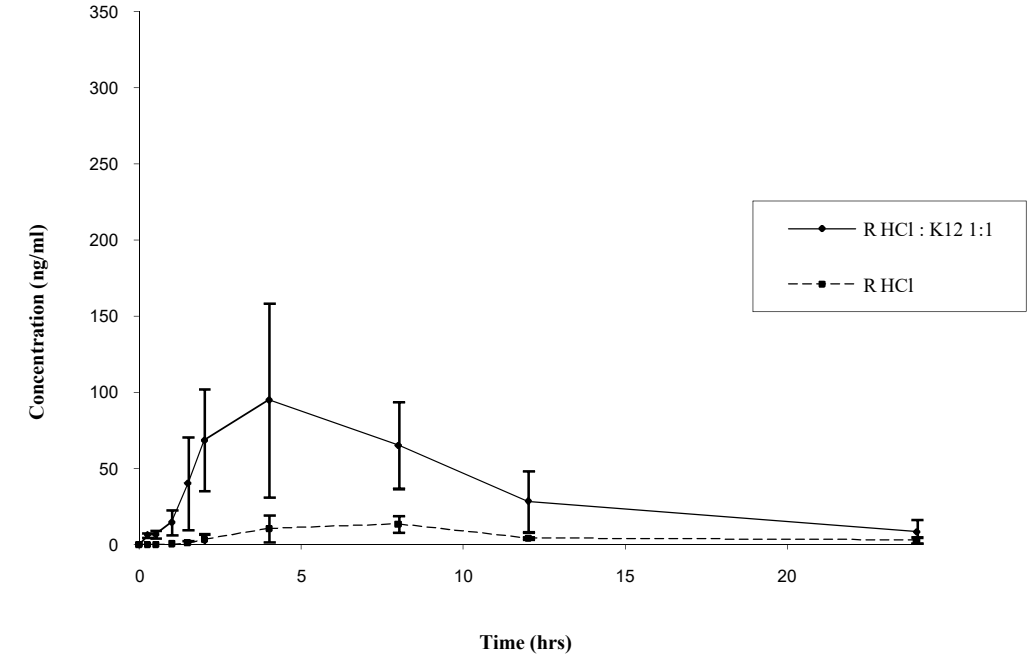

Figure 6. Pharmacokinetic evaluation of RHCL & RHCL:K-12 spray dried mixture in female Spargue Dawley rats following oral administration

The extent of the mean plasma exposures of raloxifene was 7 fold higher in animals treated with spray dried RHCL compared to animals treated with pure RHCL. Thus, the mean Plasma $AUC_{0\text{-last}}$ in animals that received the spray dried RHCL and pure RHCL was 931 ± 72.2 ng.h/mL and 138 ± 26.7 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 spray dried RHCL with Plasdone K12 as compared to RHCL. The corresponding mean C_{max} values for these treatment groups were 116 ± 44.6 ng/ml, and 16.9 ± 7.3 ng/ml and these were significantly different (p = 0.0052 by *ANOVA*). Bonferroni's multiple pair comparison tests showed significant increase with the spray dried composition compared to RHCL.

Conclusion

In the conclusion, the spray dried form of raloxifene HCl with Plasdone K12 in a ratio of 1:1 reduced drug crystallinity, increased the rate and extent of dissolution significantly than that of pure drug which might be due to the nano size of dispersion. The pharmacokinetics of spray dried composition (1:1 RHCL: K12) by following oral administration was evaluated in rats. The results revealed that extent of the mean plasma exposures of RHCL was 7-fold higher in animals treated with spray dried mixture of RHCL, K12 (1:1) compared to animals treated with RHCL. The result indicated that the spray drying techniques using different hydrophilic carriers like Plasdone K12 would be a promising approach to increase rate of dissolution and enhancement bioavailability development of solid oral dosage form contains poorly water soluble drugs likes raloxifene HCl.

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Conflict of Interests: The author declare no conflict of interests

References

[1]. Kerry JH, Gordon NA, Steven WB, Ross AJ, Wayne DL, Neil GP, Eugene CR, Cheryl AT, Paul KST, Robert EW. Influence of peroxide impurities in povidone and crospovidone on the stability of raloxifene hydrochloride in tablets: identification and control of an oxidative degradation product. Pharm Dev Tech. 2000; 5(3): 303-308.

[2]. Delmas PD, Bjarnason N H, Mitlak B, Ravoux AC, Shah A, Huster W, Draper M, Christiansen C. Effects of Raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N.Engl. J. Med 1997; 337: 1641–1647.

[3]. Mitlak BH, Cohen FJ. In search of optimal long term female hormone replacement: the potential of selective estrogen receptor modulators.Horm Res 1997; 48:155–163.

[4]. Garg A, Singh S, Rao VU, Bindu K, Balasubramaniam J. Solid State Interaction of Raloxifene HCl with Different Hydrophilic Carriers during Co-grinding and its Effect on Dissolution Rate. Drug Dev. Ind. Pharm 2009; 35(4): 455-470.

[5]. Martin A. 2003 Physical Pharmacy fourth ed. Williams and Wilkins Baltimore. p.231-240.

[6]. Patterson JE, James MB, Forster AH, Lancaster RW, Butler JM., Rades T. Preparation of glass solutions of three poorly water soluble drugs by spray drying, melt extrusion and ball milling. Int J. Pharm. 2007; 336: 22-34.

[7]. Chaumeil JC. A method of improving the bioavailability of poorly soluble drugs. Methods Find. Exp. Clin. Pharmacol .(1998) 20: 211–215

[8]. Otsuka M, Kaneniwa N. Effects of grinding on the physicochemical properties of cephalexin. Chem. Pharm. Bull. 1984; 32: 1071–1079.

[9]. Friedrich H, Nada A, Bodmeier R. Solid state and dissolution rate characterization of Co-ground mixtures of nifedipine and hydrophilic carriers. Drug Dev.Ind.Pharm. 2005; 31: 719-728.

[10]. Sugimoto M, Okagaki T, Narisawa S, Koide Y, Nakajima K. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel co-grinding method using water-soluble polymer. Int. J. Pharm 1998; 160: 11–19.

[11]. Suzuki H, Ogawa M, Hironaka K, Ito K , Sunada H. A nifidipine co-grpund mixture with sodium deoxycholate. I. Colloidal particle formation and solid state analysis. Drug Dev Ind Pharm. 2001; 27 (9): 943-949.

[12]. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of poorly water-soluble drug using water soluble carriers. Eur. J Phar. Biopharm. 2007; 65: 26-38.

[13]. Masters K 2002. Spray drying in practice. In: SprayDry Consult

International ApS (Eds.), Charlo ttenlund, Denmark.

[14]. Giunchedi P, Conte U. Spray drying as a preparation method of microparticulate drug delivery systems: An overview. S. T. P. Pharm. Sci . 1995; 5 : 276-290.

[15]. Giunchedi P, Conti B, Genta I, Conte U, Puglisi G. Emulsion spray drying for the preparation of albumin loaded PLGA microspheres. Drug Dev. Ind. Pharm. 2001; 27: 745-750.

[16]. Alanzi FK, El-Badry M, Ahmed MO, Alsarra IA. Spray-dried HPMC microparticles of indomethacin: impact of drug-polymer ratio and viscosity of the polymeric solution on dissolution. Sci. Pharm. 2007; 75: 63-79.

[17]. Chen R, Tagawa M, Hoshi N, Ogura T, Okamoto H, Danjo K. Improved dissolution of an insoluble drug using a 4-fluid nozzle spray drying technique. Chem. Pharm. Bull 2004; 52: 1066-1070.

[18]. Filipovic-Grcic J, Perissutti B, Moneghini M, Voinovich D, Martinac A, Jalsenjak I. Spray dried carbamazepine loaded chitosan and HPMC microspheres: preparation and characterization. J. Pharm. Pharmacol. 2003; 55: 921-931.

[19]. Moretti MD, Gavini E, Juliano C, Pirisino G, Giunchedi P. Spray dried microspheres containing ketoprofen formulated into capsules and tablets. J. Microencapsui. 2001;18:111-121.

[20]. Alanzi FK, El-Badry M, Alsarra IA. Improvement of Albendazole dissolution by preparing microparticles using spray-drying technique. Saudi Pharm. J. 2006; 14: 100-107.

[21]. Balasubramaniam J, Bindu K, Rao VU, Ray D, Haldar R, Brzeczko AW. Effect of superdisintegrants on dissolution of cationic drugs. Dissol. Technol. 2008; May: 18-25.

[22]. Hancock BC, Zografi G. Characteristic and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci. 1997; 86: 1–12.

[23]. Williams AC, Timmins P, Lu M, forbes RT. Disorder and dissolution enhancement: Deposition of ibuprofen on to insoluble polymers. Eur. J. Pharm. Sci. 2005; 26: 288-294.

[24]. Betageri GV, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int. J. Pharm 1995; 126: 155–160.

[25]. Valizadeh H, Nokhodchi A, Qarakhani N, Zakeri-Milani P, Azarmi S, Hassanzadeh D, Lobenberg R. Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, lactose, sorbitol, dextrin, and Eudragit® E100. Drug Dev. Ind. Pharm 2004; 30: 303–317.

[26]. Vippangunta SR, Maul KA, Tallavajhala S, Grant DJW. Solid state characterization of nifedipine solid dispersion. Int. J. Pharm. 2002; 236: 111-126.

[27]. Hancock BC, Parks M. What is true solubility advantage for amorphous pharmaceuticals? Pharm Res. 2000; 17 (4): 397-403.