Molecular State of Chlorpheniramine in Resinates

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Chlorpheniramine (CPM) maleate was prepared as a series of resinates by the batch method. The several resinates were investigated by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and infrared (IR) spectrometry. The results from DSC and XRPD showed that the molecular state of the entrapped drug changed from the crystalline to amorphous state. IR spectra indicated that only CPM species was entrapped in the resinates. Moreover, it also showed that the positively charged amine group of the drug interacted with the sulfonate groups of the resin by ionic association. The dissolution of the drug and resinates was also studied where it was found that the dissolution of the resinates was retarded by their crosslinked structure and markedly affected by the quantity of resin.

Key words chlorpheniramine maleate; ion exchange; X-ray diffraction; differential scanning calorimetry; infrared spectrometry

It has been recognized that the physicochemical properties of a drug can be changed in a number of ways. For example, a significant decrease in crystallinity and improvement in the dissolution rates of glibenclamide and oxazepam were observed with inclusion complexes of cyclodextrins.^{1,2)} The use of a vacuum or microwave energy to prepare felodipine surface solid dispersions led to a significant improvement in drug dissolution, which was caused partly by the amorphous state of the drug.³⁾ The ground drug and mixture, depending on the grinding time, were less crystalline and dissolved to greater extent in organic solvents than the intact drug.^{4,5)} A resinate is a complex of a drug and resin⁶⁾ and it can be used to formulate sustained-release products, some of which have been marketed. A large number of drugs have been extensively studied as resinates such as propranolol HCl, some NSAIDs and dextromethorphan HBr.^{7–9)} Furthermore, encapsulated resinates with some polymers have been prepared, and it has been claimed that a more controllable release was obtained.¹⁰⁾ However, information about the molecular state of a drug in the resinate is rare.

Therefore, this work was carried out to investigate the molecular state of a drug manipulated as a series of resinates. Chlorpheniramine (CPM) maleate and Amberlite® IRP 69 (in powder form) were used as the model drug and resin, respectively. This resin is an insoluble, strongly cationic exchanger with 8% cross-linkage derived from a sulfonated copolymer of styrene and divinylbenzene (Fig. 1). The molecular state of the resinates as well as the drug was investigated by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and IR. In addition, the dissolution of samples was also determined and discussed.

Experimental

Materials Amberlite® IRP 69 (Sigma, U.S.A.), CPM maleate (Sigma, U.S.A.), monobasic potassium phosphate (Wako, Japan) and sodium hydroxide (Jensei, Japan) were used.

Purification of Resin The resin (20 g) was placed in a 250 ml beaker and 200 ml distilled water was added. The slurry was stirred with a magnetic bar for 5 min, and allowed to settle for 15 min; then, the supernatant was removed by decantation. The resin was washed another two times according to the above procedure. The washed resin was collected by filtration and dried overnight in a hot air oven at 50 °C. The dried resin was kept in a tight vial until preparation of the resinates.

Preparation of Resinates The resin (1 g) was weighed and added to

100 ml of 0.15, 0.5 or 1.0% w/v CPM maleate solution. The mixtures were left in the dark at room temperature (25 °C) for 48 h and periodically shaken. The resinates were isolated by filtration and washed with an excess of distilled water which was then collected and added to the previous filtrate. The resinates were dried overnight in a hot air oven at 50 °C, and stored in a tight vial. The drug content in each final filtrate, which consisted of the filtrate and the washing water, was analyzed by UV spectroscopy (UV-160, Shimadzu, Japan) at 261 nm. The amount of drug loaded on the resinates was obtained by subtracting the amount of drug remaining in the final filtrate from the initial amount.

Preparation of CPM Base CPM base was prepared by making CPM maleate solution alkaline with 1.0N sodium hydroxide. Then, ether was added and the mixture was shaken gently. The ether phase was removed and evaporated on a water bath until only CPM base remained. Finally, the CPM base was kept in a vacuum chamber until investigation.

DSC A differential scanning calorimeter (DSC 7, Perkin Elmer, U.S.A.) was used and each sample was placed in an aluminum pan and crimped with its cover (Perkin Elmer, U.S.A.). The heating and cooling rates were 20 and 200 °C/min, respectively. All measurements were obtained over 25–250 °C under nitrogen.

XRPD A Rigaku X-ray powder diffractometer was used and measuring conditions were as follows: CuK α radiation, Ni filtered, graphite monochromator, voltage 35 kV and current 10 mA. All samples were run at 1° (2 θ) min⁻¹ from 5 to 35° (2 θ).

IR Spectrometry IR spectra were obtained using a Fourier transform infrared spectrometer (FT/IR-7300, Jasco, Japan) and measurements were carried out on KBr disks.

Dissolution Study The dissolution of the drug and resinates was studied using the USP paddle apparatus.¹¹⁾ The sample was accurately weighed to obtain the equivalent of 15 mg of drug and added to vessels containing 450 ml phosphate buffer, pH 7.0 $\pm$ 0.2.¹¹⁾ The temperature and paddle speed were set at 37 $\pm$ 0.1 °C and 50 $\pm$ 1 rpm, respectively. At suitable times, the amount of drug released was analyzed by UV spectroscopy.

Water Content Determination Karl Fisher titration with an Aquacounter® (AQU-6, Hiranuma, Japan) was used.

Results and Discussion

No water was detected in the CPM maleate. On the other

Fig. 1. Structure of Amberlite® IRP 69

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Table 1. Obtained Resinates

Resinate	CPM content (% w/w)	Water content (% w/w)	CPM content on a dry basis ^a (% w/w)
Resinate I (RS I)	12.31	10.63	14.67
Resinate II (RS II)	30.59	10.49	35.06
Resinate III (RS III)	43.21	7.99	48.23

a) Water content of dried resin = 18.34% w/w.

Fig. 2. DSC Curves of Resin (a), CPM Maleate (b), RS I (c), RS II (d), and RS III (e)

hand, the resin and the resinates contained high and varying amounts of water, even when dried overnight at 50 °C. The drug content without and with (on a dry basis) water subtraction is shown in Table 1. In a certain quantity of resinate, it was found that the amount of drug calculated from the drug content without water subtraction underestimated the actual drug content calculated from the drug content on a dry basis (6.11, 2.52 and 2.63% w/w in RS I, RS II and RS III, respectively). To obtain the actual drug content as required, the drug content on a dry basis was used to calculate each quantity of resinate, which contained the equivalent drug content, for the dissolution study.

Molecular State of Drug in Resinates Figure 2 shows the DSC curves of the resin, CPM maleate and resinates. CPM maleate has an endothermic peak at 138 °C, indicating the temperature of drug melting, whereas no peak over the range 25–250 °C was observed in the DSC curves of the resin and all resinates. The XRPD patterns of the samples are shown in Fig. 3. It appears that the molecular state of CPM maleate is crystalline, but the resin is amorphous. The resinates also showed a halo' pattern. DSC and XRPD

Fig. 3. X-Ray Patterns of Resin (a), CPM Maleate (b), RS I (c), RS II (d), and RS III (e)

Fig. 4. IR Spectra of Resin (a), CPM Maleate (b), and CPM Base (c)

showed that the molecular state of the entrapped drug in the resinates changed from the crystalline to the amorphous state. From this it appears that the drug is dispersed monomolecularly in the resinates.¹²⁾

Interaction in Resinates IR spectra of the resin, CPM maleate and resinates are shown in Figs. 4–5. The three peaks at 1586, 1358 and 865 cm⁻¹, corresponding to the stretching of the carbonyl group (C=O), carbon-oxygen group (C–O) and ethylene group (C=C) of the maleate

Fig. 5. IR Spectra of RS I (a), RS II (b), and RS III (c)

species, disappeared in IR spectra of the resins. This confirmed the absence of maleate species in the resins, in accordance with the theory that only a positively charged species can exchange on a cationic exchanger.¹³⁾

The IR spectrum of the CPM base was also measured and this is shown in Fig. 4. Comparing the IR spectra for CPM maleate, CPM base, resin and resins, the IR spectra of the resins could be divided into two different regions. One around the region of 800 to 2000 cm^{-1} showed the existence of major characteristic peaks of CPM base (indicated with arrows), whose intensities increased on increasing the amount of drug entrapped in the resins. This indicated that the CPM species was entrapped in the resins. The other, from 2000 to 4000 cm^{-1} , was more similar to the CPM maleate (salt form) and resin spectra, at the same region, than to that of the CPM base and resin spectra. This confirmed the stretching of the positively charged amine group (NH^+) in the IR spectra of the resins. Furthermore, the NH^+ peak of the drug was shifted from 2457 cm^{-1} to around 2719–2753 cm^{-1} in the resins. The above evidence shows that the CPM species in the resins exists in the positively charged form which interacts with the sulfonate groups in the resin. This kind of ionic association is referred as a “salt bridge” (Fig. 6).¹⁴⁾ Like the hydrogen-bonding effect, the degree of this ionic association, which closely relates to the H-donating and accepting ability of an ion pair, significantly affects the NH^+ stretching. As the ionic association increases, the NH^+ stretching decreases and subsequently shifts to a lower frequency, and *vice versa*. Therefore, the shifting of the NH^+ stretching in the drug to a

Fig. 7. Dissolution Profiles of CPM Maleate (X), RS I (O), RS II (◇), and RS III (△)

(b)

(a)

Fig. 6. Depiction of the Ionic Association in CPM Maleate (a), and in Resins (b)

higher frequency in the resins suggests that the ionic association in the resins is weaker than in the drug. One explanation might be that the H-accepting ability, corresponding to the basicity, of the sulfonate group is weaker than that of the carboxylate group.¹⁵⁾ Moreover, a related text attributing the interaction in the resinate to a weak ionic association in which no chemical bond was formed, supports this hypothesis.¹³⁾ In conclusion, CPM was dispersed monomolecularly in the resins and an ionic association was formed between the sulfonate groups of the resin and the NH^+ group of CPM.

Release Study The dissolution of the drug and resins is presented in Fig. 7. The dissolution rate of the drug was faster than that of the resins. The retard release in the resins, in spite of the amorphous molecular state of the drug, was attributed to their crosslinked structure which resists drug diffusion through the resin beads.^{8,9)} The amount of CPM released increased from 61.93 to 87.54 and 96.36% w/w in RS I, RS II and RS III, respectively, indicating that drug distribution in the resins greatly affected the amount of drug released. This was due to the decreasing quantity of resin in RS I, RS II, RS III, respectively. A detailed explanation was proposed in a recently published study showing that increasing the quantity of the resin reduced the effectiveness

Table 2. Retained Fraction in Resinates

Resinate ^{a)}	Quantity of resin ($\times 10^{-3}$ g)	Exchange capacity ^{b)} (meq)	CPM retained ^{c)} (meq)	Retained fraction ^{d)}
RS I	87.2	0.3750	0.0146	0.0389
RS II	27.8	0.1195	0.0048	0.0402
RS III	16.1	0.0692	0.0014	0.0202

a) All resinates contain the equivalent of 15 mg CPM maleate. b) Quantity of resin multiplied by total exchange capacity of resin (4.3 meq/g). c) MW of CPM maleate=390.8. d) CPM retained divided by exchange capacity.

of the vehicle; unfortunately, no experimental evidence was provided.¹⁶⁾ The relationship determining the fraction of drug retained is presented in Table 2. It was found that the fraction of drug retained in the resinates reached an equilibrium value. This behavior suggests that the quantity of the resin in resinates directly affects the amount of drug released. At an equivalent drug content, the proportion of the quantity of drug required for that retained fraction (Table 2) to the quantity of drug released increases on increasing the quantity of resin in the resinates, which consequently leads to less drug release.

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