International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 1, 2016

Original Article

PREPARATION AND EVALUATION OF RAPIDLY DISSOLVING TABLETS OF RALOXIFENE HYDROCHLORIDE BY TERNARY SYSTEM FORMATION

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Received: 22 Sep 2015 Revised and Accepted: 18 Nov 2015

ABSTRACT

Objectives: Enhancing the dissolution rate of raloxifene hydrochloride for the preparation of rapidly disintegrating tablets with subsequent rapid dissolution.

Methods: Binary and ternary solid dispersions (SDs) with different carriers were prepared at various drug: carrier ratios including cremophor RH 40, polyvinylpyrrolidone (PVP K30), poloxamer 407 and gelucire 44/14 as carriers and were evaluated by drug content, In-vitro dissolution studies, Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) analysis analysis. The most efficient solid dispersion was selected for preparation of rapidly dissolving tablets.

Results: SDs showed enhanced dissolution rate compared to the unprocessed drug. Differential scanning calorimetry revealed that enhancement in drug dissolution was mainly due to a change in its crystalline structure. FTIR studies revealed no interaction between the drug and excipients. The dissolution pattern of the drug from the prepared tablet depended on the components of the tablets with those containing a combination of super-disintegrants (crospovidone and croscarmellose) in the presence of citric acid as channeling agent and pH modifier being the best.

Conclusion: The study presented a system capable of increasing the dissolution rate of raloxifene with successful incorporation in rapidly disintegrating tablets with subsequent fast dissolution.

Keywords: Raloxifene hydrochloride, Binary solid dispersion, Ternary solid dispersion, Raloxifene dissolution rate, Rapidly dissolving tablets.

INTRODUCTION

Raloxifene hydrochloride (RHL) is an orally active, selective estrogen receptor modulator [1]. It has estrogen agonist effects on bone and cholesterol metabolism but behaves as a complete estrogen antagonist on uterine and breast tissue [2]. It can reduce the risk of spinal fractures with high potential of reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis [3]. It is being investigated for the prevention and treatment of osteoporosis in elderly men [4, 5]. Based on the Biopharmaceutical Classification System, RHL is classified as Class-II drug meaning that the drug is highly permeable but poorly soluble [6]. This means that the oral bioavailability of the drug is dissolution rate limited. In addition, RHL suffers from extensive presystemic metabolism which is dominated by glucuronidation in the intestine and liver [7]. The combined effect of poor dissolution and extensive first-pass metabolism leads to a very low bioavailability (2.6±0.4%) [8] Accordingly, enhancing the drug dissolution is expected to increase the oral bioavailability of RHL. The benefit will become even greater if the selected excipients and/or dissolution enhancement technique can inhibit the presystemic metabolism [9]. In the past, several techniques were performed to improve the dissolution rate and hence the bioavailability of RHL. These include binary solid dispersion system [10, 11], nanoparticle engineering [12], bioadhesive microspheres composed of inclusion complex [13] and self-nano emulsifying drug-delivery systems [14]. To the best of our knowledge, no reports were available in the literature on ternary solid dispersion system with polymers having enzyme inhibitory potential and henceforth we made an attempt to formulate binary and ternary solid dispersion of the drug with different polymers having enzyme inhibitory potential. This together with rapid dissolution can provide a greater chance for the drug to escape from the metabolism due to enzyme saturation and/or inhibition. In addition, enhanced dissolution can eliminate the variability in drug absorption. The present study encompasses the formulation and evaluation of fast disintegrating tablets with subsequent rapid dissolution. This was achieved via a ternary solid dispersion formation with several carriers having an inhibitory effect on the UDP-glucuronosyltransferase and other metabolizing enzymes. These included cremophor RH 40, polyvinyl pyrrolidone (PVP K30), poloxamer 407 and gelucire 44/14 [15].

MATERIALS AND METHODS

Materials

Raloxifene hydrochloride (RHL), polyvinylpyrrolidone (PVP K30) and Aerosil 200 were obtained as generous gift samples from Pharaonia Pharmaceuticals Pharo Pharma, Alexandria, Egypt. Poloxamer 407 and Cremophor RH 40 were purchased from Basf Co, Ludwigshafen, Germany. Gelucire 44/14 was obtained from Gattefosse Saint Priest Cedex France. Tween 80 and Citric acid were purchased from Adwic, El-Nasr Pharmaceutical Chemical Co., Cairo, Egypt. Avicel PH 102, croscarmellose sodium, crospovidone, magnesium stearate, and sucralose were kindly supplied as gift samples from Sigma pharmaceutical industries, Egypt. All chemical reagents of analytical grade.

Methods

Construction of calibration curves for raloxifene HCL

The quantification of the drug in binary and ternary solid dispersions and tablets as well as aqueous samples from the dissolution experiments were determined by UV-spectrophotometry (Thermo Fisher Evolution 300, Japan). A stock solution of raloxifene (1000 µg/ml) was prepared by weighing 50 mg of RHL which was quantitatively dissolved in 50 ml of methanol. This solution was used to prepare serial dilutions of the drug (2-10 µg/ml). The highest concentration was scanned with UV-Visible spectrophotometry in range 200 to 600 nm using methanol as a blank and λmax were recorded at 286 nm. The absorbance values of the prepared concentrations were recorded at 286 nm and a calibration curve was constructed by plotting the absorbance as a function of drug concentration. The calibration curve was linear in the tested range, and the standard regression equation was Y = (0.0714±0.0009) X–(0.0060±0.0018).

Preparation of solid dispersions

Table (1) presents the composition of the prepared formulations. RHL binary and ternary solid dispersions were prepared by the solvent evaporation method. The drug was dissolved in the solvent system which comprised a mixture of ethanol and acetone (70: 30%). The required amount of carrier was added under magnetic stirring until complete solubility. The solvent was removed completely by evaporation at 55±0.5 °C. Aerosil 200 was included in solid dispersion containing low melting point polymers to ensure the formation of the flowable product.

This was achieved by mixing aerosil powder with the solid dispersion just before congealing. Mixing continued until the formation of dry product. The resultant solid dispersion was then powdered and stored in an airtight container until further use.

Table 1: The composition of the prepared binary and ternary solid dispersion systems

Code	Drug	PVPK30	Gelucire 44/14	Aerosil 200	Cremophor RH40	Poloxamer 407	Dissolution Efficiency (%)*
Control	1	-	-	-	-	-	44±2.1
Binary systems							
B1	1	1	-	-	-	-	73±4.0
B2	1	2	-	-	-	-	75±3.0
B3	1	3	-	-	-	-	74±2.9
B4	1	-	1	1	-	-	57±2.3
B5	1	-	2	1	-	-	60±1.8
B6	1	-	3	2	-	-	61±1.3
B7	1	-	-	1	1	-	54±1.7
B8	1	-	-	1	2	-	55±0.3
B9	1	-	-	2	3	-	57±2.3
B10	1	-	-	-	-	1	65±0.7
B11	1	-	-	-	-	2	65±3.4
B12	1	-	-	-	-	3	67±1.3
Ternary systems							
T1	1	0.5	0.5	0.5	-	-	77±4.5
T2	1	1	1	0.5	-	-	81±2.6
T3	1	0.5	-	-	-	0.5	70±2.2
T4	1	-	-	0.5	0.5	0.5	76±3.4
T5	1	-	0.5	0.5	0.5	-	57±2.5

*n = 3, data represent mean of three observations

Differential scanning calorimetry

Thermograms of the samples (RHL, excipients, binary and ternary solid dispersions) were recorded using a differential scanning calorimeter (DSC-60, Shimadzu, Japan). Samples equivalent to 2–3 mg of the drug were loaded into aluminum pans and the lids were crimped using a Shimadzu crimper. The thermal behavior of each sample was investigated under nitrogen at a heating rate of 10 °C/min, covering temperature ranges of 25–300 °C. The instrument was calibrated with an indium standard (mp= 156.5 °C, ΔH_{fus}= 28.41 J/g). Data analysis was conducted using the TA-60 WS thermal analysis software.

Fourier transforms infrared spectroscopy

FTIR spectra of RHL, pvp k30, gelucire 44/14, cremophor RH 40, poloxamer 407 and aerosil 200, and their binary and ternary solid dispersions were recorded using a Bruker Tensor 27 FTIR spectrometer (Bruker Optics GmbH, Ettlingen, Germany) equipped with DLaTGS (DeuteratedL-alanine Triglycine Sulfate) detector. Samples were mixed with potassium bromide (spectroscopic grade) and compressed into discs using hydraulic press (cap 15T), before scanning from 4000 to 200 cm^{-1}. Analysis of the spectra was carried out using the Bruker OPUS (OPtical User Software) Data Collection Program.

Determination of drug content

Samples of the solid dispersions equivalent to 60 mg of the drug were dissolved in minimum quantity of methanol and volume was made up to 50 ml. This was suitably diluted with methanol before the determination of the drug content using UV spectrophotometry at 286 nm using the solvent as blank.

Determination of drug dissolution

The dissolution studies employed the USP method 2 (paddle method) dissolution apparatus (Copley Scientific Dis 6000, Nottingham, United Kingdom). Water containing 0.1% w/v Tween 80 was used as a dissolution medium (1000 ml). This was maintained at 37±0.5 °C and stirred at a speed of 50 rpm. The drug (60 mg or equivalent) in the form of unprocessed powder, solid dispersion or tablet was added to the dissolution vessels while stirring. Samples (5 ml) were taken at appropriate time intervals (5, 10, 20, 30, 45 and 60) and immediately replaced with fresh dissolution medium to maintain sink conditions. These samples were subjected to immediate filtration through a 0.45 µm membrane filters. The first 2 ml of the filtrate was discarded and the samples were assayed for drug content using the UV spectrophotometry at 286 nm, after appropriate dilution with the dissolution medium. The cumulative amounts of the drug dissolved (expressed as % of the total drug added) were plotted as a function of time to produce the dissolution profiles. The dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (determined using the nonlinear trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100 % dissolution in the same time [16]. In addition, the amount of drug dissolved in the first 5 min (Q5) was calculated. These parameters were used for comparison.

Preparation of rapidly disintegrating tablets (RDTs)

The ternary SD formulation showing the best release pattern was used to prepare the rapidly disintegrating tablets which contained an amount equivalent to 60 mg of the drug per tablet. The tablets were prepared according to the formula presented in table 2. All ingredients were passed through an 800 µ sieve (sieve set according to DIN 4188). The powdered drug or its equivalent SD was mixed with all excipients other than lubricant for 5 min using the bottle method. The obtained blend was lubricated with magnesium stearate for another 5 min, before compression into tablets, weighing 608 mg using 14 mm punch. This process employed a single punch tablet press machine (Royal artist. Mumbai, India) and the compression force were adjusted to produce tablets having a hardness of 4-5 kilopond. The hardness tests were performed by Hardness tester (Erweka Apparatus TB24, Germany) [17].

Table 2: Master formula for preparation of 60 mg RHL tablets

Ingredients	F1 (mg/tablet)	Control (1) (mg/tablet)	F2 (mg/tablet)	F3 (mg/tablet)	Control (2) (mg/tablet)
RHL or an equivalent SD (T2)	210	60	210	210	60
Avicel PH 102	300	450	300	300	450
Croscarmellose sodium	25.5	25.5	25.5	51	25.5
Crospovidone	25.5	25.5	25.5	–	25.5
Citric acid	–	–	12	12	12
Sucralose	20	20	20	20	20
Aerosil 200	10	10	10	10	10
Magnesium stearate	5	5	5	5	5
Total tablet weight	596	596	608	608	608
Disintegration time(sec)*	102±3.8	28±1.2	24±2.9	19±2.6	17±0.4
Dissolutionefficiency (%)*	46±3.5	37±1.7	67±1.3	54±2.3	55±3.5

*n = 3, data represent mean of three observations

Evaluation of rapidly disintegrating tablets

Uniformity of weight

Tablets (20) were selected randomly. The weight of individual tablet was recorded, and the average mass and the deviation from the average were calculated. Not more than 2 of the individual masses can deviate from the average mass by more than ±5.0% and none can deviate by more than twice that percentage [18].

Tablet friability

The friability of the tablets was measured in Friability tester (Erweka TA3R, Germany). A sample of whole tablets corresponding as near as possible to 6.5g (10 tablets) was used. The tablets are carefully deducted prior to testing, and the weight was recorded before being subjected to 100 revolutions in the friabilator. Intact tablets were collected and subjected to a dedusting before recording the weight. If obviously cracked, cleaved, or broken tablets are found in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test is repeated twice and the mean of the 3 tests determined. A loss of less than 1% in weight (obtained from a single test or from the mean of 3 tests) is considered acceptable for most products [19].

Uniformity of dosage units

The individual contents of active substance of 10 dosage units taken at random were determined spectrophotometrically. The preparation complies with the test if each individual content is between 85% and 115% of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75% to 125% of the average content. If one individual content is outside the limits of 85% to 115% but within the limits of 75% to 125%, the test was repeated on another 20 dosage units taken at random. The preparation complies with the test if not more than one of the individual contents of 30 units is outside 85% to 115% of the average content and none is outside the limits of 75% to 125% of the average content [20].

***In vitro* disintegration time**

The disintegration test was carried out using tablet disintegration tester (Copley Scientific, Colwick, Nottingham, United Kingdom). Six tablets were placed individually in each tube and basket rack is positioned in a 900 ml distilled water, which is maintained at 37±0.5 °C and the time taken for the complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds [21].

Wetting time

This is carried out to measure the time, which is required for the complete wetting of tablets. A filter paper was placed in a small Petri dish containing 6 ml of distilled water. Allura red powder was placed on the surface of the tablet before placing the tablet on the wet filter paper. The time corresponding to the appearance of red color on the tablet surface was recorded and taken as the wetting time [22].

RESULTS AND DISCUSSION

Solid state characterization of SDs

The drug content values were in the range of 92 to 103% (w/w). This excludes any segregation of the drug or polymer during SD formation. The solid state characterization involved thermal analysis using the DSC, FTIR and dissolution studies.

Differential scanning calorimetry (DSC)

Fig. 1 and 2 present examples of DSC trace of RHL in the pure state and in binary and ternary solid dispersion systems. The DSC thermogram of RHL showed a typical single sharp endothermic peak at 268.41 °C with melting enthalpy 100.70 J/g (fig.1). This endotherm corresponds to the melting point of the drug and reflects its crystalline nature. The recorded data correlates well with the published data which revealed the melting transition in the range of 265.9 to 271 °C for RHL [23, 24].

Pure pvp k30thermogram showed a broad endothermic peak with an onset of 50 °C and end set of 130 °C (fig. 1). This endotherm can be attributed to the liberation of adsorbed moisture from the hygroscopic polymer. The recorded thermogram is similar to that reported by other investigators in literature reports [25]. The DSC profile of pure poloxamer 407 revealed a sharp endotherm with a Tm of 57.28 °C. This endotherm reflects the melting transition of the surfactant (fig. 1). This finding agrees well with the published data on the same substance [26, 27]. The DSC trace of aerosil 200 (fig. 1) did not demonstrate any detectable endothermic or exothermic peaks. This thermal behavior is expected for this material taking into consideration the amorphous nature of aerosil. Similar explanation was reported after obtaining similar results and was confirmed with X-ray diffraction [28].

For pure gelucire 44/14 (fig. 1), the thermogram showed a single endothermic peak corresponding to its melting transition at 43.9 °C conforming to the specification of the material. This is in good agreement with the recorded data for the thermal analysis of the surfactant [29]. With respect to chromophore RH 40, the peak corresponding to melting transition which is expected to be at 20 °C was not recorded in the range of temperature tested. The thermogram revealed a broad endothermic peak at 244 °C which can be attributed to the decomposition of the surfactant. This finding correlates well with supplier specifications for this material.

Preparation of SD of the drug with increasing concentration of pvp k30 (fig. 1), resulted in a significant reduction in the Tm of the drug. This was associated with broadening of the melting transition and reduction in the enthalpy of the transition. The effect was intensified with increasing the ratio of the polymer in the SD. This effect can be explained on the base of amorphization of the drug after SD formation. Formation of amorphous structure can be attributed to the possible dispersion of drug molecules within the network structure of the hydrophilic polymer after evaporation of solvent [30].

Preparation of solid dispersion of RHL with gelucire 44/14 required the addition of aerosil 200 as a solid carrier to develop the flowable

product. This system showed thermal behavior which depended on the ratio of gelucire 44/14 (fig. 1). The Tm of the endothermic peak of the drug was gradually reduced with increasing the ratio of gelucire 44/14. The reduction in the Tm was associated with a reduction in the size and enthalpy of the transition. These behaviors can be attributed to the decrease in crystallinity of drug when dispersed in gelucire. A similar explanation was reported for the same surfactant with another drug [31]. For SDs with poloxamer 407, the DSC traces of the SD (fig. 1) were characterized by a gradual decrease in the Tm of the endothermic peak of the drug with increasing the ratio of the surfactant. The enthalpy of the endotherm was marginally reduced. This finding suggests incomplete amorphization of the drug after solid dispersion formation with poloxamer 407 at the tested weight ratios. The melting transition of the polymer was recorded in all SDs and its Tm showed marginal reduction compared to the pure state.

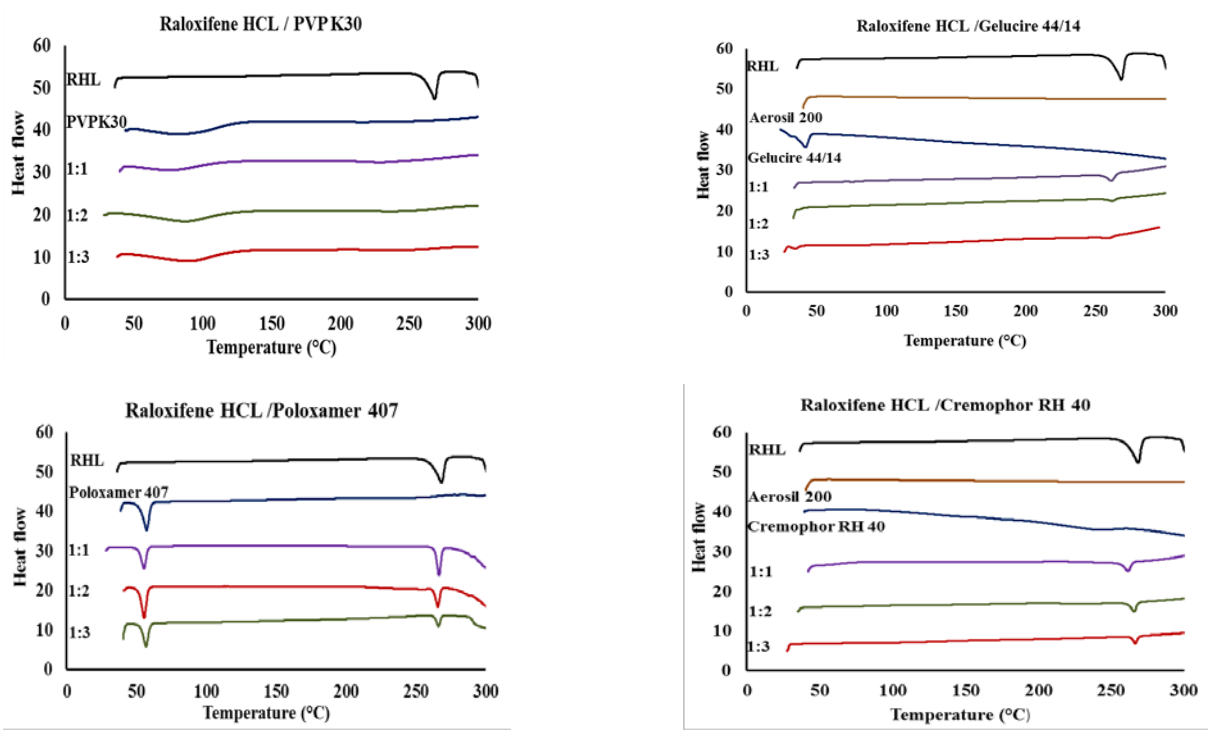

Fig. 1: Examples of the DSC traces of pure Raloxifene HCL (RHL), dispersion carriers and their binary solid dispersion systems

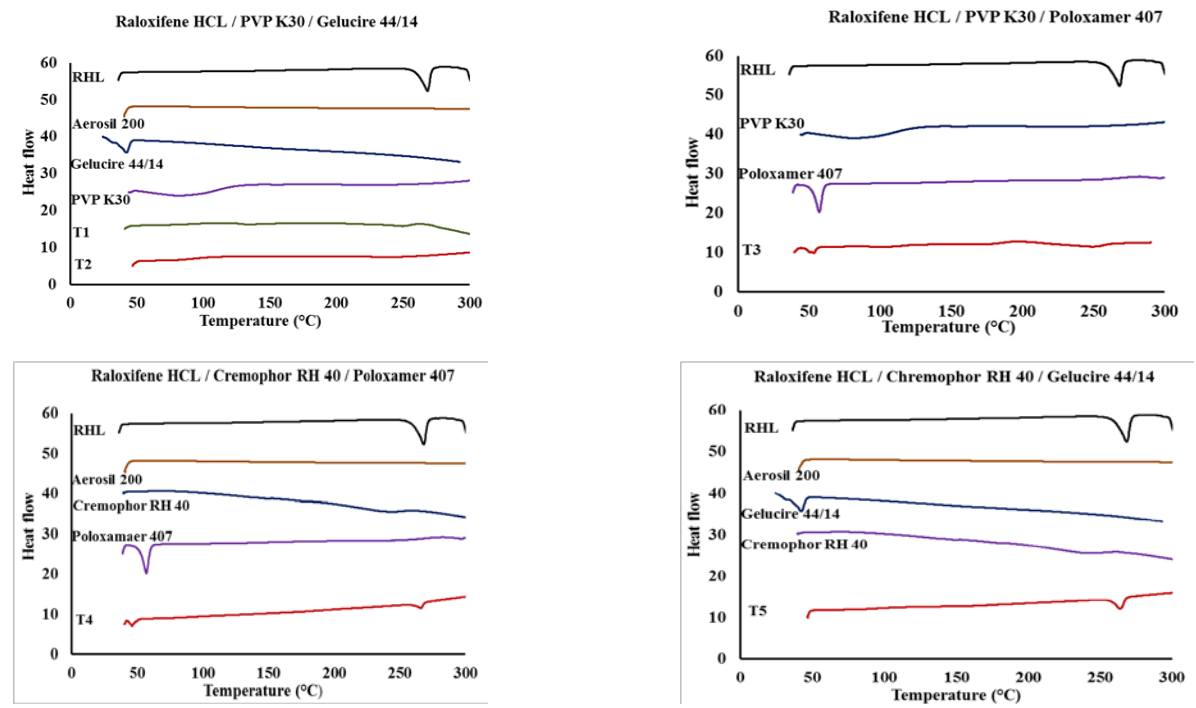

Fig. 2: Examples of the DSC traces of pure Raloxifene HCL (RHL), dispersion carriers and their ternary solid dispersion systems

Preparation of solid dispersion of RHL with cremophor RH 40 required the addition of aerosil 200 as a solid carrier to develop the flowable product. The thermogram (fig. 1) showed a gradual reduction in the Tm and the enthalpy of the main endothermic peak of the drug compared to its profile in the pure state. However, the recorded reduction in the enthalpy did not indicate a complete change to the amorphous structure.

Preparation of ternary solid dispersion (T1) of RHL with pvp k30 and gelucire 44/14 along with aerosil 200 at a weight ratio of 1: 0.5:0.5: 0.5, produced a DSC trace (fig. 2), showing a very broad endothermic peak of the drug. This endotherm was detected at significantly lower Tm and was shown to have a lower enthalpy compared to that obtained in cases of pure drug or the corresponding binary solid dispersions. Increasing proportions of the polymers abolished the endothermic peak of the drug as in the case of formulation T2 (1:1:1: 0.5; drug: PVP K30: Gelucire 44/14: Aerosil 200). This effect can indicate the possible formation of amorphous solid in both solid dispersions.

Preparation of ternary solid dispersion (T3) of RHL with poloxamer 407 and pvp k30 at a weight ratio of 1: 0.5: 0.5, resulted in broadening of the endothermic peak of the drug with a significant reduction in the Tm (fig. 2). This can be attributed to the combined effects of PVP K30 and poloxamer 407.

With respect to the ternary solid dispersion (T4) of RHL with poloxamer 407 and cremophor RH 40 in, the presence of aerosil 200 the DSC trace (fig. 2) showed the combined effect for the two excipients in which the Tm was marginally reduced.

Finally, preparation of ternary solid dispersion (T5) of the drug with gelucire 44/14 and cremophor RH 40 along with aerosil 200 changed the thermal behavior of the drug compared with its unprocessed form (fig. 2). This change was manifest as a reduction in the Tm and enthalpy of the melting transition of the drug. Once again, this change can represent the combined effect of gelucire 44/14 and Cremophor RH 40.

FTIR spectroscopy

Fig. (3 and 4) show the FTIR spectra of the drug in the pure state or as binary and ternary solid dispersion formulations. The spectrum of the pure excipients is also shown. The FTIR spectrum of the unprocessed drug revealed the characteristic absorption bands of the drug. These include that corresponds to the phenolic OH group which was shown at 3144 cm^{-1}. The bands between 2800 and 3100 cm^{-1} can be assigned for the stretching of aliphatic and aromatic C–H bonds. The peak at 1642 cm^{-1} can be attributed to the carbonyl group which shifted to right due to the conjugation. Bands between 1470 and 1597 cm^{-1} can be due to the stretching vibrations of aromatic C=C. The band at 1466 cm^{-1} is due to S-benzothiofuron. The C–N stretching was observed as a peak at 1357 cm^{-1}. The phenolic C–O stretching vibration appeared at 1233 cm^{-1} due to the conjugation of oxygen with the ring which shifts the compound to higher energy. The ether C–O–C stretching produced two bands, one at 1042 cm^{-1} for symmetric stretching and the other at 1207 cm^{-1} asymmetric stretching. Ketone C–(CO)–C stretching vibration appeared at 1170 cm^{-1}. The strong band at 835 cm^{-1} can be attributed to the aromatic =C–H out of plane bending vibrations. The band at 807 cm^{-1} can be due to thiophene C–H. Two small peaks were recorded in 1914 and 1890 cm^{-1} indicating para-di-substitution on the aromatic ring. The recorded spectrum agrees well with that reported by other investigators for the same drug [32].

The FTIR spectrum of pure pvp k30 (fig. 3) revealed the characteristic peak of the carbonyl group which was recorded at 1662 cm^{-1}. The hygroscopic nature of the polymer was indicated by the presence of a peak for the OH-stretching which was noticed at 3447 cm^{-1}. This peak can be attributed to the presence of moisture and confirms the recorded broad endothermic in the DSC experiments. The band at 2956 cm^{-1} can be due to C–H stretching [33].

The FTIR spectrum of the binary SD of the drug with pvp k30 (fig. 3) reflected overlapping of the characteristic absorption bands of the hydroxyl and carbonyl groups of drug and the polymer. This hindered the detailed investigation of the possible interaction between the drug and PVP.

FTIR spectra of gelucire 44/14 (fig. 3) showed the characteristic peaks at 2922 and 2879 cm^{-1} which are related to the C–H stretch. The absorption band corresponding to the C=O stretching was noticed at 1736 cm^{-1}. The C–H bending vibration was recorded at 1467 cm^{-1} and the C–O stretching was noticed at 1355, 1280, and 1114 cm^{-1}. The presence of moisture was indicated by a broad band at 3459 cm^{-1}. This is correlated well with the published spectrum for the surfactant [34]. The FTIR spectrum of aerosil 200 (fig. 3) showed a broad absorption band in the range of 3600–3200 cm^{-1}. This can be due to the OH–stretching. This OH group results from intermolecular hydrogen bonding between the adsorbed moisture and the silica oxygen. In addition, a broad absorption band was noticed at 1115 cm^{-1} and can be assigned for the strong Si–O linkage of aerosil. Similar spectrum was reported and was explained similarly [35].

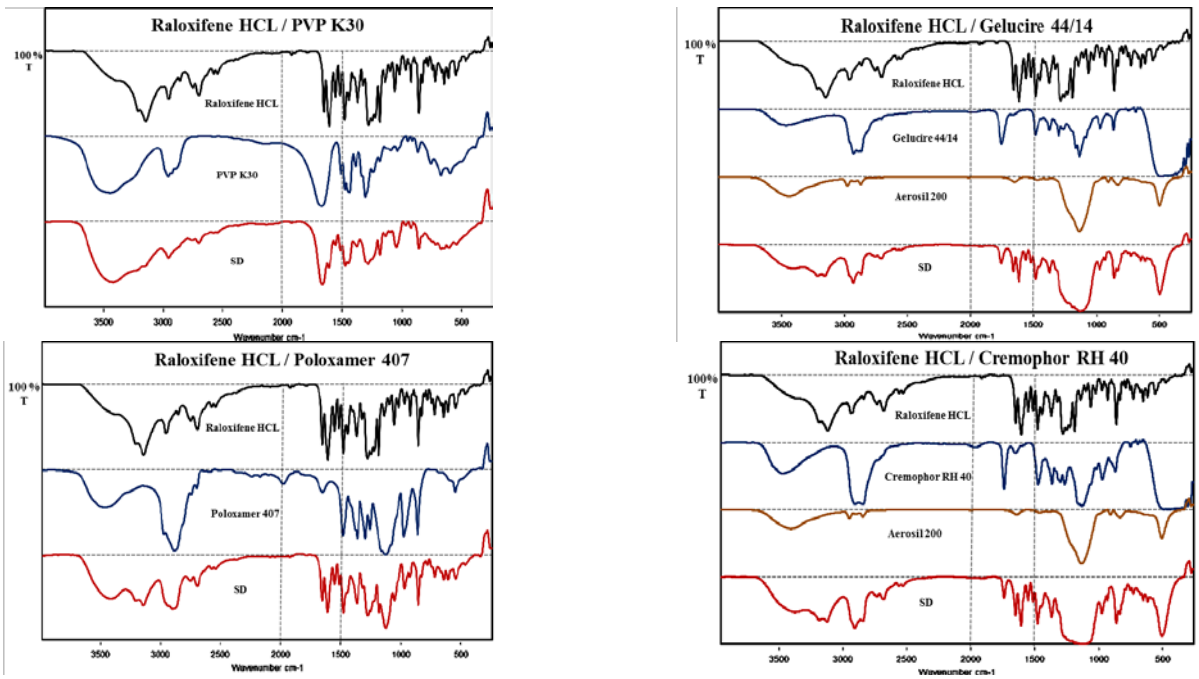

Fig. 3: FTIR spectra of Raloxifene HCL and its binary solid dispersion (SD) systems

The FTIR spectrum of the SD of the drug with gelucire 44/14 in the presence of aerosil 200 revealed the characteristic peaks of the drug with those corresponding to the phenolic OH and carbonyl groups being recorded in a similar position compared with the unprocessed drug (fig. 3). This eliminates any interaction between the drug and the gelucire.

The FTIR spectrum of poloxamer 407 (fig.3), showed a broad band at ~3453 cm^{-1} corresponding to the O–H group with a strong absorption band being noticed at 2886 cm^{-1} due to aliphatic C–H stretching. The absorption band of C–O stretching was seen at 1113 cm^{-1}. This spectrum correlates well with the published spectrum for the same surfactant [36]. The recorded spectra for the binary SD of the drug with poloxamer 407 showed evidence for the characteristic band of the drug (phenolic OH and carbonyl groups; fig. 3). Overall, the recorded spectrum indicated no interaction between the drug and the polymer. The spectrum of pure cremophor RH 40 (fig. 3), showed the absorption band of the OH group which was seen as a broadband at ~ 3504 cm^{-1}. The aliphatic CH bond was expressed as bi-forked band with two apices at 2861 and 2925 cm^{-1}. The peak carbonyl group of the ester was found at 1734 cm^{-1}. The ether C–O–C stretching was manifested as a strong broad band at 1113 cm^{-1}. This spectrum is similar to that published spectrum for the same surfactant [37]. The FTIR spectrum of the SD of the drug with cremophor RH 40 in the presence of aerosil 200 revealed the specific peaks of the drug which were recorded in the same positions as in the case of unprocessed drug (fig. 3). The results were consistent with the data generated from DSC and confirmed the absence of any interaction between the drug and cremophor RH 40 in the presence of aerosil 200.

The FTIR for the ternary solid dispersion of RHL/pvp k30/gelucire 44/14 in the presence of aerosil 200 (T1) showed the characteristic bands of the drug at 3144 cm^{-1} (phenolic–OH) and 1600 cm^{-1} (carbonyl group). Increasing the concentration of polymers in the ternary solid dispersion system (T2) resulted in overlapping of the absorption band corresponding to the phenolic OH of the drug with the hydroxyl group originating from the hygroscopic nature of PVP (fig. 4). Overall, the recorded spectrum indicated no interaction between the drug and the carriers.

The FTIR for the ternary solid dispersion of RHL/pvp k30/poloxamer 407 (T3) showed the characteristic bands of the drug at 3144 cm^{-1} (phenolic–OH) slightly shifted to the left at 3207 cm^{-1}. Also, the band corresponding to the carbonyl group of the drug overlapped with that of the carbonyl group of the PVP K30 (fig. 4). Overall, the recorded spectrum indicated no interaction between the drug and the carriers.

The FTIR for the ternary solid dispersion of RHL/chromophore RH 40/poloxamer 407 in the presence of aerosil 200 (T4) showed the characteristic bands of the drug at slightly different positions compared with the pure drug (fig. 4). So phenolic–OH and the carbonyl group were shown at 3207 and 1650 cm^{-1}, respectively.

The FTIR for the ternary solid dispersion of RHL/cremophor, RH 40/gelucire 44/14 in presence of aerosil 200 (T5), showed a slight shift in the characteristic absorption bands of the drug (fig.4). The phenolic OH was shown at 3206 cm^{-1} and the carbonyl group was noticed at 1651 cm^{-1}.

In vitro dissolution study

The dissolution pattern of raloxifene was monitored from the pure unprocessed state and its binary and ternary solid dispersion systems with different polymers. Recorded dissolution profiles are shown in fig. 5 and 6. These profiles were used to calculate the dissolution efficiency values which are shown in table1. The dissolution profile of unprocessed drug reveals poor dissolution. This is indicated by the amount of drug dissolved with time as only 23±1.1% of the drug was dissolved in the first 5 min with a maximum of 60±2.6% of drug being liberated after 60 min. The overall dissolution efficiency during the course of study was only 44±2.9 %. The recorded data agree well with that reported by other investigators for the drug in the same dissolution media [38].

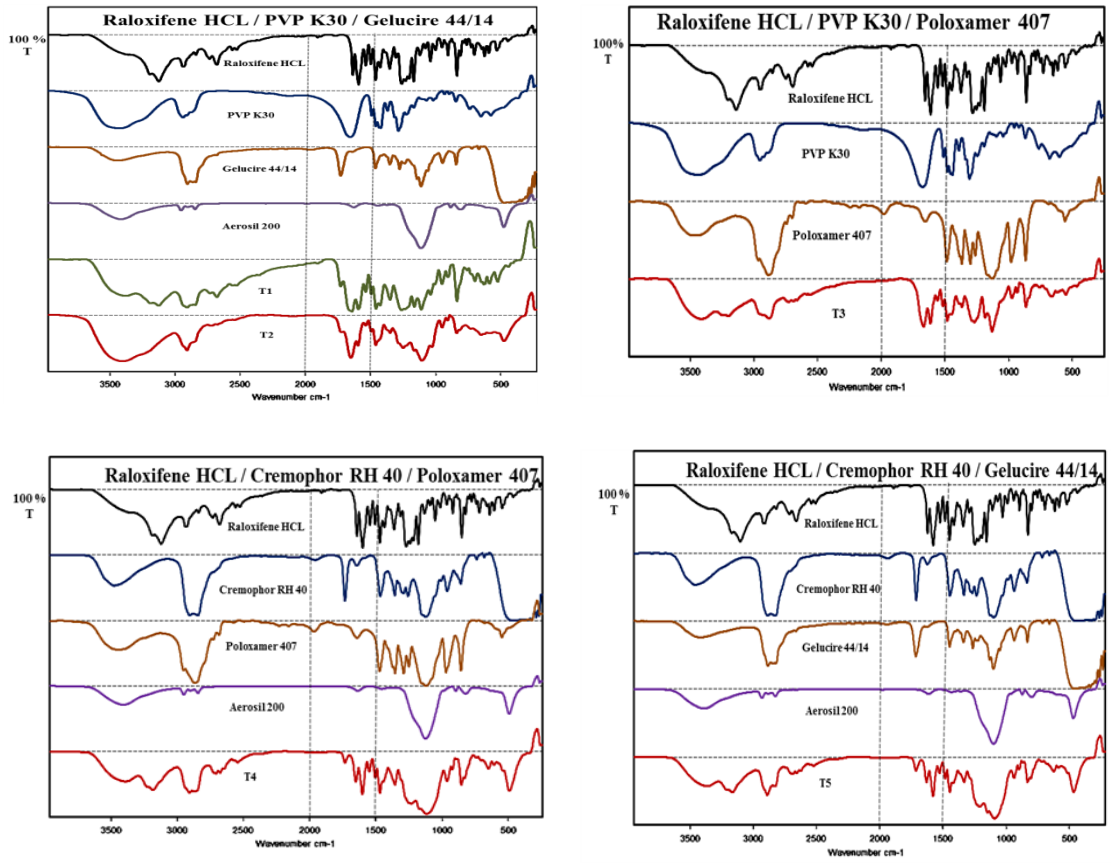

Fig. 4: FTIR spectra of Raloxifene HCL and its ternary solid dispersion (SD) systems.

In vitro dissolution study

Preparation of SD of the drug with pvp k 30 resulted in a significant increase in the dissolution rate. This effect was evident even upon using the polymer at a 1:1 weight ratio with the drug. This system was able to increase significantly the amount drug released in the first 5 min to reach 72±4.6% (P<0.01, compared to the unprocessed drug). The overall dissolution efficiency was also increased significantly to reach 73±4.0% (fig. 5, table: 1). Further increase in the concentration of the polymer did not result in significant change in the dissolution pattern of the drug compared with the SD system containing a 1:1 weight ratio of the drug to the polymer. The recorded increase in the dissolution rate of the drug after solid dispersion formation can be attributed to the amorphization of the drug with the recorded results suggesting that most of the drug was changed to the amorphous structure at a 1:1 ratio with pvp k30. Solid dispersion formation with PVP was previously shown to enhance the dissolution rate of the drug with the enhancement being attributed to changing the drug crystal to the amorphous structure [39].

Preparation of solid dispersion of the drug with gelucire 44/14 resulted in the formation of paste-like product which was adsorbed on aerosil 200 to form free-flowing system. This system led to a significant increase in the dissolution rate compared with the unprocessed drug. The amount of drug liberated in the first 5 min was increased to reach 40, 41 and 42%, from SD containing the drug with gelucire at weight ratios of 1:1,1:2 and 1:3, respectively (fig. 5). Dissolution efficiency exceeded 61±1.3% in the case of SD containing the drug with the polymer at 1:3 weight ratio. Gelucire44/14 induced enhancement in dissolution rate after solid dispersion formation can be attributed to partial conversion of the crystalline drug to amorphous form with contribution from the wetting effect of gelucire which can be impacted by a reduction in interfacial tension between the drug and dissolution medium. The self-emulsifying property of gelucire which keeps the drug in the solubilized state after emulsification was also considered in the literature [40]. It is important to note that the efficacy of gelucire was lower than that obtained in the case of pvp k30 SD.

Preparation of the binary system of the drug with cremophor RH 40 resulted in the formation of paste-like product which was adsorbed on aerosil 200 to form free-flowing system. This system resulted in the better dissolution of the drug compared to the unprocessed powder (fig. 5) with effect starting to be significant at a 1:1 weight ratio of the drug to the polymer. At this weight ratio the system liberated 43±2.3% of the drug in the first 5 min. The amount of drug dissolved at this time was significantly higher than that obtained from the unprocessed drug (P= 0.01). The overall dissolution efficacy was 5±1.7%. The recorded enhancement in the dissolution rate can be due to self-emulsifying properties of cremphor RH 40 with a reduction in the interfacial tension between the hydrophobic drug and dissolution medium resulting in enhancing the wettability of drug particles [41]. Minor contribution from partial change in the crystalline structure is possible as indicated from the DSC studies. It is important to note that incorporation of chromophore at higher concentration resulted in a marginal increase in the dissolution rate of the drug compared with the system containing 1:1 (drug to chromophore). This indicates that a 1:1 ratio was enough to produce the required wetting effect.

Preparation of SD of the drug with poloxamer 407 resulted in a significant enhancement in the dissolution rate of the drug compared with the unprocessed powder (P<0.01). This was indicated in the case of SD containing the drug with poloxamer at 1:1 weight ratio which liberate of 59±2.3% of the drug in the first 5 min. The overall dissolution efficiency was 65±0.7% (fig. 5, table: 1). Increasing the concentration of poloxamer 407 in the SD from 1:1 (drug to surfactant) to 1:2 and 1:3 increased the amount dissolved in the first 5 min to reach 62±5.0% and 64±1.6%, respectively. This enhanced dissolution rate can be related to wetting effect, micellar solubilization with a contribution from decreased crystallinity. Similar explanation was reported for the same surfactant after enhancing the dissolution rate of other lipophilic drugs [42]. It is important to note that the recorded increase in the dissolution rate from SD containing a high concentration of poloxamer compared with that obtained from a 1:1 ratio did not satisfy the expectations. This can be attributed to a possible increase in viscosity of the diffusion layer at the higher concentration of poloxamer with subsequent reduction in the diffusion coefficient of the drug in the bulk. A similar explanation was reported for SD containing a high concentration of the same surfactant [43]. Recrystallization of the drug as poloxamer 407 may be less able to maintain the high concentration of drug in the supersaturated state can provide another explanation [44].

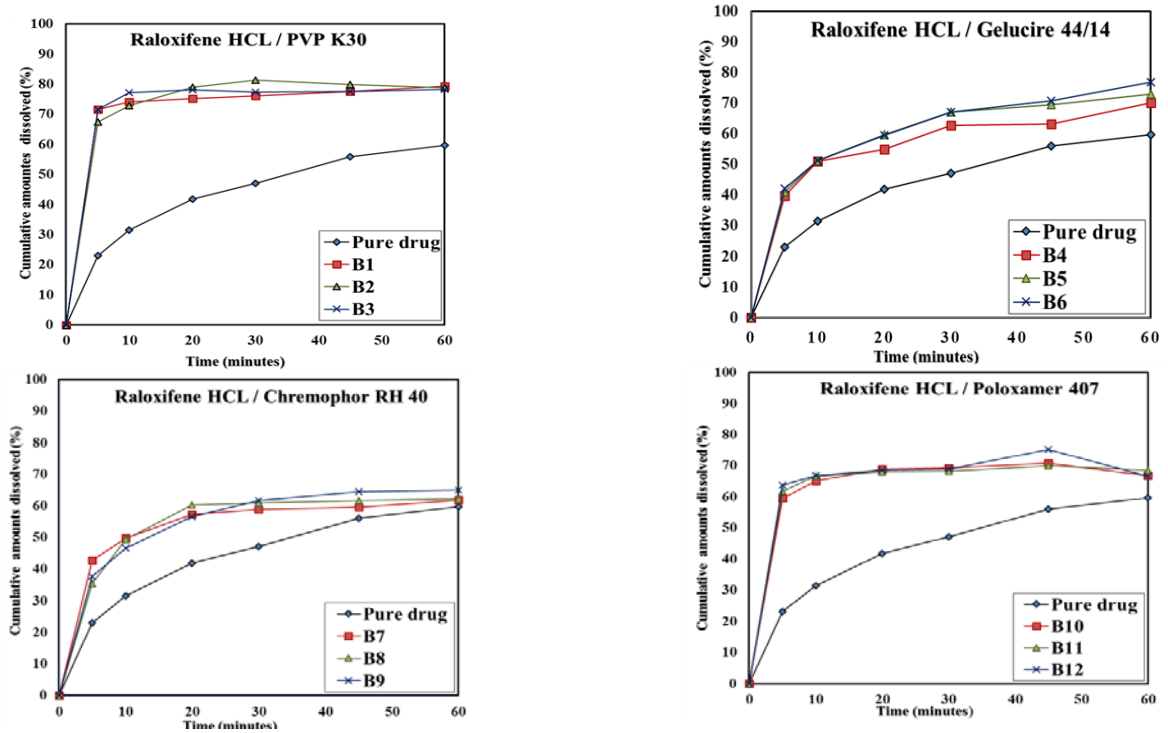

Fig. 5: The dissolution profiles of Raloxifene HCL from pure powder or from binary solid dispersions (Error bars were omitted for clarity, formulation details are presented in table: 1)

To maximize the possibility of dissolution enhancement ternary solid dispersions were prepared using the drug with two excipients. Formulation of a ternary system of the drug with pvp k30and gelucire 44/14 resulted in a system with a low melting point and required the addition of aerosil as a carrier. This ternary system provided a faster dissolution rate compared to both the unprocessed drug and the corresponding binary system. The ternary system containing the drug with pvp k30 and gelucire 44/14 at 1:1:1 weight ratio liberated 76±1.0% of the drug in the first 5 min with the overall dissolution efficiency approaching 81±2.6% (fig. 6 and table: 1). The same ternary system was shown to be efficient for enhanced dissolution of other drugs [45].

The ternary solid dispersion of the drug with pvp k30and poloxamer 407 (1:0.5:0.5) resulted in better dissolution of the drug compared to the unprocessed powder with effect starting to be significant ($P<0.01$) in the first 5 min (72±3.1%) revealing the better wetting ability of the surfactant-based polymer attributed to micellar solubilization of raloxifene and the better solubilizing effect of the hydrophilic carrier (fig. 6). The dissolution profile revealed a gradual decline in the release pattern after 45 min. This can be ascribed to possible recrystallization of the drug due to supersaturation. It is important to note that this effect was absent from other systems containing either pvp k30 or poloxamer 407. Absence of such phenomenon can be explained on the bases that the binary systems contained a higher concentration of pvp k30 which was enough to provide the antinucleant effect. The same reason can explain the absence of recrystallization process in case of a binary system containing poloxamer which influence the viscosity of the medium. In addition the recorded dissolution rate was lower in the case of binary poloxamer system reducing the possibility of supersaturation. Similar effect behavior was recorded with other lipophilic drugs with the process being explained similarly [46, 47].

In case of the ternary SD (T4) of the drug with cremophor RH 40 and poloxamer407, the product required incorporation of aerosil as a carrier to produce a free flowing system. This system was able to liberate significantly higher amounts of the drug compared to the unprocessed drug with the amount dissolved in the first five min reaching 67±2.1%. Overall dissolution efficiency was 76±3.4%. This enhancement in the dissolution rate of the drug can be explained on the bases of increased wettability and micelle solubilization as both carriers being surfactants decrease the interfacial tension between the drug and the dissolution solution.

As for the previous ternary system, the solid dispersion of the drug with cremophor and Gelucire required addition of aerosil 200 as a carrier to produce a free flowing system. This system failed to provide rapid dissolution compared with unprocessed powder of raloxifene Hcl. The amount dissolved in the first 5 min was 29±3.4%. However, the overall dissolution efficiency was increased significantly compared with the unprocessed drug to reach 55±4.8% (fig. 6). The overall enhancement in the dissolution pattern can be explained by the self-emulsification property of gelucire 44/14 and cremophor RH 40. The release values of this ternary system were similar to the binary SD (B4 & B7), increasing the dissolution by approximately the same degree.

It is clear from the results that the enhanced dissolution is mainly dependent on the type of polymer in the solid dispersion rather than the concentration of polymer. The rank order of dissolution enhancement was pvp k30>poloxamer 407>gelucire 44/14>cremophor RH 40 for the binary systems. For ternary systems the order was (pvp k30&gelucire 44/14)>(pvp k30 & poloxamer 407)>(cremophor RH 40&poloxamer 407)>(cremophor RH 40 & gelucire 44/14). These results were in agreement with the recent studies which explained that the dissolution profile can be improved by preparation of SD including amorphous carrier like pvp k30 along with carrier has surface activity or self-emulsifying properties such as gelucire 44/14, cremophor RH 40, and poloxamer 407 [48].

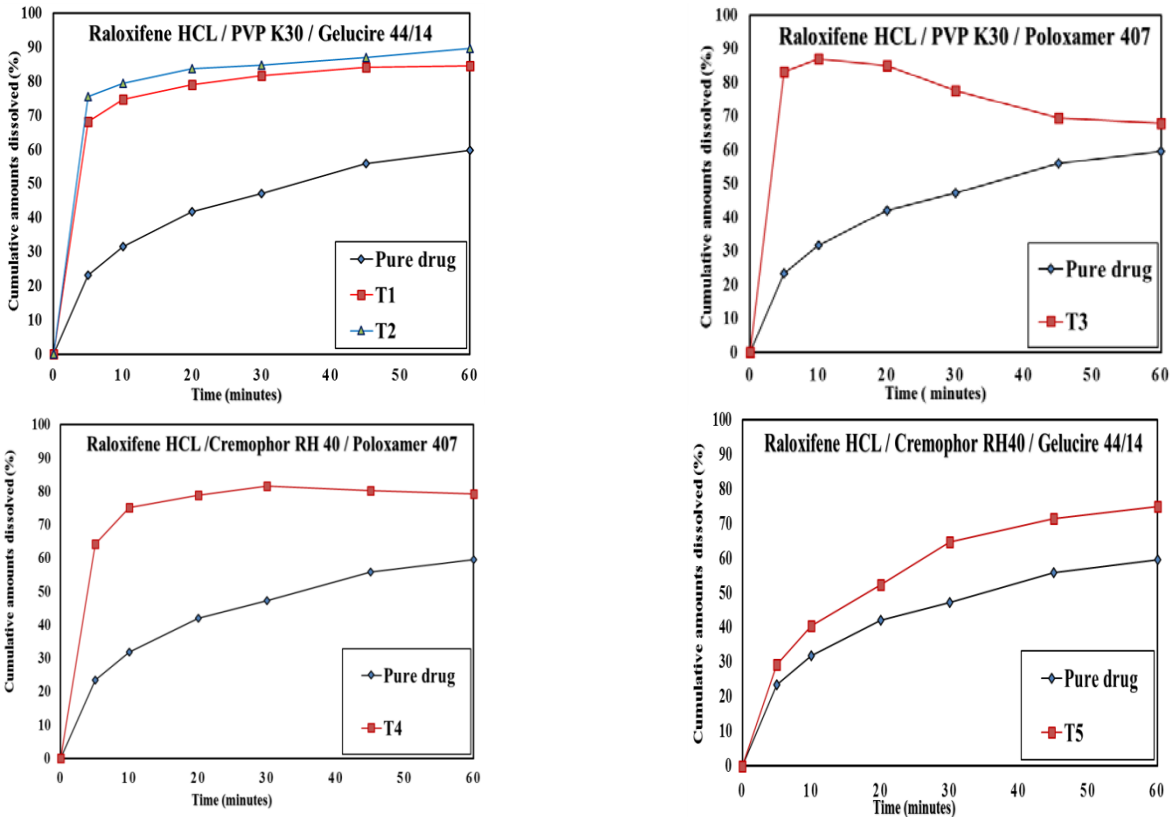

Fig. 6: The dissolution profiles of Raloxifene HCL from pure powder or from ternary solid dispersions (Error bars were omitted for clarity, formulation details are presented in table: 1).

The low solubility and slow dissolution of drugs is primary due to their hydrophobic nature which results in poor wetting of the drug particle with the dissolution medium. Solid dispersion formation is one of the effective strategies which can eliminate poor wettability making the first step in drug dissolution an easy process [49]. The benefit is even greater as this technique depends on hydrophilic carriers which can prevent the aggregation of fine particles exposing a higher surface area of drug to the dissolution medium. In addition, the presence of surface-active agent or/and self-emulsifying carriers in the solid dispersion can enhance dissolution via reduction in the interfacial tension preventing the formation of any water insoluble surface layers [50]. Finally SD formulation can create higher energy metastable forms of the drug which is rapidly dissolving. These aspects can explain the recorded dissolution enhancement of raloxifene hydrochloride after solid dispersion formation with various carriers [51].

Characterization of rapidly disintegrating tablets

The prepared tablets were found to be of uniform weight because the maximum deviation of tablet weight was 1.32% which complies with the acceptance limit (±5%). This reflects good flow ability of the formulation. Recorded friability values were in the range of 0.28 to 0.99%. This is acceptable based on the acceptance criteria of the BP. The drug content of the prepared tablets was in the range of 90 to 101%. The tablets exhibited very short wetting time values which ranged from 17 to 38 s. This indicates the porosity of the tablets. Rapid wetting was reflected by the very rapid disintegration with disintegration time being less than 30 sfor all formulation except F1 which disintegrated after 102 s. These results are expected for tablet formulations employing super-disintegrants like crospovidone and croscarmellose. Similar results have been reported for rapidly disintegrating tablets utilizing the same excipients [52].

The dissolution rate of the drug from tablets after disintegration has been used to determine whether the drug particles subjected to crushing or bonding during compression [53]. Amorphous raloxifene SD (T2) when subjected to the compression force a drastic drop in the dissolution rate of raloxifene SD from all tablet formulations was recorded (fig. 7). Indicating that the dissolution rate of raloxifene SD was influenced by the compression pressure. This is clear from the results of the dissolution rate of tablets which showed lower dissolution efficiency compared with the corresponding solid dispersion formulation (table: 1 and 2). However, the recorded dissolution pattern of raloxifene tablets containing the solid dispersion was better than the corresponding control tablet containing the unprocessed drug powder (table: 2). The dissolution rate of the tablets depended on the excipients with the addition of citric acid to the tablet ingredients enhancing the dissolution rate of the drug from the tablet formulation (table: 2).

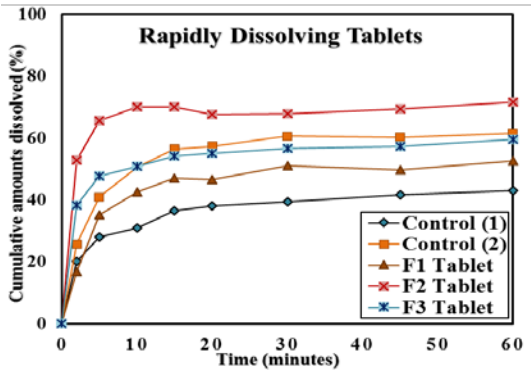

Fig. 7: Dissolution profiles of rapidly dissolving tablets. (Error bars were omitted for clarity. The details of tablet formulations are presented in table: 2)

The overall results of tablet dissolution indicate the superiority of using a combination of super-disintegrants (croscarmellose sodium and crospovidone) in the ratio of 1:1 along with citric acid as the channel forming agent in the formulation of orally disintegrating tablets of RHL. In addition to the channeling effect of citric acid, it can modify the pH of the diffusion layer around the drug particle with subsequent increase in the solubility of the drug in the diffusion layer. This can increase the dissolution rate of the drug from the tablet and will explain the recorded better dissolution pattern of control tablets containing citric acid compared with the free citric acid corresponding tablets.

CONCLUSION

Solid dispersion technique was able to enhance the dissolution rate of RHL with dissolution efficiency being dependent on the type of the polymer rather than the concentration of polymer in the SD. Enhanced dissolution was mainly due to a physical change in the drug crystal rather than solubilizing effect of the tested polymers. SDs containing pvp k30 and gelucire 44/14 in presence of aerosil 200 was selected for preparation of rapidly disintegrating tablets with subsequent rapid dissolution. Proper selection of tablet excipient was essential in preparation of rapidly disintegrating tablets with combination of super disintegrants being better especially in the presence of citric acid as a channeling agent and as a pH modifier.

CONFLICT OF INTERESTS

The authors confirm that this article content has no conflicts of interest.

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