

## **REPORT**

# **Preparation of levodopa/carbidopa compound drug resins**

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**Abstract:** The main objective of this study was to prepare the levodopa/carbidopa compound drug resins and investigate affecting factors such as drug concentration, temperature, particle size. The drug resins were made by bath method and the effects of above factors during the process of preparation was studied. Studies on the stabilities of drugs and drug resins were carried out by HPLC. The Results showed that the preparation of drug resins was influenced by drug concentration, resin particle size, reaction temperature and solvent concentration. In certain conditions the degradation peaks were found in the chromatograms of levodopa and carbidopa while the drug-resins remained undegraded. The study indicates that the drug resin technology is an effective way of improving stability of the drug and possesses certain sustained-release effects.

**Keywords:** Levodopa, carbidopa, ion exchange resin, stability.

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## **INTRODUCTION**

One pharmacological treatment of the Parkinson's disease is based on the increase in the dopamine levels in brain by levodopa application. Levodopa has the ability to cross the blood-brain barrier, and be converted to dopamine by dopa decarboxylase and increase the dopamine content. However, only 1% of the levodopa absorbed could enter the brain through blood-brain barrier, leading to a decrease in cardiovascular side-effects and notably hypotension. Levodopa is administrated in association with, in previous investigations, a dopa decarboxylase inhibitor like carbidopa, which allows levodopa into the brain which convert to effective dopamine. L-3, 4-Dihydroxyphenylalanine (Levodopa) is used to replenish DA in PD. Carbidopa, the dopa decarboxylase inhibitors, is also a common drug in treating Parkinson's disease by preventing peripheral metabolism of Levodopa to dopamine (Lukasz Szyrwił *et al.*, 2013; Owen Y. Chao *et al.*, 2012; Seung-Nam Kim *et al.*, 2014; David Devos *et al.*, 2014). The plasma half lives ( $t_{1/2}$ ) of levodopa and carbidopa are 1~3 h and they were slightly soluble in water. Since levodopa and carbidopa both contain 2-3 phenolic hydroxyl groups, they are very unstable when exposed to air, oxidation or water solution.

Ion-exchange resins are cross-linked and water-insoluble polyelectrolyte, which have been widely used in drug delivery system recently (Jong-Il Kim *et al.*, 2013; Gut *et al.*, 2008; Yoshinobu and Mariko, 2011; Puttewar *et al.*, 2010). Much of the research on drug delivery systems has

been focused on oral controlled-release dosage forms. Thanks to its physio-chemical stability, uniform size, spherical shape, the ion-exchange resins can be coated easily and are noted for their reproducible drug release ability in ionic environment. Once the ionized active ingredient of drug is loaded onto the resins by an exchanging reaction, a drug resinate is formed. The body's natural counter ion concentration stabilizes drug release relieving the concern of a burst release profile. The sustained release profile form will reduce the side effects and maintain relatively constant plasma concentration (Mandal *et al.*, 2010; Kikuchi and Takayama, 2010). In recent years, the resin received more attention (Qinhai *et al.*, 2011; Bhoyar and Amgaonkar, 2011; Varaporn and Greepol, 2008). Since levodopa and carbidopa both can be ionization dissolved, it is possible to develop the sustained release suspension using ion exchange resins as carriers. The drug is contained in the inner structure of the resins, which can protect the drug from being exposed and improve drug stability.

The objective of this study is to prepare the levodopa/carbidopa compound resins with ion exchange resin and investigate the drug loading, release profile and its stabilities.

## **MATERIALS AND METHODS**

### **Materials**

Levodopa and carbidopa, model drugs, were purchased from Suizhou Hongqi Chemical Company (Hubei province, China). The cation-exchange resin Amberlite® IRP69 (sodium polystyrene sulfonate, Na<sup>+</sup> form,

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crosslinkage of 8%) was provided by Rohm and Haas Company, Philadelphia, USA. The cation-exchange resin 001\*7 (sodium polystyrene sulfonate) was obtained from Shanghai chemical reagent company, China. Resins (500 g) was purified twice with 1000mL of distilled water, 95% ethanol, 1M HCl, 1M NaOH and then 1000mL of distilled water was used to remove the residue. Each treatment took at least 3h by a batch process. After filtration, the resin was dried at 37°C. All the other chemicals were of reagent grade and were used without further purification.

#### **Analytical method**

In the present study, the analysis of drugs and drug resins were performed by Ultraviolet spectrophotometer (UV-2401 PC, SHIMADZU Corporation) and high-performance liquid chromatography (HPLC), in which a Diamonds C18 column (5µm, 250mm; DIKMA, USA) and an injection loop of 20µl were used. The mobile phase of levodopa was the methanol solution (methanol: water, 2.5:97.5 w/w), with flow rate of 0.6 ml/min, UV detector wavelength of 280 nm, column temperature of 30°C. The composition of the mobile phase of carbidopa was NaH<sub>2</sub>PO<sub>3</sub> solution (Adjusted to pH 2.7 with phosphoric acid) and methanol (95:5), with flow rate of 1 ml/min, UV detector wavelength of 280 nm, and column temperature of 30°C. The entire run time is 10 min.

#### **Preparation of Drug-Resin Complexes (Halder et al., 2005)**

The drug/Amberlite® IRP69 complexes were prepared by a batch process. The resin particles were dispersed in drug aqueous solution under magnetic stirring at a certain temperature and then the resins were washed with deionized water repeatedly and dried in oven at 40°C to constant weight.

Since levodopa and carbidopa were slightly soluble in water and soluble in acid medium, an acid medium was chosen to prepare the resins. This is attributed by the fact that the H<sup>+</sup> in acid medium could compete with levodopa and carbidopa at the active site and lead to decreased loading capacity. Thus, HCl at an optimized concentration of 0.001mol/L were used for preparation.

#### **Effect of Temperature on the preparation of levodopa – resins**

Levodopa (50 mg) was first dissolved in 100 ml HCl (0.001 mol/L) solution and the Amberlite IRP-69 (100 mg) was then added. The solution was vigorously agitated at 500rpm for 2h at 303, 308, and 313K. The temperature was kept constant within ±0.1K. A small amount of supernatant was obtained at predetermined time intervals and the drug concentration was measured. The exchange amounts (Q\*) were obtained by means of the following equation 1 and 2.

$$Q^* = \frac{(C_0 - C^*)V}{W_R} \quad (1)$$

$$E = \frac{(C_0 - C^*)}{C_0} \quad (2)$$

where C<sub>0</sub> and C\*(mg/ml) are the initial and equilibrium concentrations of drugs, V (ml) is the volume of the drug solution, and W<sub>R</sub> (mg) is the amount of ion-exchange resin, Q\* denotes the exchange amount per ion-exchange resin at the equilibrium time, E is the availability of drug.

#### **Effect of levodopa concentration on the preparation**

Levodopa (30mg, 50mg, 70mg) was first dissolved in 100 ml HCl (0.001mol/L) solution and the Amberlite IRP-69 (100mg) was then added. The solution was vigorously agitated at 500rpm for 2h at 298K. The temperature was kept constant within ±0.1K. A small amount of supernatant was obtained at predetermined time intervals and the drug concentration was measured. The exchange amounts (Q\*) were obtained by means of the following equations 1 and 2.

#### **Effect of HCl concentration on the levodopa drug-resins preparation**

Levodopa (50mg) was first dissolved in 100ml HCl (0.001mol/L, 0.005mol/L, 0.01mol/L) solution and the Amberlite IRP-69 (100 mg) was then added. The solution was vigorously agitated at 500 rpm for 2 h at 298 K. The temperature was kept constant within ±0.1 K. A small amount of supernatant was obtained at predetermined time intervals and the drug concentration was measured. The exchange amounts (Q\*) were obtained by means of the following equations 1 and 2.

#### **Effect of carbidopa concentration on the preparation**

Carbidopa (30mg, 50mg, 70mg) was first dissolved in 100 ml HCl (0.001mol/L) solution and the Amberlite IRP-69 (100mg) was then added. The solution was vigorously agitated at 500 rpm for 2 h at 298 K. The temperature was kept constant within ±0.1K. A small amount of supernatant was obtained at predetermined time intervals and the drug concentration was measured. The exchange amounts (Q\*) were obtained by means of the following equation 1 and 2.

#### **Effect of Temperature on the preparation of carbidopa– resins**

Carbidopa (50 mg) was first dissolved in 100 ml HCl (0.001mol/L) solution and the Amberlite IRP-69 (100 mg) was then added. The solution was vigorously agitated at 500 rpm for 2h at 303, 308, and 313 K. The temperature was kept constant within ±0.1 K. A small amount of supernatant was obtained at predetermined time intervals and the drug concentration was measured. The exchange amounts (Q\*) were obtained by means of the following equation 1 and 2.

### Effect of HCl concentration on the carbidopa drug-resinates preparation

Carbidopa (50mg) was first dissolved in 100ml HCl (0.001mol/L, 0.005mol/L, 0.01mol/L) solution and the Amberlite IRP-69 (100mg) was then added. The solution was vigorously agitated at 500rpm for 2h at 303, 308, and 313K. The temperature was kept constant within  $\pm 0.1$ K. A small amount of supernatant was obtained at predetermined time intervals and the drug concentration was measured. The exchange amounts ( $Q^*$ ) were obtained by means of the following equation 1 and 2.

### Determination of drug content in the Drug-Resin Complex

Drug content was determined by accurately taking drug-resin complexes (25 mg) and dissolving it in 50ml HCl solution (0.1 mol/L). The mixture was vigorously agitated at 1000 rpm for 4 hours and the temperature was kept at  $315 \pm 0.1$  K. Samples were taken until the desorption reached at equilibrium, and the drug content was determined using UV spectrophotometer.

### Drug release study

Drug release tests were carried out according to the USP paddle (apparatus II) method by a ZRS-8G Intelligent Dissolution Tester Apparatus (Tian Jin University Radio Factory, Tian Jin, China) with 1000mL medium mixed at 100rpm. The dissolution media was 0.15mol/L NaCl at  $315 \pm 0.1$  K. Five milliliters of the medium was collected at predetermined time intervals and were filtered with 0.45 $\mu$ m nylon filters. The samples were analysed by UV spectrophotometer.

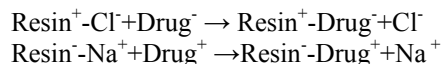
### Studies on the stability of the Drug-Resin Complex

Levodopa-resins containing 1mg levodopa were accurately weighed and suspended in 10ml water. 0.5ml 30%  $H_2O_2$ , 1mol/L NaOH, 1mol/L HCl, were put into the 10ml 0.1mg/ml levodopa solution and resin suspension. Carbidopa resins containing 2mg carbidopa were accurately weighed and suspended in 10ml water. 0.5ml 30%  $H_2O_2$  were put into the 10ml 0.1mg/ml carbidopa solution and resin suspension. The other two suspensions and two 10ml 0.2mg/ml carbidopa solution were exposed to ultraviolet lamp for 15 hours and heated on the water bath at  $90^\circ$  for two hours. Then the supernatant was then analyzed using the HPLC system.

## RESULTS

### Preparation of the drug resinates

Levodopa/ carbidopa compound is a new drug combination treating Parkinson's disease, which is unstable. Complexation with the resin, strongly acidic Amberlite IRP69, is a simple and efficient technique to increase its stability. Levodopa and carbidopa being soluble in HCl solution has desirable ionization power. The exchange process of drug release follows Equations.



### Effect of temperature, levodopa concentration and HCl concentration on the preparation of levodopa-resinates

As is shown in fig. 1, the exchange amounts ( $Q^*$ ) and availability ( $E^*$ ) of drug increased with the rise in temperature.

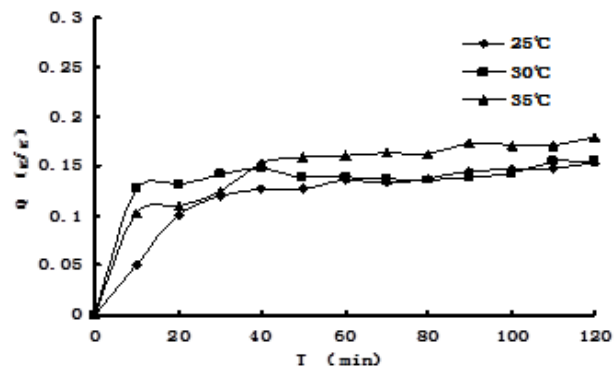


Fig. 1: Effect of Temperature on the preparation of levodopa-resinates.

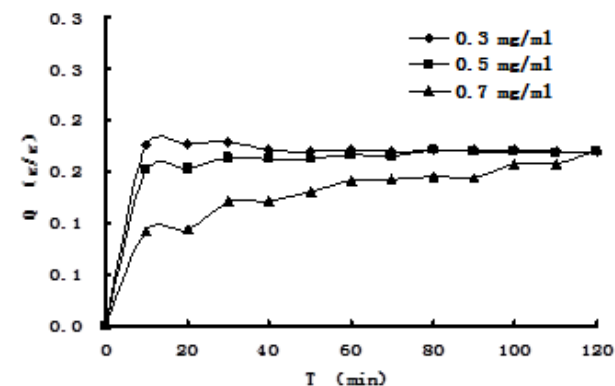


Fig. 2: Effect of levodopa concentration on the preparation.

It can be seen from the fig. 2, as the levodopa concentration increased, the exchange amounts ( $Q^*$ ) increased marginally while the availability of drug ( $E^*$ ) decreased.

As is shown in fig. 3, the exchange amounts ( $Q^*$ ) and availability of drug ( $E^*$ ) were increased as the HCl concentration increased. The concentration of hydrogen ions have great influence on the ion-exchange process.

### Effect of carbidopa concentration, temperature and HCl concentration on the preparation

From the fig. 4, we can see as the carbidopa concentration increased, there was a corresponding increase in exchange amounts ( $Q^*$ ). The availability of drug ( $E^*$ ) is lowest at the initial concentration of 0.5 mg/ml.

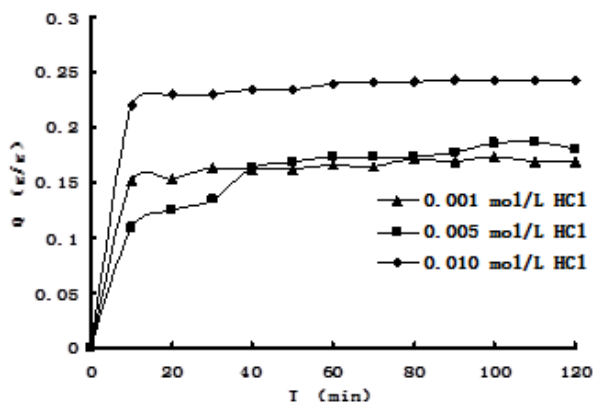


Fig. 3: Effect of HCl concentration on the preparation.

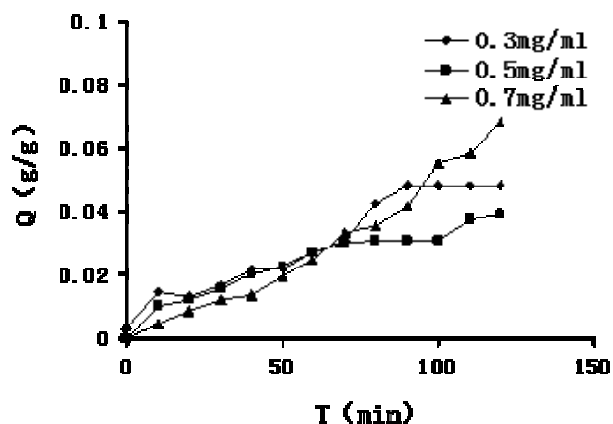


Fig. 4: Effect of carbidopa concentration on the preparation.

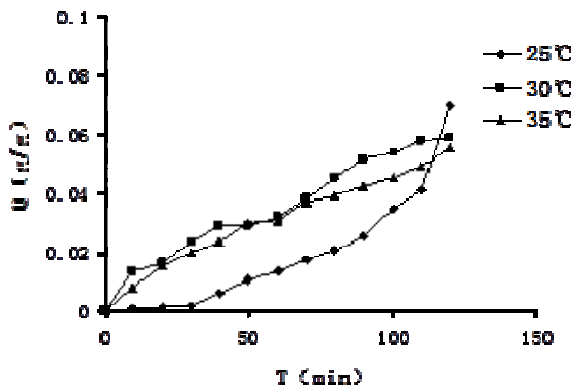


Fig. 5: Effect of Temperature on the preparation of carbidopa-resonates.

The fig. 5 shows that the exchange amounts ( $Q^*$ ) and availability of drug ( $E^*$ ) decreased with rising temperature. It brings us to a conclusion that the temperature decreasing is beneficial for the preparation of carbidopa-resonates.

From the fig. 6, the concentration of hydrogen ions in this preparation could not be too low or too high. We can see that the exchange amounts ( $Q^*$ ) and availability of drug ( $E^*$ ) were highest at the 0.005mol/L HCl.

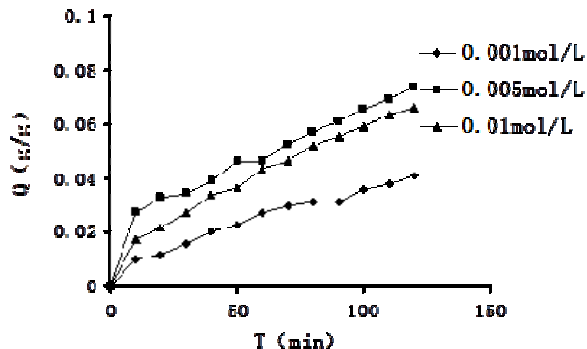


Fig. 6: Effect of HCl concentration on the carbidopa-resinate preparation.

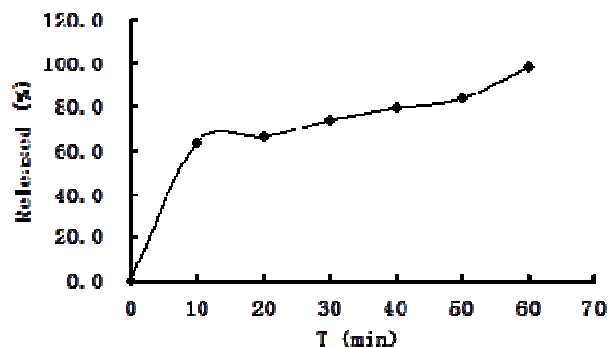


Fig. 7: *In vitro* levodopa release.

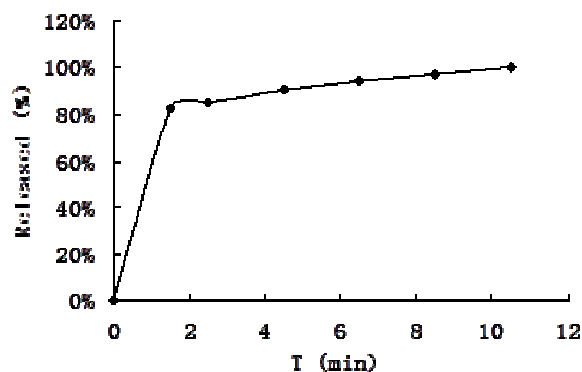


Fig. 8: *In vitro* carbidopa release.

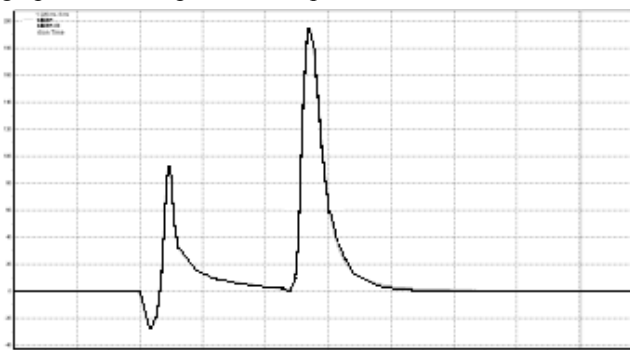
#### *In vitro drug release*

From the curves, almost all levodopa was desorbed for an hour, as compared to 10 min in the case of carbidopa. We can see to some extent the resinates could improve the sustained-release profile. However, to achieve satisfying sustained-release effect, the drug-resin complex should be coated with a semipermeable membrane.

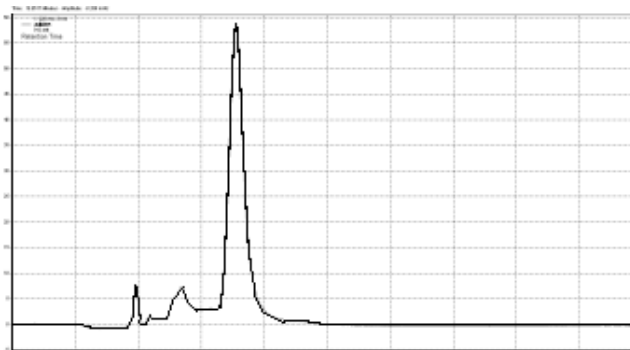
#### *Investigation on the stability of the Drug-Resin Complex*

From the high performance liquid phase diagram, degradation peaks were found in the chart of levodopa solution under the acid, alkaline and oxidizing conditions. However, no degradation peaks were found in the case of levodopa-resin suspension. Also, degradation peaks were

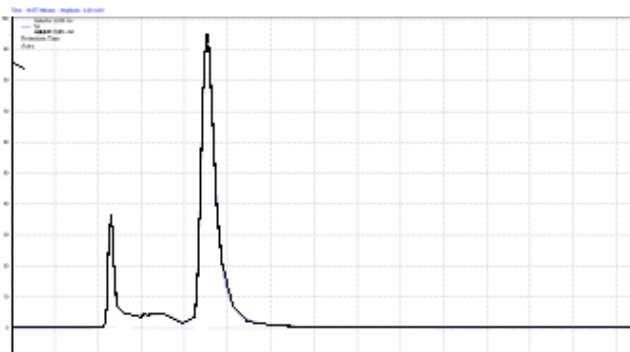
observed in the chart of carbidopa solution under the oxidizing, lighting and high temperature conditions. On the contrary, no degradation peaks were found in the graph of carbidopa-resin suspension.



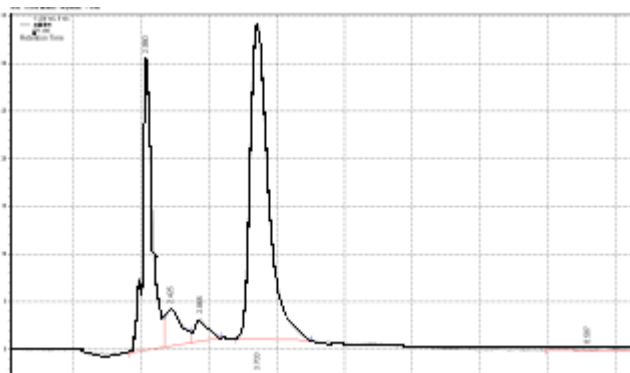
**Fig. 9:** Levodopa solution.



**Fig. 10:** Levodopa solution in acidic medium.



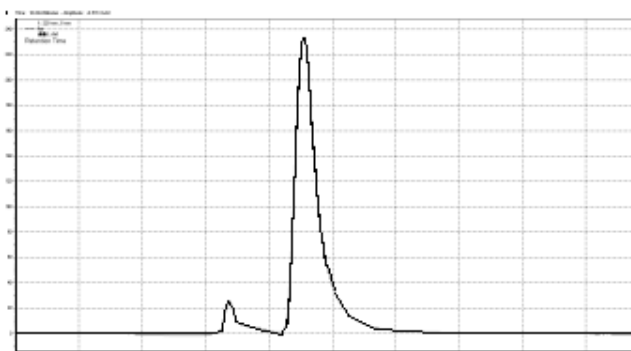
**Fig. 11:** Levodopa-resin suspension in acidic medium.



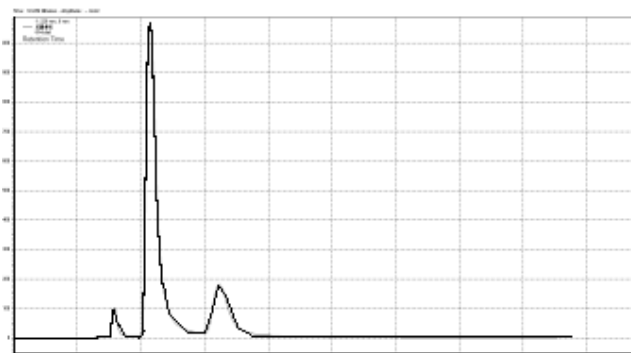
**Fig. 12:** Levodopa solution in the alkaline medium.

## DISCUSSION

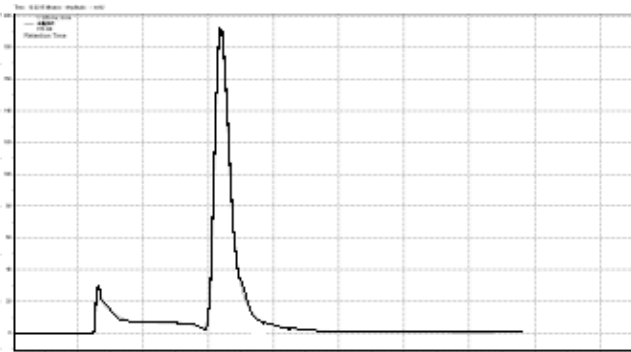
Temperature increasing is beneficial for the preparation of levodopa-resonates because the ion exchange and adsorption process is an endothermic reaction. Excess  $H^+$  ions in solution which have more binding affinity to the group of resin compete with drug for binding. The concentration of hydrogen ions have great influence on the carbidopa-resinates preparation. The preparation of carbidopa-resonates is an exothermal reaction, so the temperature decreasing is beneficial for the preparation of carbidopa-resonates. large  $H^+$  in rare HCl is competing with pharmaceutical ions in the solution and the lower concentration of  $H^+$  could not make carbidopa fully ionized.



**Fig. 13:** Levodopa-resin suspension in the alkaline medium.



**Fig. 14:** Levodopa solution under oxidizing conditions.



**Fig. 15:** Levodopa-resin suspension under oxidizing conditions.

The results of the stability of the drug-resin complex showed that the drug stability was increased by drug-resins loading, probably because the resins can isolate the drug from the outside medium and act as a barrier to prevent the influx of foreign electrolytes. The technology could potentially be used to develop sustained release formulations.

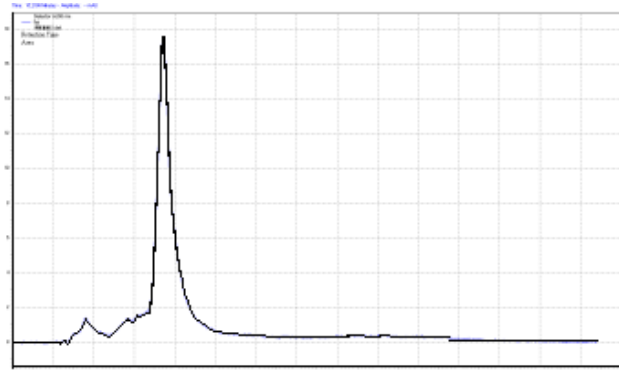


Fig. 16: Carbidopa solution.

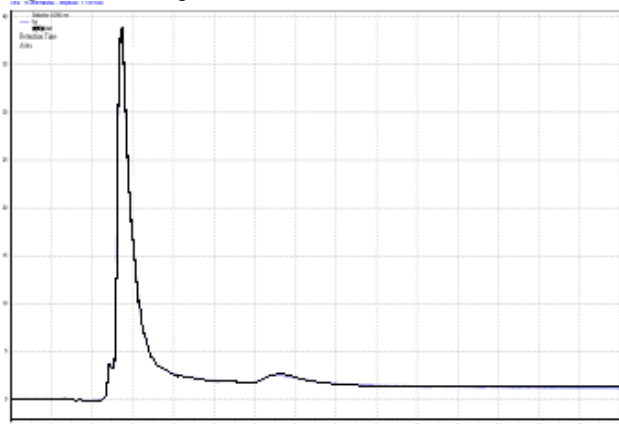


Fig. 17: Carbidopa solution in the alkaline medium.

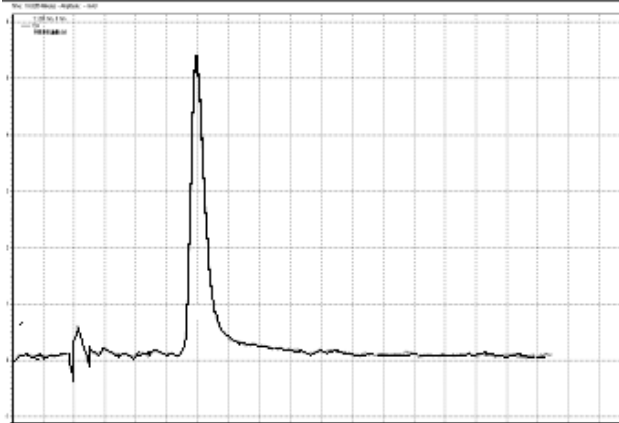


Fig. 18: Carbidopa -resin suspension in the alkaline medium.

## CONCLUSION

Levodopa/carbidopa compound drug resins were prepared by a batch process using a strongly acidic cation-exchange resin Amberlite IRP69 as the carrier. The effects

of the drug concentration, reaction temperature, and the solvent concentration on the process of ion exchange were studied. The results of levodopa-resin show that the exchange amounts ( $Q^*$ ) and availability ( $E$ ) increases as the temperature rises. As the concentration of levodopa increased, the exchange amount increased marginally while availability of drug decreased. The  $Q^*$  and  $E$  were relatively higher as the HCl concentration increased. The results of carbidopa-resin showed that increased carbidopa concentration increases the exchange amount but the availability of drug is lowest at the initial concentration of 0.5mg/ml. The exchange amounts and availability of drug decrease with the temperature increasing. The  $Q^*$  and  $E$  were highest at the 0.005mol/L HCl. The levodopa-resin had a sustained-release profile for one hour *in vitro* while carbidopa-resin exhibited a sustained-release profile for ten minutes indicating that the drug resins have some sustained-release effects.

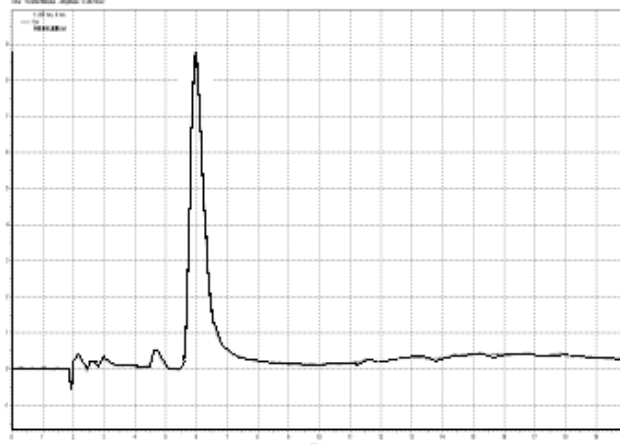


Fig. 19: Carbidopa solution under lighting.

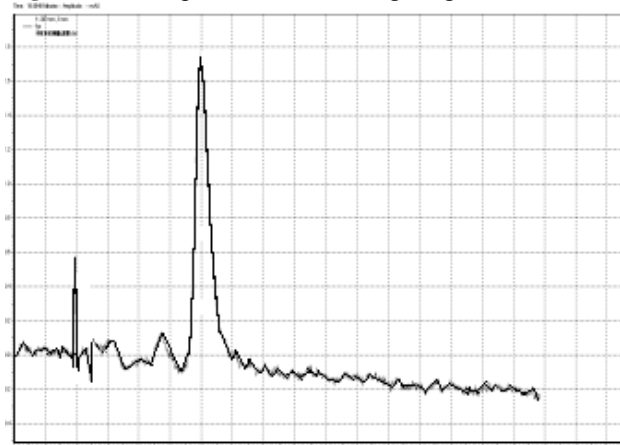


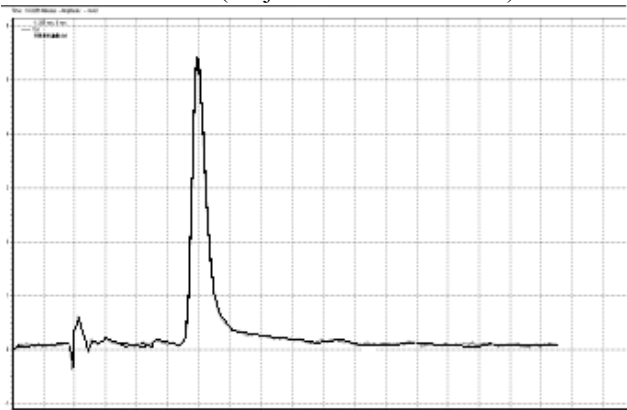
Fig. 20: Carbidopa -resin suspension under lighting.

To achieve satisfactory sustained release profile, we could combine the drug-resins with micro encapsulation or coating technique to further manipulate drug release profiles. In the next step, we will carry out the coating technique study by fluid-bed, the drug-resin could be coated with a semi permeable membrane. Investigation on the stability tells that the drug-resins were more stable

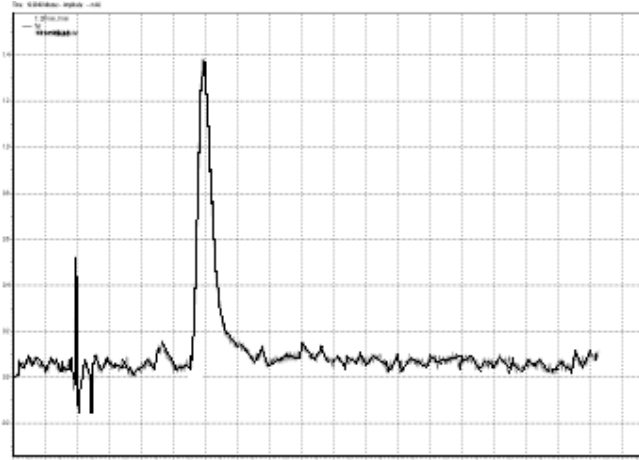
than the drugs. The technology could be applied in sustained release research.

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**Fig. 21:** Carbidopa solution under high temperature.



**Fig. 22:** Carbidopa-resin suspension under high temperature.

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