Enhanced Dissolution and Bioavailability of Raloxifene Hydrochloride by Co-grinding with Different Superdisintegrants

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The present study investigated the effect of co-grinding raloxifene HCL (RHCL) with different superdisintegrants, namely crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG), using a ball mill, in order to determine the potential effect on dissolution rate and bioavailability of raloxifene hydrochloride (RHCL). The dissolution studies of the co-ground compositions and the corresponding physical mixtures were carried out in U.S. Pharmacopeia (USP) Type II apparatus. The solid state interactions of the co-ground and the physical mixtures were evaluated by differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The pharmacokinetics of co-ground mixture (1 : 5 RHCL : CP) and milled RHCL was evaluated following oral administration (25 mg/kg) in healthy female Sprague-Dawley rats. DSC studies showed that the crystalline nature of RHCL was reduced after co-grinding with superdisintegrants, while co-grinding with CP resulted in significant particle-size reduction of the mixture. Significant enhancement in dissolution rate was observed with co-ground mixture of RHCL with CP (1 : 5). The extent of the mean plasma exposures of RHCL was 7-fold higher in animals treated with co-ground mixture of RHCL, CP (1 : 5) compared to animals treated with milled RHCL. Co-grinding of RHCL with CP, reduced drug crystallinity, increased the rate and extent of dissolution, and improved bioavailability.

Key words raloxifene HCl; crospovidone; co-grinding

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]

Solubility can be enhanced by using several methods. Techniques such as micronization,[5,6] co-grinding,[7—9] solid dispersions,[10] 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.

Grinding is a well-established technique which is relatively cheap, fast and easy to scale-up. However, desired changes sometimes not only occur in physical properties, such as specific area and shape, but also occur in the reduction of drug stability, or polymorphic transformation may also occur.[11—13] Compared with other solubilization techniques, the co-grinding method does not need organic solvent processes involving environmental and health concerns and also involves cheap and simple instruments whereas other techniques, for example, super critical fluids and spray drying technology involve very expensive sophisticated instruments. Co-grinding can be carried out under either dry or wet conditions with various milling devices, such as ball, jet and hammer mills. Milling of a substance that is dispersed in a nonsolvent (wet milling) prevents the formation of dust and particle agglomeration. A common disadvantage of wet milling process is the partial dissolution that can cause an uncontrolled recrystallization (especially during drying) or chemical instability. More, research work has been done using dry milling conditions for co-grinding.[7,14] The properties of milled product are dominated by the surface properties of the crystal face. In the case of poorly water soluble substances, the newly created surface is hydrophobic and thus poorly wettable. Because of aerophilicity of such hydrophobic substances, the dissolution rate is not increased as we would expect from the increase in total surface area according to Noyes–Whitney equation. Many authors have reported on the use of co-grinding method for the enhancement of dissolution rate of various drugs, for example, digoxin, estradiol, sprinolactone, ketoprofen, indomethacin and phenytoin. The enhancement of dissolution rate which results in improvement of bioavailability of poorly soluble drugs has been demonstrated by various investigators.[14—16]

In an earlier study[4] we had investigated the effect of co-grinding of RHCL with different hydrophilic carriers such as polyvinyl pyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), HPC and sodium alginate. As a continuation, the present study was undertaken to investigate the effect of co-grinding RHCL with different superdisintegrants, namely crospovidone (CP), croscarmellose sodium (CCS) and sodium starch glycolate (SSG), using a ball mill, in order to determine the potential effect on dissolution rate and bioavailability of RHCL.

Experimental

Materials Raloxifene (Glochem Industries Ltd., Hyderabad, India) was purchased from the source indicated. Croscarmellose sodium (Ac-di-sol®, FMC biopolymer) and SSG (Glycol YS®, Roquette) were purchased from Signet (Mumbai, India). Crospovidone (Polyplasdone XL) were in-house materials (ISP). All other reagents used were of analytical grade.

Methods. Preparation of Co-ground Mixtures RHCL (5, 15, 25 g) and superdisintegrants (5, 15, 25 g) having drug to disintegrant ratios of 1 : 1, 1 : 5 and 5 : 1 were co-ground at 200 rpm for 120 min using a planetary ball mill (Model-PM 100, Retsch, Haan, Germany). The 120 min consists

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four cycles each of 30 min. After completion of one cycle, the powder was removed from the wall of the vessel with spatula for proper grinding.

Preparation of Physical Mixture The corresponding physical mixtures were prepared by trituration in a mortar with a pestle for 30 min, using milled drug with respective superdisintegrants.

Particle Size Measurement The particle size of prepared mixtures was determined by laser diffractometer (Scirocco 2000(A), Malvern Instruments, Worcestershire, U.K.). The relative frequency of the diameter of the particle was obtained by calculation based on volume distribution. The particle size at 10% (d_{10}), 50% (d_{50}), and 90% (d_{90}) of total fraction were obtained. The particle size at 90% of total fraction was used. The values were the average of 10 measurements.

Differential Scanning Calorimetry (DSC) Thermal curves of each sample were recorded by simultaneous differential scanning calorimeter (TA Instruments Q 1000, Bangalore, India). Each sample (*ca.* 2—3 mg) was scanned in aluminum pan at a heating rate of 10 °C/min over the range of 50—300 °C with an empty aluminum pan used as reference. Samples were heated under nitrogen atmosphere (flow rate of N_2, 50 ml/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 40 kV, a current of 30 mA 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 FT-IR spectra were obtained using FT-IR spectrometer (Nicolet 5700, Thermo Scientific, Madison, WI, U.S.A.) 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, U.S.A.) at 50 rpm with 1000 ml of water with 0.1% Tween 80 at 37±0.5 °C. Six capsules of each batch containing powder sample equivalent to 30 mg RHCL filled into size 2 capsules 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, 60 min) and was simultaneously analyzed spectrophotometrically at λ_{max} of 285 nm (Cary 50 UV-spectrophotometer attached with dissolution apparatus; Cary, NC, U.S.A.). The time required for 30% of drug to be released ($T_{30\%}$) 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, U.S.A.).[17]

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

In this equation, y, represents the cumulative % drug released; x, the time in min; min, the baseline of % drug released at time 0 min; max, the plateau of % drug released at time 60 min 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 12 h light/dark at room temperature (21 to 24 °C) and relative humidity of 50 to 70% and acclimatized to study area conditions for at least 5 d 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 h post dose with free access to water. Individual oral doses of the test and reference samples were prepared (25 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 1 ml of water and dosed again. Serial blood samples (250 μl) 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 (200 mM) per ml of blood as anticoagulant. Blood samples were held on ice until centrifuged at 10000 rpm; 4 °C for 10 min. 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, U.S.A.) by multiple reaction monitoring (MRM) and Positive ionization mode. The samples were prepared for analysis by liquid–liquid extraction using *tert*-butyl methyl ether (TBME). Chromatography was performed on a 150 mm×4.6 mm Kromasil C_{18} Column (Thermo) using isocratic elution with 80 : 20 methanol and aqueous 10 mM 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 1 ng/ml to 2000 mg/ml.

Pharmacokinetic Data Analysis The area under the drug concentration–time curve from zero to 24 h ($AUC_{0\to24\,h}$) and mean residence time (*MRT*) were calculated using noncompartmental analysis (WinNonlin 2.1, Pharsight Corp., Mountain View, CA, U.S.A.). 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

Particle Size Measurement Table 1 enlists the particle sizes (d_{10}, d_{50}, and d_{90}) of drug before and after grinding, physical mixtures and co-ground mixtures in 1 : 1, 1 : 5 and 5 : 1 ratios of all disintegrants.

Drug before and after Grinding: Milling of drug alone in ball mill for 120 min at 200 rpm results in significant reduction of d_{90} (76 μm), approximately 60% when compared with that of unmilled RHCL (125 μm).

Mixtures of Drug and Disintegrants before (Physical Mixtures) and after Grinding (Co-ground Mixtures): The d_{90} of physical mixtures and co-ground mixtures of RHCL and CP

Table 1. Particle Size (Mean±S.D., n=10) of RHCL, Superdisintegrants and Prepared Mixtures of RHCL with Superdisintegrants

Batch name	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
Unmilled RHCL	7.32	37.31	125.47
Milled RHCL	1.48	14.25	75.71
CCS	16.52	38.74	101.09
PM RHCL : CCS 1 : 1	2.98	26.47	96.27
CM RHCL : CCS 1 : 1	2.29	24.84	84.27
PM RHCL : CCS 1 : 5	8.56	34.67	105.01
CM RHCL : CCS 1 : 5	9.10	34.40	87.99
PM RHCL : CCS 5 : 1	1.57	16.35	80.34
CM RHCL : CCS 5 : 1	1.57	15.78	83.08
SSG	25.05	44.16	75.19
PM RHCL : SSG 1 : 1	2.72	28.90	78.27
CM RHCL : SSG 1 : 1	2.04	24.24	66.99
PM RHCL : SSG 1 : 5	9.31	40.64	77.36
CM RHCL : SSG 1 : 5	8.97	39.53	72.73
PM RHCL : SSG 5 : 1	1.52	16.04	73.94
CM RHCL : SSG 5 : 1	1.50	14.86	69.05
CP	37.72	116.88	318.25
PM RHCL : CP 1 : 1	6.77	71.31	313.24
CM RHCL : CP 1 : 1	2.05	18.37	59.71
PM RHCL : CP 1 : 5	22.95	103.86	306.05
CM RHCL : CP 1 : 5	5.11	17.33	40.07
PM RHCL : CP 5 : 1	2.04	25.04	216.85
CM RHCL : CP 5 : 1	1.39	13.81	64.97

in 1 : 1 ratio were 313.24 and 59.71 μm respectively (Table 1). The results indicate that a significant reduction in d_{90} can be achieved with co-grinding of RHCL with CP. The d_{90} of physical mixtures of RHCL and CCS, SSG in 1 : 1 ratio were 96.27 and 78.27 μm, respectively. The d_{90} of corresponding co-grinding mixtures were 84.27 and 66.99 μm, respectively. The results indicate that there is no significant difference in the d_{90} of physical mixtures and corresponding co-ground mixtures of these superdisintegrants. Thus, co-grinding of RHCL and these two disintegrants was not effective to reduce particle size.

The d_{90} of physical mixtures of RHCL and CCS and SSG in ratios 1 : 5 and 5 : 1 were 105.01, 80.34 μm and 77.36, 73.94 μm respectively (Table 1). The d_{90} of corresponding co-ground mixtures were 87.99, 83.08 μm and 77.36, 73.94 μm, respectively. An increase or decrease in the amount of either CCS or SSG in physical and co-ground mixtures did not result in significant reduction of d_{90}.

The d_{90} of physical mixtures of RHCL and CP in ratios 1 : 5 and 5 : 1 were 306.05 and 216.85 μm respectively (Table 1) and the d_{90} of corresponding co-ground mixtures were 40.07 and 64.97 μm respectively. Thus, an increase or decrease in the amount of disintegrant in physical and co-ground mixtures resulted in significant reduction of d_{90}. The particle size by co-grinding with CP was reduced by approximately 47% when compared with milled drug. The reduction in particle size of drug with CP at 1 : 5 ratio was approximately 68% when compared with the particle size of unmilled drug. It was also evident that ball milling is not effective in reducing the particle size of CCS and SSG. When the drug alone ball-milled, mechanically micronized substances are electrostatically charged and, in most cases, they are agglomerated because of their cohesive behavior.[18] The agglomeration of particles during ball-milling can be prevented by using different disintegrants. These disintegrants gets absorbed onto the newly created particle surfaceses. In this study, among all the disintegrants CP is the best one since it resulted in significant particle size reduction.

Differential Scanning Calorimetry (DSC) DSC studies were performed on the individual components and on the freshly prepared co-ground and physical mixtures in order to study the interaction between RHCL and the carriers in the solid state (Figs. 1—3).

RHCL exhibited a single sharp melting endothermic peak at 267 °C. The DSC thermograms of superdisintegrants showed a broad endothermic peak in the range of 50—110 °C, which may be attributed to the endothermic relaxation. The DSC thermograms further indicated that all disintegrants are amorphous and both the physical and co-ground mixtures resulted in significant decrease in the intensity of the melting endothermic peak of RHCL. The study also further revealed that the extent of reduction in crystallinity was proportional to the concentration of superdisintegrant used.

X-Ray Diffraction (XRD) XRD studies were undertaken to consolidate the DSC data indicating the reduction of the crystallinity of RHCL with CP. Therefore, the XRD patterns of RHCL (unmilled and milled), CP physical mixture, and co-ground mixture in 1 : 5 ratio were observed. The diffraction spectrum of unmilled 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 (Fig. 4A). The milled drug also showed similar superimposable diffraction pattern indicating that the crystallinity of the drug was unaffected by milling of drug alone (Fig. 4B). XRD pattern of CP showed no sharp peaks, indicating its amorphous nature (Fig. 4C).

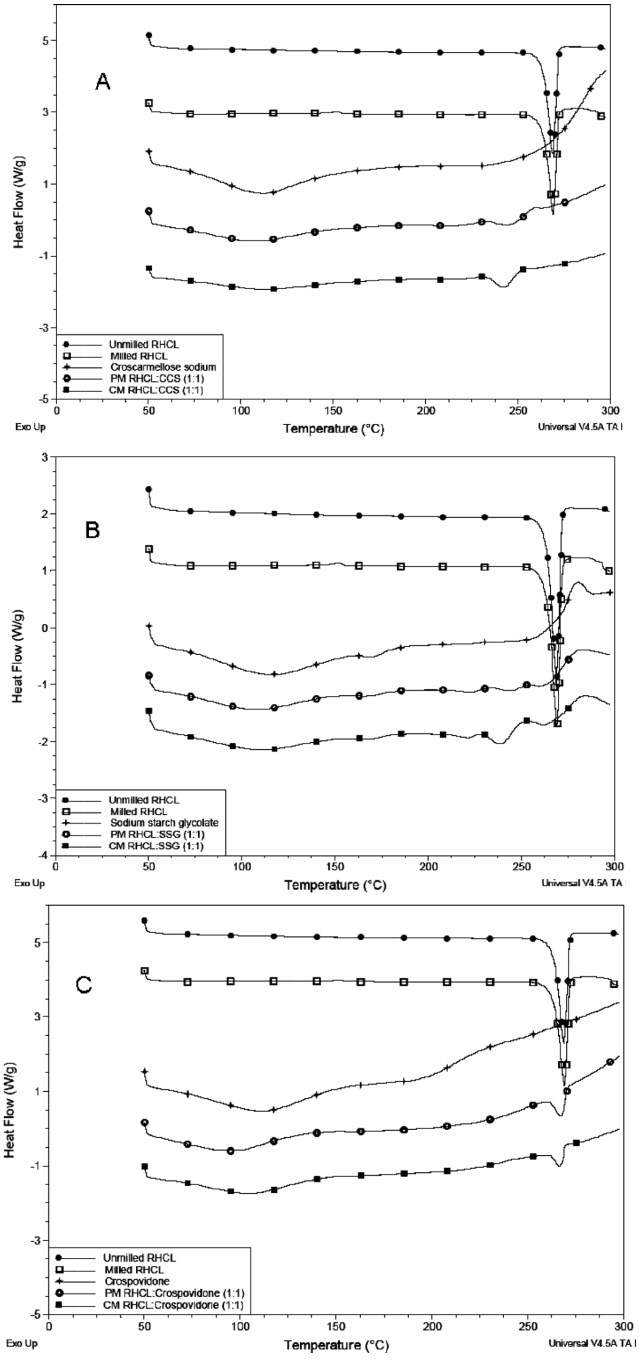

Fig. 1. DSC Thermograms of RHCL and in 1 : 1 Ratios with Different Superdisintegrants

A, CCS; B, SSG; C, CP.

All the principal peaks of RHCL were present in their physical mixtures and co-ground mixtures, although with lower intensity. No new peaks could be observed, suggesting the absence of interaction between the drug and the carrier.[10,19,20] The prominent peaks from RHCL at 2θ of 14.4, 15.7, 19.0, 21.1, and 22.6 were clearly seen at the same position in the physical mixture (Fig. 4D). However, in co-ground

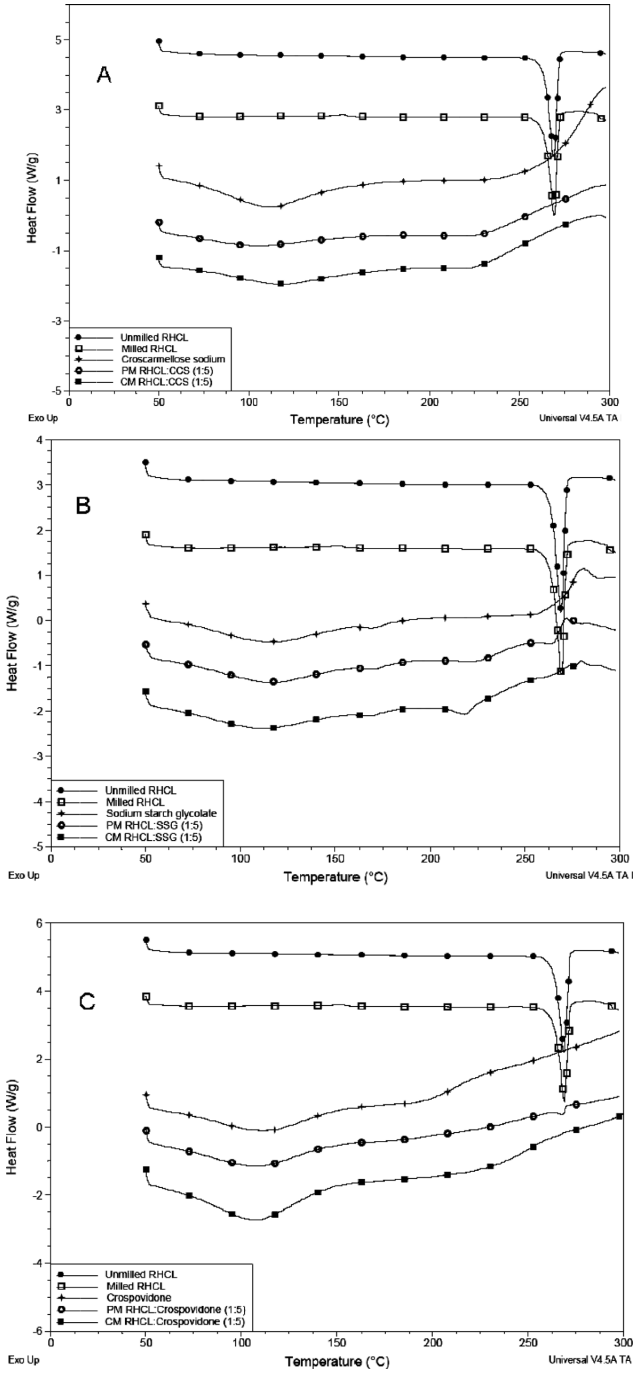

Fig. 2. DSC Thermograms of RHCL in 1 : 5 Ratios with Different Superdisintegrants

A, CCS; B, SSG; C, CP.

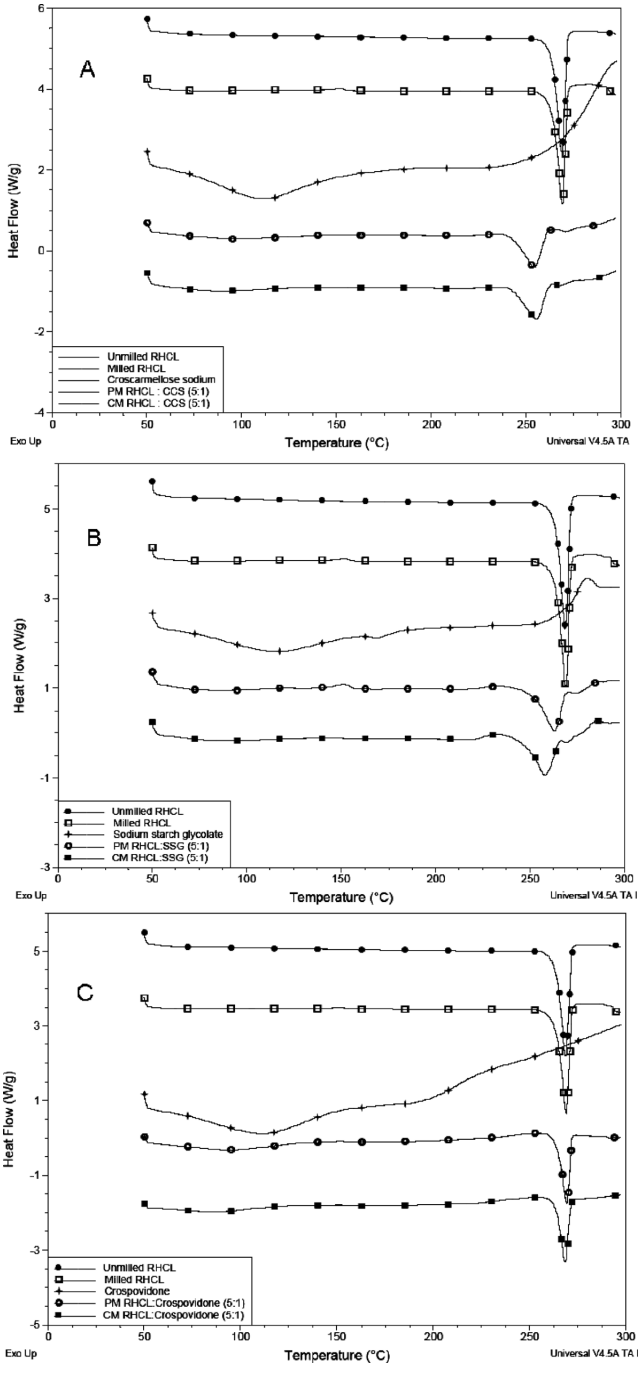

Fig. 3. DSC Thermograms of RHCL in 5 : 1 Ratios with Different Superdisintegrants

A, CCS; B, SSG; C, CP.

mixture, similar diffraction peaks were observed at 2θ of 14.4, 15.7, 21.1, and 22.6. These peaks were broadened and reduced in intensity when compared with the diffraction peaks of corresponding physical mixture (Fig. 4E). A relative reduction of diffraction intensity of RHCL in co-ground mixture than physical mixture at these angles suggest that either the crystal quality is reduced or change is induced in the crystal orientation or only some of the drug is still present in the crystalline form.[21—23] RHCL therefore existed in a very less crystalline state in co-ground mixture with CP. The corresponding physical mixture showed a higher degree of crystallinity than the co-ground mixture. These results are similar to DSC results.

FT-IR FT-IR studies showed that there was no significant change in the spectrum of co-ground mixture when compared with drug alone, as incorporation of RHCL into the disintegrants did not change the position of its functional groups. The absence of shifts in the wave numbers of the FT-IR peaks (Fig. 5) of the co-ground mixture vis-à-vis the physical mixture indicates the lack of significant interaction between the drug and the carrier in the mixture.[22,23] Thus these results ratify the absence of any well-defined interaction between RHCL and the disintegrants used, more particularly with CP.

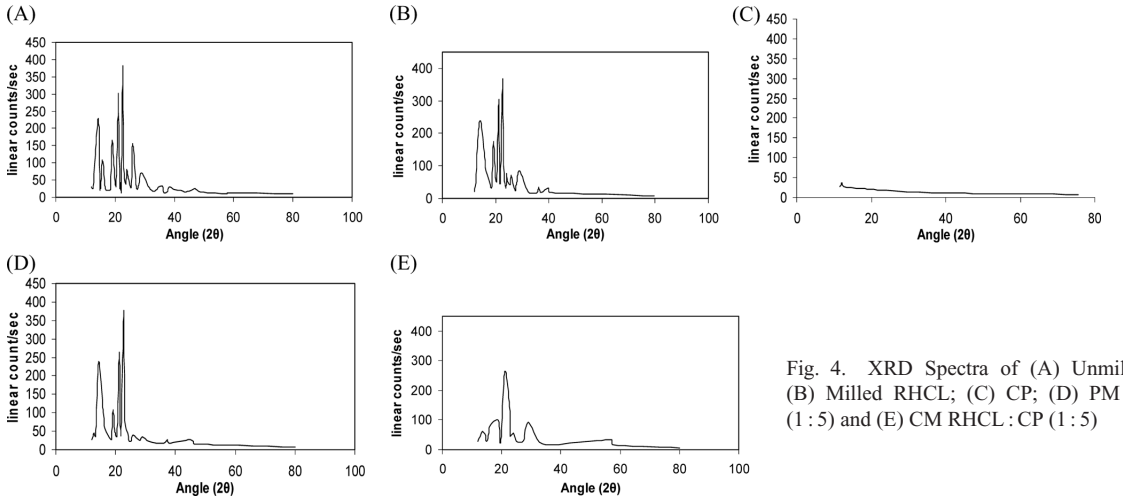

Fig. 4. XRD Spectra of (A) Unmilled RHCL; (B) Milled RHCL; (C) CP; (D) PM RHCL : CP (1 : 5) and (E) CM RHCL : CP (1 : 5)

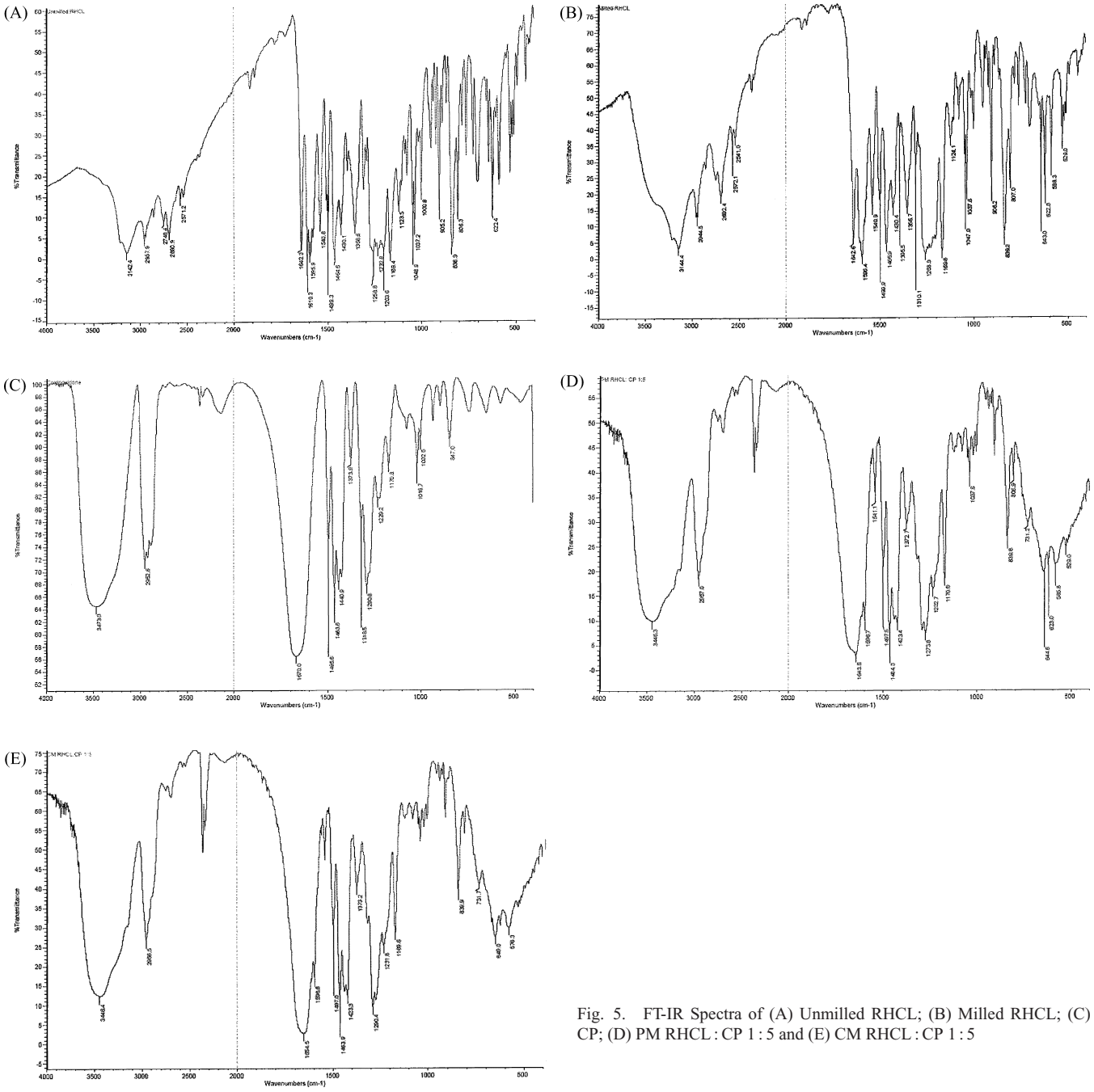

Fig. 5. FT-IR Spectra of (A) Unmilled RHCL; (B) Milled RHCL; (C) CP; (D) PM RHCL : CP 1 : 5 and (E) CM RHCL : CP 1 : 5

Table 2. $T_{30\%}$ of RHCL, Physical Mixtures and Co-ground Mixtures of RHCL with the Different Superdisintegrants Used in the Study

Sample	$T_{30\%}$
Unmilled RHCL	NA
Milled RHCL	NA
PM RHCL : CCS 1 : 1	NA
CM RHCL : CCS 1 : 1	NA
PM RHCL : CCS 1 : 5	NA
CM RHCL : CCS 1 : 5	NA
PM RHCL : CCS 5 : 1	23.5454
CM RHCL : CCS 5 : 1	16.6278
PM RHCL : SSG 1 : 1	NA
CM RHCL : SSG 1 : 1	NA
PM RHCL : SSG 1 : 5	NA
CM RHCL : SSG 1 : 5	NA
PM RHCL : SSG 5 : 1	23.5454
CM RHCL : SSG 5 : 1	16.6278
PM RHCL : XL 1 : 1	21.1812
CM RHCL : XL 1 : 1	17.0569
PM RHCL : XL 1 : 5	19.5776
CM RHCL : XL 1 : 5	10.4434
PM RHCL : XL 5 : 1	22.5191
CM RHCL : XL 5 : 1	19.6959

***In Vitro* Release Studies** Table 2 shows the $T_{30\%}$ of RHCL, physical mixtures and co-ground mixtures of RHCL with the different superdisintegrants used in the study and Figs. 6A and B show the dissolution profile of physical and co-ground mixtures of RHCL with different disintegrants in the ratio of 1 : 5.

$T_{30\%}$ was used for comparing the rate of drug release since in most of the cases drug release was less than 50%. In case of co-ground mixtures containing CCS and SSG, the drug release seemed to decrease with an increase in their concentration and none of these compositions were able to achieve even 50% of drug release. However, in case of co-ground and physical mixtures with CP, drug release increased with an increase in CP concentration. Out of the three ratios studied, co-ground mixtures containing RHCL and CP in the ratio of 1 : 5 improved the dissolution significantly (Fig. 6B). In general drug release from co-ground mixtures was always higher than their corresponding physical mixtures (Fig. 6A).

The decrease in drug release with an increase in concentration of both CCS and SSG could be attributed to the swelling nature of both these disintegrants. CCS, typically has a unique fiber shaped morphology and these individual fibers can act as hydrophilic channels to absorb water deeply into the system and has the tendency to swell to the extent of

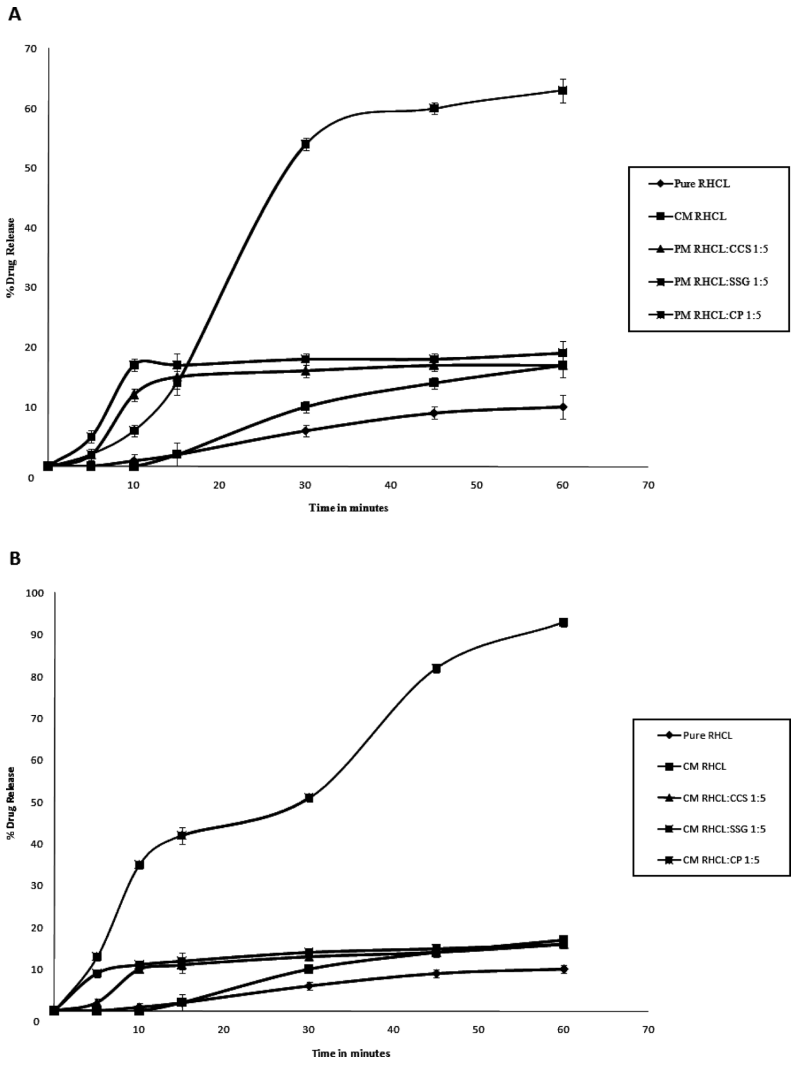

Fig. 6. Dissolution Profile of (A) PM RHCL : CP (1 : 5); (B) CM RHCL : CP (1 : 5)

Table 3. 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)	$AUC_{0—last}$ (ng·h/ml)	$AUC_{0—inf}$ (ng·h/ml)	$MRT_{0—t}$	$T_{1/2}$ (h)
RAL–PVPP XL (1 : 5)	2 (1.0—4.0)	254±177	1260±426	1304±407	5.6±1.2	3.8±1.9
Pure raloxifene	8 (4.0—8.0)	16.9±7.30	138±26.7	184±13.5	9.8±2.1	8.8±2.8

more than 100% of their original diameter, when exposed to water. Similarly, SSG, also because of its spherical morphology, has the tendency to absorb water and retain it and shows upto 250% increase in their original particle diameter, when exposed to water.[24,25] This tremendous volume increase in their particle diameter could serve as an impediment for the drug to release and could explain the decrease in drug release observed with an increase in their respective concentrations. However, CP because of its porous morphology tends to absorb water by a 'wicking' mechanism[26] when exposed to water without considerable swelling, thus enhancing the wettability of the hydrophobic drug. This further explains the fact that the drug release increases with an increase in the proportion of CP.

Drug release from both the physical and co-ground mixtures containing RHCL and CP in ratio of 1 : 5 seemed to show a 'biphasic' release pattern. In case of the physical mixture the initial release (up to 10 min) is much slower (approx. 5%, Fig. 6A) and starts to increase between 15 to 30 min, while in case of the co-ground mixture the initial release (up to 15 min) is higher followed by a gradual increase up to 30 min and again picks up.

As has been discussed above, when exposed to dissolution medium, CP tends to absorb water by 'wicking' mechanism. The relative amount of CP in both the mixtures is considerably higher when compared to the drug. In case of physical mixture the drug particles may not be intimately mixed with CP, as one would except in a co-ground mixture. This probably could explain the observed time lag and the initial high release from the physical and co-ground mixtures, respectively.

Pharmacokinetic Study The pharmacokinetic parameters of RHCL were determined after oral administration of RHCL and co-ground mixture of RHCL with CP in the ratio of 1 : 5. The co-ground RHCL : CP in ratio of 1 : 5 was selected on the basis of *in-vitro* dissolution studies as discussed above. The plasma concentration time data of RHCL are shown in Fig. 7 and their mean pharmacokinetic parameters are shown in Table 3.

The extent of the mean plasma exposures of raloxifene was 7 fold higher in animals treated with co-ground mixture of RHCL compared to animals treated with RHCL pure drug. Thus, the mean plasma $AUC_{0—last}$ in animals that received co-ground mixture of RHCL and RHCL was 1260±426 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 showed significant increase with co-ground as compared to RHCL.

The corresponding mean C_{max} values for these treatment groups were 254±177 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 co-ground mixture compared to RHCL. The median T_{max} of RHCL in animals that received the co-ground mixture and pure drug was 2 and 8 h, 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 co-ground 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.

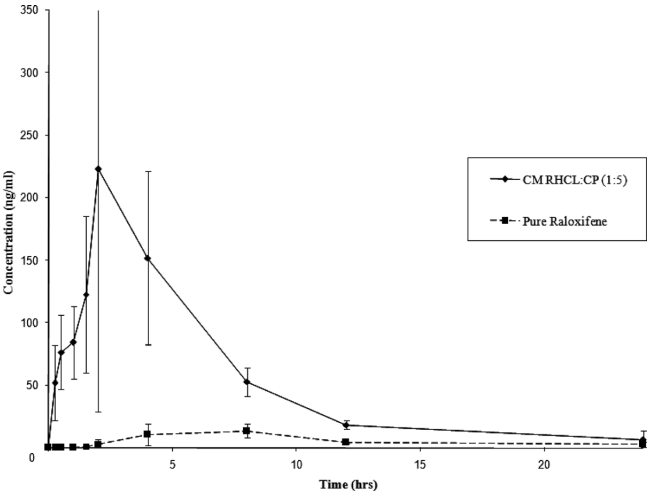

Fig. 7. Plasma Concentration–Time Data of Co-milled and Pure Raloxifene Samples in Female Sprague-Dawley Rats Following Oral Administration in 1% Gelatin Gel Sandwich (Dose: 25 mg/kg Free Base)

Conclusion

Co-grinding of RHCL with CP 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 out of the superdisintegrants evaluated, CP was found to be a better carrier for RHCL.

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