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ORIGINAL ARTICLE

Complexation between risperidone and amberlite resin by various methods of preparation and binding study

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Abstract

Purpose: The purpose of this work was to investigate the effect of preparation methods and the drug-to-resin ratio on complex formation between risperidone and amberlite resin. *Methods*: The existence of such resin complex may provide taste-masking properties to the dosage forms. It is important to determine when and how the complex forms. Therefore, in this study, the complexes of risperidone and amberlite resin were prepared by granulation, solution, and freeze-drying methods at various drug-to-resin ratios. The physical mixtures of drug–resin were used to compare the results of complexes prepared by granulation, solution, and freeze drying. The complexes were evaluated by various methods of characterization including differential scanning calorimetry, X-ray diffraction, spectroscopy (near infrared, Fourier transform infrared, and Raman), drug release, and binding studies. *Results*: Complexation between risperidone and amberlite was investigated for various preparation methods. It was found that complexation occurred at lower amounts of amberlite resin (drug-to-resin ratios of 1:1 and 1:2) when solution form of drug was contacted with the resin as in the case of solution and freeze-drying techniques compared with granulation (drug-to-resin ratios of 1:4 and 1:6). Characterization studies such as differential scanning calorimetry, X-ray diffraction, spectroscopic techniques, and drug release studies differentiated complexes from the physical mixtures. Binding studies between them revealed that the binding was linear with solubility of the drug limiting the adsorption capacity. *Conclusions*: Results of the study highlighted the importance of the preparation methodologies to formulate complexes. When the drug and the resin were simply mixed physically, no complexation occurred. Thus, a careful evaluation of manufacturing procedure would indicate the nature and extent of complexation.

Key words: *Amberlite; binding; complexation; freeze drying; granulation; risperidone*

Introduction

Ion-exchange resins are high-molecular-weight polymers with cationic and anionic functional groups and the most frequently employed polymeric network is a copolymer of styrene and divinylbenzene. Typical function of such resins in the product formulation could vary from masking the taste of drug by complexation[1–3] to sustain the release of the drugs by forming drug–resin complexes called resinates[4,5]. In other cases, it has been used to stabilize the drugs[6]. Other forms of ion-exchange resins have been used as tablet disintegrant, for instance, potassium salt of polacrilex was used as a tablet disintegrant for β-lactam antibiotics by Gao et al.[7]

An important aspect of drug product development is the understanding of product variability with formulation and processing changes. This understanding allows an industry to control their products better so that there are fewer surprises when the products are developed by robust methods. In the FDA, there is an increased emphasis on product and process understanding as reflected by the white paper on the cGMP of the twenty-first century.

In case of risperidone orally disintegrating tablet, a cation-exchange resin (amberlite) is listed as an ingredient

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of the product formulation and this study was aimed at investigating possible complexation between risperidone and amberlite by various methods of preparation. As reported in the literature, the method of preparation greatly impacts drug entrapment efficiency by complexing agent[8]. However, such knowledge does not exist for risperidone amberlite complexes. Therefore, as a part of this study, it is important to know when and how it forms complexes. Four different preparation methods were investigated for the possible complex formation between risperidone and amberlite to address the complexation behavior. The complexes were characterized by their thermal and crystallographic behavior as well as by spectroscopic methods. The spectral methods included use of near-infrared (NIR), Fourier transform infrared (FTIR), and Raman spectra. It is also important to know how the complexes are formed. Therefore, a binding study was also carried out between risperidone and amberlite to understand the binding mechanism.

Materials and methods

Chemicals

Amberlite (Sigma-Aldrich, St. Louis, MO, USA), risperidone (99–101% purity, Ph. Eur.; Interchem Corp., Paramus, NJ, USA), hydrochloric acid, tartaric acid, sodium hydroxide pellets, and methanol (HPLC grades; Fisher Scientific, Suwanee, GA, USA) were used as received. For all the experiments, distilled and deionized water was used, which is equivalent in quality to purified water, USP.

Preparation of physical mixture

Risperidone and amberlite were mixed in turbula mixer at 72 rpm for 15 minutes. The ratios used for risperidone-to-amberlite were 1:1, 1:2, 1:4, and 1:6. These were further characterized as described below.

Preparation of drug–resin complexes

Complex A

Amberlite resin (0, 1, 2, 4, and 6 g) was mixed with 1 g of risperidone and sufficient 0.1 N HCl was added to make granules. The wet granules were dried in oven at temperature below 50°C until constant weight was obtained. They were then passed through the sieve (US 40 mesh) and characterized.

Complex B

Amberlite resin (0, 1, 2, 4, and 6 g) was mixed with tartaric acid (0.2 g), and risperidone (1 g) was added to this mixture by geometric dilution. Sufficient water was added to the mixture to obtain granules. The granules were dried in an oven at a temperature below 50°C until constant weight was obtained. They were then passed through the sieve (US 40 mesh) and characterized.

Complex C

Amberlite resin (0, 1, 2, 4, and 6 g) was soaked in 40 mL of 0.1 N HCl overnight with magnetic stirring. To this, 50 mL of risperidone solution in 0.1 N HCl (0.02 g/mL) was added and mixed. The resultant solution was stirred for 24 hours at room temperature (RT) and then filtered. The cakes were then dried in an oven at temperature below 50°C until a constant weight was obtained. The complexes obtained were subjected to characterization studies.

Complex D

Amberlite resin (0, 1, 2, 4, and 6 g) was suspended in 25 mL of NaOH solution (0.078 M, pH 12.41) overnight with magnetic stirring. To this, 1 g of risperidone was added and stirred for 24 hours. The samples were freeze-dried at temperature of −10°C in a triad freeze drier (Fisher Scientific) and subsequently characterized.

Characterization methods

Physical mixture and complexes of risperidone and amberlite prepared by various methods were characterized using the following methods.

Differential scanning calorimetry

Thermal scans were obtained on differential scanning calorimetry (DSC;2920 Modulated DSC; TA Instruments, New Castle, DE, USA) for a milligram of samples placed in a hermetically sealed aluminum pan and heated from RT to 300°C at a rate of 10°C/min. Duplicate runs were made for each sample.

X-ray diffraction

X-ray diffraction (XRD) patterns were collected for duplicate samples on MD-10 mini diffractometer (MTI Corp., Richmond, CA, USA) in 2θ range of 16–74° at a scan step size of 0.5° for 2000 seconds. The X-ray tube (Cu Kα radiation, 25 kV, 400 μA) was warmed for 10 minutes prior to measurements. Analysis was performed using MD-10 software (version 2.01).

Near-infrared spectroscopy

NIR spectra were collected using an NIR spectrophotometer (6500; Foss NIRSystems, Silver Spring, MD, USA) equipped with a scanning grating monochromator and a diffuse reflectance apparatus (rapid content analyzer). The tablets were positioned on the instrument and the NIR spectra were collected in the range 1100–2500 nm wavelengths in 2-nm increments. The spectra were collected twice for each sample to exclude

any spectral differences due to positioning of the sample. Data were collected using Vision software (version 3.2, Foss NIRSystems) and analysis was performed using Unscrambler (version 9.0, Camo Process, Oslo, Norway).

Attenuated total reflectance–Fouirer transform infrared spectroscopy

Spectra were collected using Nexus 670 FTIR with Smart Orbit Diamond ATR spectrometer (Thermonicolet, Waltham, MA, USA) in the range 500–3000 cm^{-1} wave numbers with 4 cm^{-1} data density. A total of 50 co-ads were averaged for duplicate spectra. A laser source was used as incident light on the powder and the spectra were captured in Omnic data acquisition software (version 6.2; Thermonicolet). The spectral data were analyzed using Unscrambler.

Fourier transform Raman spectroscopy

Spectra were collected using Raman spectrometer (Nexus 670; Thermonicolet) in the range 100–3700 cm^{-1} wave numbers at a data density of 4 cm^{-1}. A laser source (power ~1 W) was used as incident light on the smooth portion of the sample until maximum Raman intensity was achieved. Raman shift (50 co-ads) for duplicate sample was captured in Omnic data acquisition software (version 6.2; Thermonicolet) and analyzed using Unscrambler.

Drug release studies

The dissolution of samples was carried out in 0.1 N HCl in a USP II apparatus (paddle at 50 rpm) using an automated Vankel system (Varian Inc., Cary, NC, USA) connected to UV spectrophotometer (Varian Inc.). The samples were weighed and filled in a size 2 hard gelatin capsule (Capsugel, Peapack, NJ, USA). The amount of samples ranged from 10 mg for 1:1 and 1:2 ratios in all the cases except complex C where it was 100 mg. For 1:4 and 1:6 ratios, the amount of formulations used were 20 mg for all complexation methods except method C in which case 200 mg of the formulations were used. The volume of dissolution media was 100 mL in all the cases. This was mainly based on entrapment efficiency results. A capsule sinker was used in the 100-mL dissolution vessels to avoid floating. The absorbance of risperidone was recorded at 275 nm by sampling at every 2-minute interval for a period of 30 minutes. No withdrawal of sample or replacement of blank media was necessary as the flow-through apparatus was used. From the calibration curve, the percent released was calculated.

Binding study

For amberlite, which is practically water insoluble, equilibrium and kinetic binding studies were both of interest. The equilibrium studies were used to assess the extent of binding of risperidone to amberlite. The kinetic binding studies were used to assess the rate at which binding occurs, and it was used to support the pivotal equilibrium binding study.

The kinetic binding study to assess the rate at which binding occurs was conducted under constant risperidone concentration with varying times of observation. A maximum dose of amberlite (500 mg for amberlite) was used for this purpose with a fixed amount of risperidone. The study was conducted with sampling at predetermined time points until the binding reached equilibrium. The samples of risperidone and amberlite were incubated at a temperature of 37°C. At various time points, the sample was withdrawn and filtered. Separate flasks were used for each time point. The filtrate was analyzed for the risperidone amounts. The complexed amount was calculated based on the mass balance.

The equilibrium binding study for determination of the affinity and capacity binding constants was conducted under conditions of constant time and varying concentrations of risperidone. A sufficient number of risperidone concentrations need to be studied to provide accurate estimates of binding constants. Typically, concentrations studied should be spaced along the spectrum from the linear binding range until maximum binding is clearly established. This would include at least two concentrations varying linearly with concentrations and at least two concentrations resulting in maximum binding. In addition, two concentrations falling below and two concentrations falling above the maximum binding concentration would be included in such a scenario. However, in the present case, solubility of risperidone was a limiting factor and, therefore, the concentrations used were 0.5, 1, 5, 10, 25, 50, 100, and 200 mg/mL in 0.1 N HCl. Risperidone solutions (5 mL) were contacted with 0.5 g of activated and dried amberlite resin. After 24 hours (time for equilibrium as determined from kinetic study), they were filtered, and the filtrate was analyzed for risperidone content. From the mass balance, the amount of risperidone complexed was calculated.

The assay involved mixing the resin with a solution of known risperidone concentration, filtering off the amberlite–risperidone complex and quantitating the unbound risperidone concentration by UV. The binding capacity, reported as mmol of risperidone bound per gram of the resin, was calculated from the amount of bound risperidone and the weight of the resin used.

Results and discussion

Many active ingredients are charged species and, therefore, lend themselves readily to ionic interactions with an ion-exchange resin. Some species get charged

in certain pH range and impart charge. Risperidone, a weakly basic drug, has been formulated with an ion-exchange resin in several formulations. Our preliminary work indicated that they form complexes in all the ratios studied depending upon the preliminary method. In this study, there was an interest to see whether the method of preparation has an influence on the complex formation or entrapment efficiency. Also the binding studies were performed to obtain valuable information regarding stability of the complexes.

Physical mixture of the drug and the resin acted as a negative control, where no complex formation occurs. The resin is insoluble in most of the aqueous or organic solvents, whereas risperidone is soluble in dilute mineral acids. However, risperidone can get charged depending on pH of the media. At a very low pH value, nitrogen at position 1 and piperidine ring might get charged leading to cleavage of the bond. Also there is a possibility of keto-enol tautomerization at very low and high pH. Therefore, dilute mineral acid as well as alkali solutions were used as drug vehicle in this study. Four different types of methods were used to prepare complexes. These included solution, freeze-drying, and granulation methods. As these are commonly used methods to prepare solid dosage forms, it is interesting to see the effect of the method of preparation of the degree of complex formation. This might be of particular interest when an ion-exchange resin will be present in the formulation. Also different ratios of drug-to-resin were used to investigate the initiation ratio of complexes. For this, 1:1, 1:2, 1:4, and 1:6 risperidone-to-amberlite ratios were used to prepare complexes by all four different methods. All the physicochemical tests were performed on the pure drug, pure resin, physical mixtures, and drug–resin complexes.

Characterization of complexes

Thermal analysis

DSC scans were obtained for all the samples and are shown in Figure 1. Risperidone and amberlite resin showed endothermic peaks at 166.7°C and 221.2°C, respectively. Physical mixtures in all the ratios were shown to exhibit both the peaks for the drug as well as the resin, without any new transitions (Figure 1), indicating that risperidone was in its crystalline form without any chemical interaction or complexation when mixed physically with the resin. For drug–resin complexes, control samples were also prepared by treating the drug alone without the resin through the same process as complexes. The melting peak for risperidone did not change showing that the method had no effect on thermal properties of the drug (Figure 1). The DSC scan of the control drug (Figure 1) showed the same endothermic melting peak at 166.70°C, thus confirming no effect of formulation methodology on drug when used alone. Complexes were prepared by various methods described in Section 'Preparation of drug–resin complexes'. DSC scans are shown in Figure 1. With different methods of preparation, the DSC scans showed disappearance of the characteristic melting peak of risperidone at different drug-to-resin ratios. For methods A and B (granulation with HCl and tartaric acid, respectively), complexation occurred at higher amounts of resin (drug-to-resin ratios of 1:4 for A and 1:6 for B). However, for other two methods such as solution (method C) and freeze drying (method D), complexation was registered at lower amounts of resin (drug-to-resin ratios of 1:1 for C and 1:2 for D). Disappearance of drug-specific peak indicates the formation of complex and that the complexes have different physicochemical properties in comparison to physical mixtures of any of the pure components. There was an interaction between risperidone and amberlite resin in those drug–resin preparations as the peaks were registered in the DSC thermograms of physical mixtures at those ratios and therefore possibility of low or no detection of the drug at higher ratios of resin is ruled out. The interaction between drug and resin could be enhanced when the drug was in a solubilized form and was contacted with resin, than when it was granulated with resin. Solution form offers more reactivity for the drug than in solid form. Thus complexation can be enhanced by using solution or freeze-drying method where the drug is first solubilized before contacting with the resin, thus enhancing the reactivity between them.

Powder X-ray diffraction analysis

The powder X-ray diffraction (XRD) patterns of risperidone, amberlite, physical mixtures, and preparations by all four methods are represented in Figure 2. The presence of intense peaks at 2θ of 21.9°, 23.1°, 24.8° along with few other peaks for risperidone is indicative of its crystalline character. Diffraction pattern of amberlite resin did not show any sharp peaks indicating its amorphous nature. Diffraction patterns of risperidone/amberlite physical mixtures were constituted by the superposition of the spectra of the single components, indicating no formation of new structure. Reduction of crystallinity of risperidone was observed at higher drug-to-resin ratios for preparations by methods A and B (1:4 for method A and 1:6 for method B), whereas for methods C and D, it was observed at lower ratios. The results of XRD studies support the results obtained by DSC studies. The results might be attributed to an interaction between the drug and the resin, suggesting the presence of a new solid phase with lower crystallinity than the free drug and the resin. Similar complexation has been explained based on XRD studies in the literature and also was shown in our previous study[8,9].

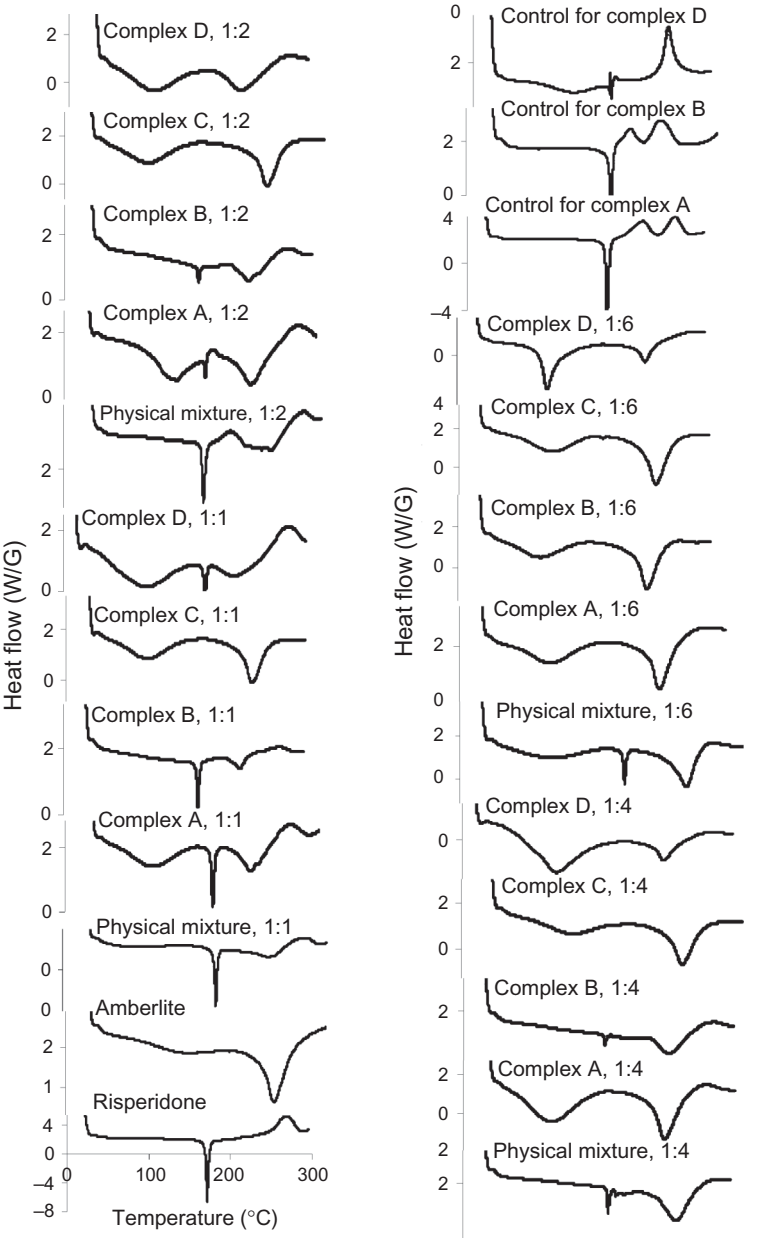

Figure 1. Differential scanning calorimetry thermograms of risperidone, amberlite, physical mixtures, controls, and complexes.

Spectroscopic studies

Spectroscopic studies were carried out to provide more evidence for complex formation. FTIR, NIR, and Raman spectroscopy were used to evaluate physical mixtures and complexes.

FTIR spectroscopy is commonly employed to study the drug–excipient interactions. In this study, it was used to investigate complexation phenomena, and the spectra of all the samples are shown in Figure 3. FTIR spectra collected in the range 700–3500 cm^{-1} (mid-IR) were investigated for the study by using FTIR spectroscopy. FTIR spectroscopy is used to identify the molecule and functional groups by means of identifying the corresponding vibrational energy levels of a molecule. Strong absorption bands at energies 1690, 1150, and between 3000 and 3100 cm^{-1} in risperidone FTIR spectra were assigned to the aryl ketone (–C=O), ester (–COO), and olefinic =C–H stretching bands, respectively. In amberlite spectra, a very broad band at 2920 and 1705 cm^{-1} were assigned to carboxylic acid functional groups, O–H and C=O (H bonded), respectively. The characteristic bands of the drug and the resin also appeared in the spectra of physical mixtures. Preparations obtained by different methods showed that complexation occurred at drug-to-resin ratios of 1:1, 1:2, 1:4, and 1:6 for complexes prepared by methods C, D, A, and B, respectively. This

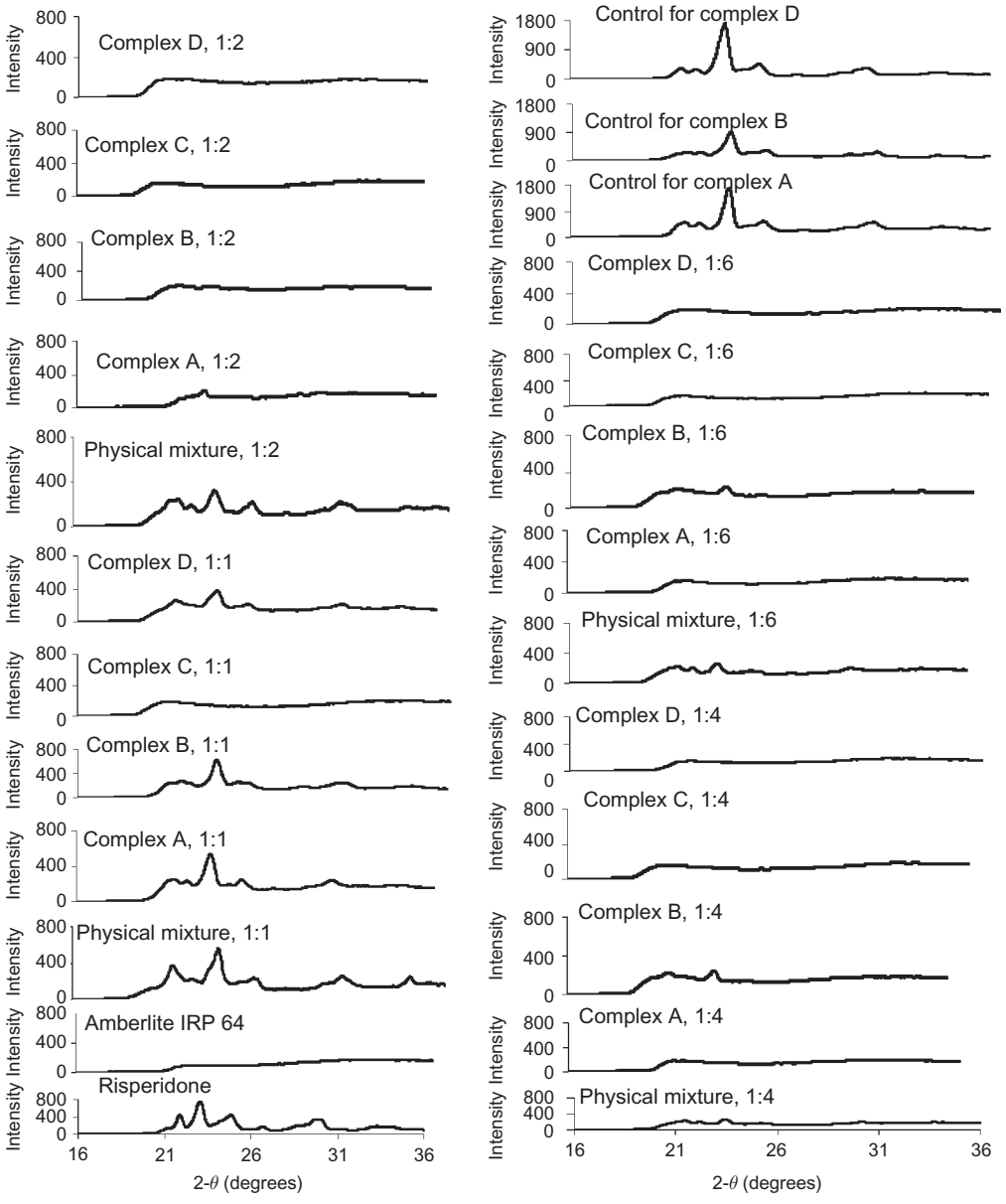

Figure 2. X-ray diffraction patterns of risperidone, amberlite, physical mixtures, controls, and complexes.

shows that complexation is dependent not only on the amount of complexing agent present but also depends on the method of preparation. The methods C and D where drug is dissolved prior to contacting with the resin shows complexation at a lower ratio as compared with granulation method where complexation is seen at a higher ratio as in the case of methods A and B. The results obtained from FTIR study supported the previous results obtained in thermal and crystallographic studies.

NIR spectroscopic studies were conducted to determine the feasibility of this method to identify and differentiate complexes from noncomplexed products. NIR spectra for all the samples are shown in Figure 4. The difference between spectra of complexes with various drug-to-resin ratios could not be distinguished. NIR absorption intensities are weaker than mid-IR region, and this technique was unable to discern the complexation ratios.

Other spectroscopic technique that is gaining momentum in online and inline mode is Raman spectroscopy. In this study, we looked at the feasibility of the technique to identify and differentiate various complexes. In the case of Raman spectra, essentially the same wavelength region as that of mid-IR is evaluated. It also involves molecular vibrational energy; however, some characteristic bands that were not registered in IR spectra were observed in Raman spectra[10]. Raman

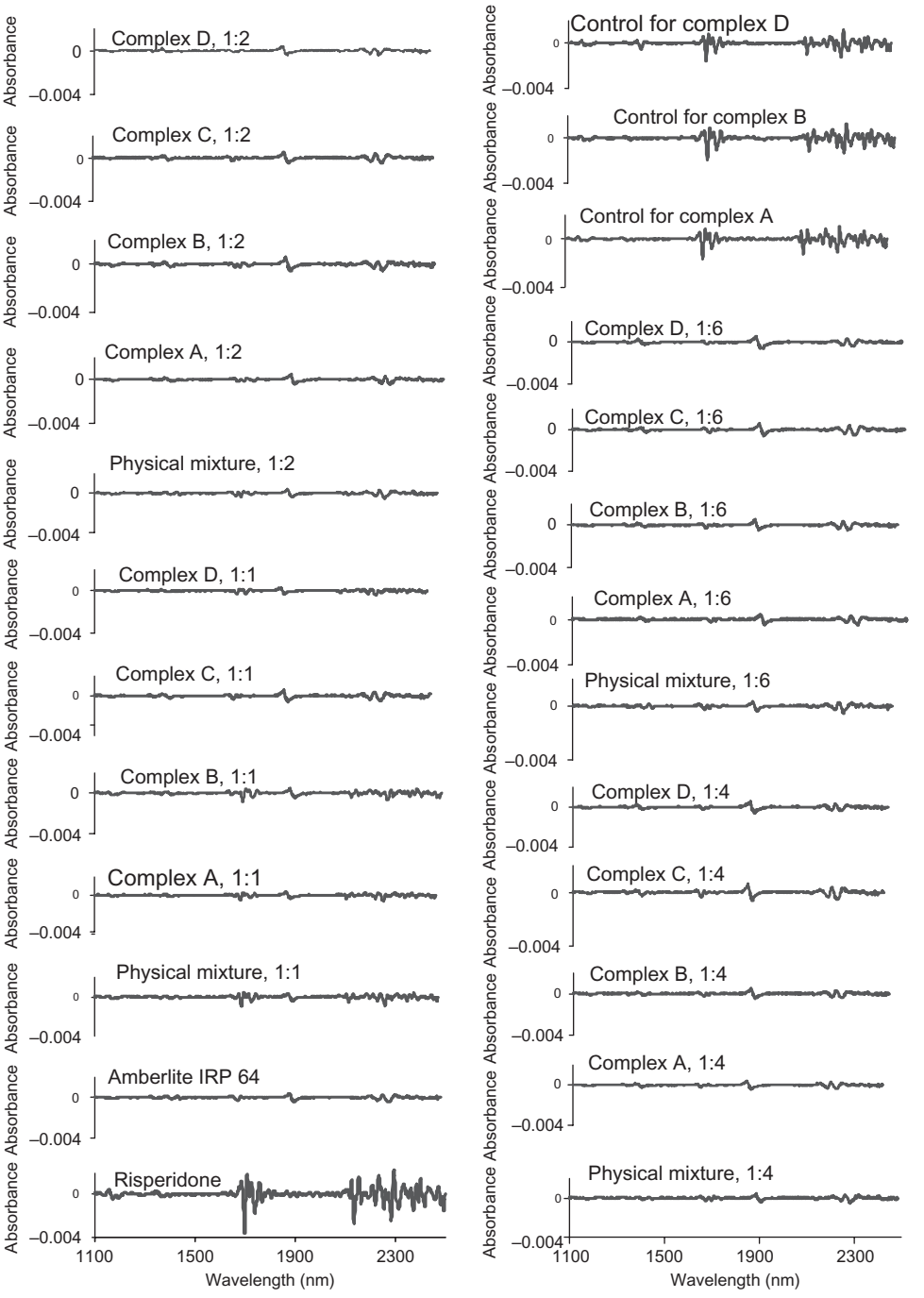

Figure 3. Near-infrared spectra of risperidone, amberlite, physical mixtures, controls, and complexes.

spectra of all the samples are shown in Figure 5. The most prominent Raman shift occurred at 3064 and 2930 cm^{-1} for risperidone and amberlite, respectively. The spectra of physical mixtures exhibited all the characteristic peaks of both the components, whereas preparations obtained by different methods showed that complexation occurred at drug-to-resin ratios of 1:1, 1:2, 1:4, and 1:6 for complexes prepared by methods C, D, A, and B, respectively. Thus the results obtained by this technique were very close to those obtained by thermal, crystallographic, and FTIR studies. Therefore, Raman spectroscopy can be used to visualize chemical shifts in the spectra of complexes.

Thus, spectroscopic studies revealed complex formation between risperidone and amberlite. The mechanism of complexation was discussed in our earlier study[11] where the functional groups involved in complex formation were identified. In this study, it was

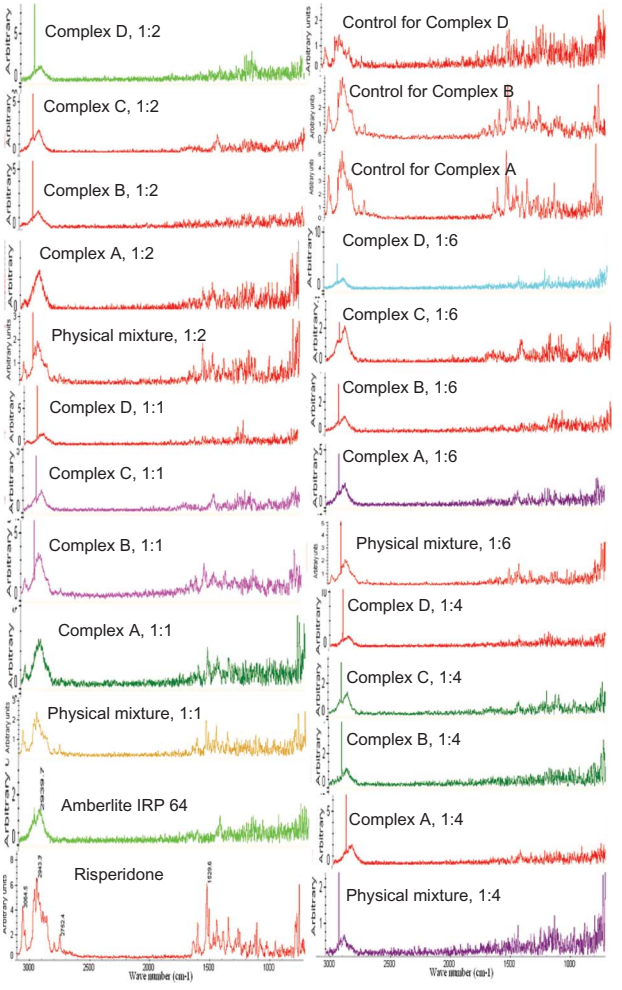

Figure 4. Raman spectra of risperidone, amberlite, physical mixtures, controls, and complexes.

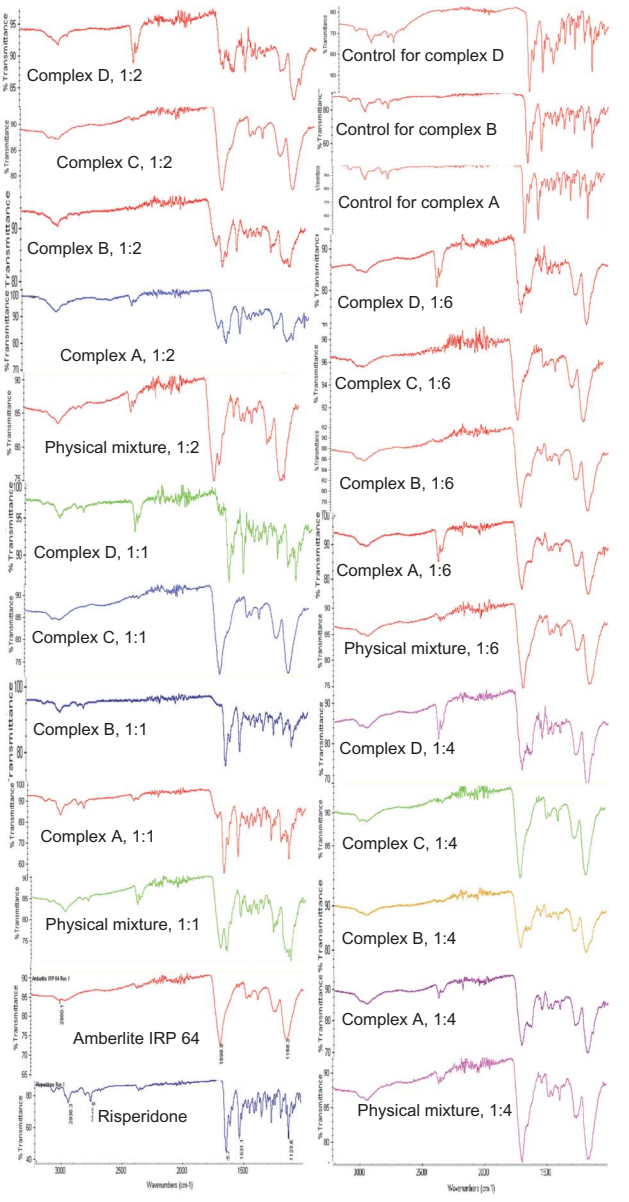

Figure 5. Fourier transform infrared spectra of risperidone, amberlite, physical mixtures, controls, and complexes.

identified that the interaction is enhanced when the resin and the drug is facilitated to interact by dissolving the drug in a solvent and then contacting with the resin, rather than by just physically mixing. In the case of granulation, the interaction is enhanced by the presence of a solvent.

Drug release studies

The drug release studies were performed for all the preparations at 1:6 ratios because at that ratio the complexation was evident from thermal, crystallographic, and spectroscopic studies. A validated UV spectrophotometric method was used for analysis. The release studies were performed in the acidic dissolution media (pH=1.2) as the formulations created were intended to release the drug immediately. For immediate release dosage forms, the release and absorption starts in the stomach as the residence time in the stomach is generally from 0.5 to 4 hours. The release was faster initially for a period of 10 minutes for the complexes as compared with the physical mixture; however, the release was prolonged after that period (Figure 6). The alteration of dissolution with complexation might be due to altered energy states. This has been also seen in other cases where complexation altered the dissolution rate of drugs[8,12]. The initial enhancement of drug release might be attributed to better wetting or modification of microenvironment pH. The later slower release of drug from the complexes as compared to physical mixture can be attributed to slower diffusion of the drug through the complexing agent and thus delaying the release of the drug in the media. Nevertheless, the drug release

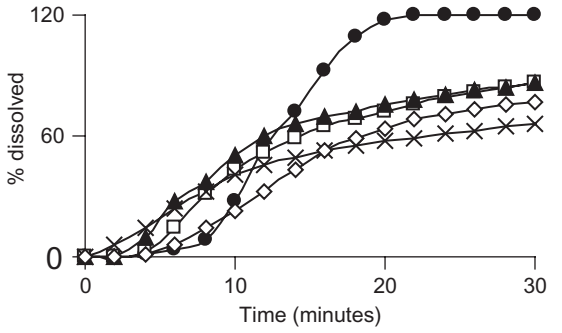

Figure 6. Drug release of risperidone from drug-to-resin ratio of 1:6. Symbols: (●) represents physical mixture, (□) represents complex A, (▲) represents complex B, (x) represents complex C, and (❍) represents complex D.

study also supported that complexation was evident between risperidone and amberlite for all four methods of preparation.

Binding study

The kinetic binding study to assess the rate at which binding occurs was conducted (Figure 7). The binding reduced initially and reached equilibrium at 24 hours. The kinetic study was conducted to obtain the equilibrium time, which was used for equilibrium binding studies. The initial drop in the binding was observed, which might be a result of desorption of bound risperidone initially. This might be due to absorbed risperidone within the resin as a result of swelling of the resin. As the resin and risperidone interacts for a longer time, adsorption of the drug on to the resin might be responsible for its complex formation.

The equilibrium binding study for determination of the affinity and capacity binding constants were conducted. The equilibrium binding of risperidone molecules from a solution to the resin at constant temperature were fitted in linear, Langmuir, and Freundlich isotherms (Figure 8). The equations are as follows:

Linear form:

$$q = KC^{*};$$

Langmuir form:

$$q = \frac{Kq_{\infty}C^{*}}{1+KC^{*}},$$

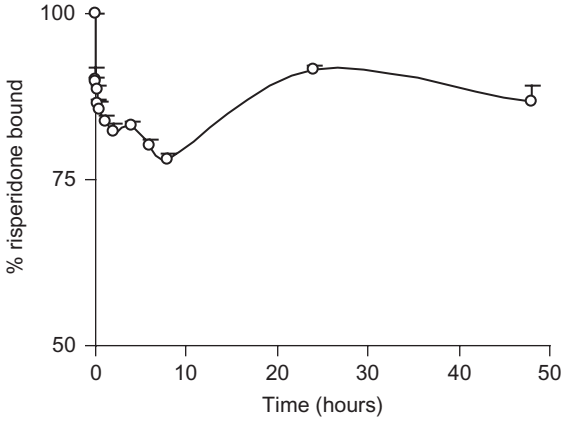

Figure 7. Kinetic binding of risperidone with amberlite.

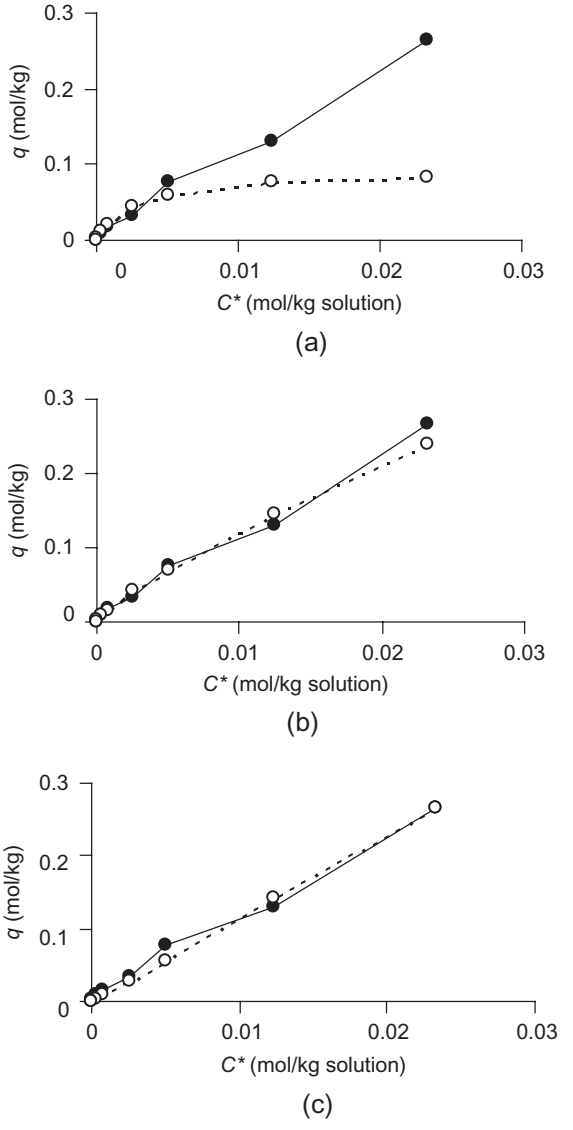

Figure 8. Adsorption isotherms of risperidone on amberlite resin (a) Langmuir, (b) Freundlich, and (c) Linear. Symbols (●) and (❍) represent actual and theoretical values, respectively.

Table 1. Adsorption isotherm values for risperidone (adsorbate) on amberlite resin (adsorbent).

Linear form	Freundlich form	Langmuir form
K=11.4 kg/mol	K=4.9 kg/mol	K=382.5 kg/mol
	n=0.8	q_∞=0.09 mol/kg

Freundlich form:

$$q = KC^{*n},$$

where q denotes adsorbed amount, q_∞ denotes loading capacity, K denotes equilibrium constant, C^* denotes the equilibrium concentration, and n is the exponent.

Plots of q versus C^* were plotted and the coefficients and constants were calculated for all the three forms (Table 1). It was found that Langmuir model failed to fit the data obtained. Freundlich and linear forms were able to fit data more accurately where linear form showed the highest fit. From this it can be seen that adsorption of risperidone on resin is linear where adsorption is known to occur in a monomolecular fashion.

Conclusions

Complexation between risperidone and amberlite was investigated for various preparation methods. It was found that complexation occurred at lower amounts of amberlite resin (drug-to-resin ratios of 1:1 and 1:2) when solution form of drug was in contact with the resin as in the case of solution and freeze-drying techniques compared with granulation (drug-to-resin ratios of 1:4 and 1:6). DSC, XRD studies, spectroscopic studies, and drug release studies were used to evaluate the complexes and differentiate them from the physical mixtures. Binding studies between them revealed that the binding depended linearly on solubility of the drug limiting the adsorption capacity. Results of the study highlighted the importance of the preparation methodologies in formulation of complexes. When the drug and the resin were simply mixed physically, no complexation occurred. Thus, a careful evaluation of manufacturing procedure would indicate the nature and extent of complexation.

Declaration of interest: The opinions expressed in this work are only of authors and do not necessarily reflect the policy and statements of the FDA. The authors report no conflicts of interest.

References

1. Douglas SJ. (1990). Process for the preparation of a ranitidine resin absorbate. Glaxo Group Research Ltd., EP 0 431 759.
2. Astruc J, Sambot A. (1970). Ion-exchange resin: Spiramycin compositions. US patent, GB 1,180,233.
3. Borodkin S, Sundberg DP. (1971). Chewable tablets including coated particles of psuedo-ephedine-weak cation exchange resin. US patent, US 3,594,470.
4. Chapman DG, Shenoy KG, Campbell JA. (1959). Sustained release of drugs in certain drug-resin complexes as judged by urinary excretion rates. Can Med Assoc J, 81:470–7.
5. Eichman ML. (1991). Sustained release drug-resin complexes. US patent 4996047.
6. Lycored. (2007). Vitamin B_{12} tablets on resin 1%. http://www.lycored.com/Retriever/web/ui/ProductDocument.aspx?DID=1&PID=733/ [accessed 14 May 2008].
7. Gao R, Shao ZJ, Fan ACL, Witchey-Lakshmanan LC, Stewart DC. (2003). Taste masking of oral Quinolone liquid preparations using ion exchange resins. US patent 6,514,492.
8. Nie S, Fan X, Peng Y, Yang X, Wang C, Pan W. (2007). In vitro and in vivo studies on the complexes of vinpocetine with hydroxypropyl-beta-cyclodextrin. Arch Pharm Res, 30:991–1001.
9. Hassan M, Sulieman M, Najib N. (1990). Improvement of the in vitro dissolution characteristics of famotidine by inclusion in β-cyclodextrin. Int J Pharm, 58:19–24.
10. Whiffen DH. (1968). Raman spectra. In: Whiffen DH, ed. Spectroscopy. 2nd ed. New York: John Wiley and Sons, Inc., 109–14.
11. Tawakkul MA, Shah RB, Sayeed VA, Khan MA. (2009). Complexation of risperidone with a taste masking resin: Application of near infra-red and chemical imaging to evaluate complexes. Pharm Dev Tech (in press).
12. Halder A, Maiti S, Sa B. (2005). Entrapment efficiency and release characteristics of polyethyleneimine-treated or -untreated calcium alginate beads loaded with propranolol-resin complex. Int J Pharm, 302:84–94.