

# Study of the Formulation Parameters Affecting the Preparation of Microencapsulated Ion-Exchange Resins Containing Venlafaxine Hydrochloride

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The objective of this study was to obtain an optimum formulation for microencapsulating venlafaxine hydrochloride ion-exchange resins. This was achieved by investigating various factors which influenced the drug release. The percentage of drug released was used as an index to investigate the individual factor. The optimum coating formulation was acquired by orthogonal experiments in which the concentration of coating material in acetone was 3%, the ratio of drug-resin complexes to coating materials was 8:1 and the ratio of plasticity-agent to coating material was 5%. The results indicated that the use of ion-exchange resins along with a suitable coating material would be a feasible way to prepare a marked prolonged release type of microcapsules by the emulsion solvent diffusion method.

**Key words:** Ion-exchange resins, venlafaxine hydrochloride, microencapsulation

Venlafaxine is a novel, non-tricyclic antidepressant. Venlafaxine imparts its antidepressant effects by inhibiting the neuronal uptake of norepinephrine, serotonin and to a lesser extent, dopamine<sup>1</sup>. It lacks monoamine oxidase activity and, more importantly, lacks the adverse effect profile of tricyclic antidepressants. Now, there has been the sustained-release preparation of this drug coming into the market, but there are no marketed products of microencapsulated ion-exchange resins containing venlafaxine hydrochloride.

Ion-exchange resins are water-insoluble, cross-linked, high-molecular weight polyelectrolyte containing salt-forming groups in repeating positions on the polymer chain. They have been widely used in versatile industrial fields including pharmaceuticals<sup>2-5</sup>. On exposure to gastrointestinal media, they exchange drug of similar charge with the surrounding medium. Drug release from the drug resin complex depends on the ionic environment within the gastrointestinal tract. Ion exchange process alone, without any barriers that can retard the influx of foreign electrolytes and efflux

of drug, cannot achieve satisfactory sustained release. Thus the drug-resin complexes are often coated with a semipermeable membrane. Several encapsulation techniques have been used to encapsulate prepared drug-resin complexes<sup>6-8</sup>. Recent studies indicate that the emulsion solvent diffusion technique is a widely used method for formulation of microcapsules<sup>9</sup>.

But several drawbacks were encountered in previous investigations on the resin microencapsulation, which were always producing multinucleated microcapsules or aggregates of microcapsules. At the same time the method is often not reproducible. Most reports about microencapsulated ion-exchange resin beads only offer a degree of sustained release, without achieving complete drug release at the end of the release test period. There have been very few detailed investigations of microencapsulation formulae to obtain optimum sustained release properties.

The aim of this investigation is to optimize the emulsion solvent diffusion method, and then to prepare mononucleated microencapsulated ion-exchange resin beads containing venlafaxine hydrochloride with sustained release properties and offering complete release by means of an optimum microencapsulation formula.

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## MATERIALS AND METHODS

Venlafaxine hydrochloride was obtained from the Big Southwest Pharmacy Factory in Cheng Du City, China; the cation-exchange resin Amberlite® IRP69 (sodium polystyrenesulfonate) was obtained from Rohm and Haas Company, Philadelphia, USA; Eudragit® RS100 and Eudragit® RL100 were obtained from Rohmpharma, Darmstadt, Germany; PEG 400 and Span 80 were obtained from the Chemistry Reagent Factory, Tian Jin, China.

### Preparation of drug-resin complexes:

Drug-resin complexes were prepared by batch method. In this, Amberlite® IRP69 (10 g) was suspended in a 5 mg/ml of venlafaxine hydrochloride (500 ml) under magnetic stirring at 45° for 4 h. The drug-resin complexes were formed by the ion exchange reaction. After cooling, the drug-resin complexes were washed free of the exchange salt and any free drug with deionized water. The drug-loaded resin beads thus obtained were dried in a fluid bed drier, passed through a 160-mesh screen and then placed in a desiccator prior to use.

### Polyethyleneglycol treatment of drug-resin complexes:

Drug-resin complexes (10 g) were mixed in a 100 mg/ml polyethyleneglycol 4000 water solution (20 ml) for 0.5 h. Then the treated fine particle drug-resin complexes were dried in the aforementioned manner, and then passed through a 160-mesh screen before coating.

### Microencapsulation methods:

Initially, Eudragit® was dissolved in 5 ml acetone, and then combined with plasticity-agent and drug-resin complexes, followed by agitating in a magnetic mixer until they were uniformly dispersed to form a suspension. This suspension was dispersed in paraffin liquid (14 ml) containing span 80 (1.6 g), then agitated at high speed at 35° for 4 h until the acetone had evaporated completely. The microcapsules were collected after filtration, rinsed with 50 ml petroleum ether, then dried at 40°, then transferred to a desiccator.

### Effect of different coating materials on drug release:

In order to investigate differences in various coating materials, drug-resin complexes were separately coated

with Eudragit® RS100 (100 mg) and Eudragit® RL100 (100 mg). Then, drug release profiles of microcapsules were evaluated.

### Effect of ratio of drug-resin complexes to coating material on drug release:

To determine the ratio of drug-resin complexes to coating material, drug-resin complexes were separately coated when the ratio of drug-resin complexes to Eudragit® RS100 was 15:1, 10:1, 8:1 and 5:1. Then, drug release profiles of the microcapsules were evaluated.

### Effect of concentration of coating materials on drug release:

The effect of concentration of coating materials was also investigated. Drug-resin complexes were separately coated with the concentration of Eudragit RS100 in acetone as 1%, 3%, and 5%. Then, drug release profiles of microcapsules were evaluated.

### Effect of ratio of plasticity-agent to coating material on drug release:

The effect of the ratio of plasticity-agent to coating material was also studied. Drug-resin complexes were separately coated with the ratio of plasticity agent PEG400 to Eudragit RS100 as 0%, 10%, and 20%. Then, drug release profiles of microcapsules were evaluated.

### The orthogonal experiment:

According to the result of the single factor investigation, the factors and levels are listed in Table 1. The orthogonal experiment with the selected three factors and three levels was arranged according to the orthogonal Table L9 (3<sup>4</sup>), with the prepared microcapsules and the drug release was investigated.

### Morphology of microcapsules:

The surface of the microcapsules was examined by scanning electron microscopy (SEM) (Jeol JSM-6400, Tokyo, Japan). Samples were gold sputter coated (BAL-TEC SCD004, Liechtenstein) for 165 seconds

**TABLE 1: FACTORS AND LEVELS IN THE ORTHOGONAL EXPERIMENT**

Level	Ratio of drug-resin to coating materials	Concentration of coating material in acetone %	Ratio of plasticity agent to Eudragit RS100 %
1	5:1	1	5
2	8:1	3	10
3	10:1	5	15

at 15 mA in an atmosphere of argon.

### ***In vitro* release studies:**

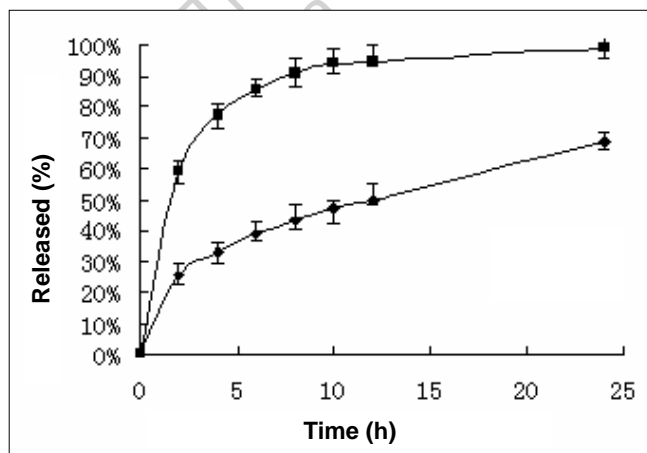
*In vitro* release studies were performed on a ZRS-8G Intelligent Dissolution Tester (Tian Jin University Radio Factory, Tian Jin, China) according to the USP paddle (apparatus II) method. A paddle stirrer set at a speed of 50 rpm and a constant temperature bath set at  $37 \pm 0.5^\circ$  were used. For this, 0.15M NaCl (500 ml) that had previously been deaerated by filtering through 0.45  $\mu$ m membrane filters, was used as the dissolution medium. Microcapsules of drug-resin complexes equivalent to 75 mg venlafaxine hydrochloride were accurately weighed. Then, samples (5 ml) were collected and passed through a 0.45  $\mu$ m membrane filter periodically for 24 h. The volume of the samples collected was replenished with fresh dissolution medium. The samples were assayed using UV spectrophotometry at 274 nm. All release tests were performed in triplicate.

### **Statistical analysis:**

The data was expressed as mean  $\pm$  SD (standard deviation). Analysis of variance (ANOVA) was used for statistical evaluation of the orthogonal experiment results. P-value of  $<0.05$  was considered to represent a statistically significant difference.

## **RESULTS AND DISCUSSION**

The effect of coating materials on drug release from microcapsules was presented in fig. 1, which showed that the drug released faster from microcapsules

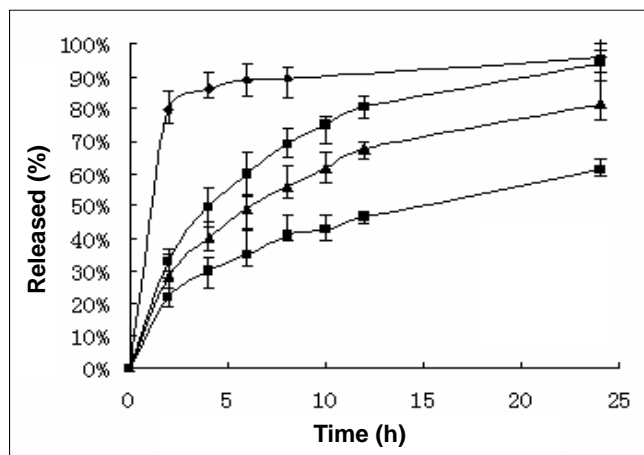


**Fig. 1:** Effect of coating material on the dissolution of venlafaxine hydrochloride from microencapsulated ion-exchange resin beads  
Dissolution of venlafaxine hydrochloride from microencapsulated ion-exchange resin beads coated with different coating materials RS 100 (—◆—) and RL 100 (—■—)

coated with Eudragit RL100 than from microcapsules coated with Eudragit RS100. Eudragit RS100 and RL100 could swell in water, digest fluid and exhibited good permeability. The amidogen in the molecular structure existed as a quaternary ammonium salt and the content of the quaternary ammonium salt was 10% to 15%. The quaternary ammonium salt content of Eudragit RL100 was higher, so the film permeability of Eudragit RL 100 was better, leading to faster drug release. Drug-resin complexes released the drug very quickly, thus the film containing Eudragit RL100 couldn't provide good sustained-release. Eudragit RS100 was used to coat the drug-resin complexes.

The effect of ratio of drug-resin complexes to coating material on drug release was presented in fig. 2. This showed that the drug released fastest from the microcapsules when the ratio of drug-resin complexes to coating material was 15:1. As the ratio of drug-resin complexes to coating material increased, the thickness of film also increased, and thus the rate of drug release decreased.

The effect of concentration of coating materials in acetone on drug release was presented in fig. 3. This showed that the drug release decreased as the concentration of coating materials increased. As the concentration of the coating solution increased, the film formed became denser, the holes formed were smaller and less in number, the drug penetration rate became slower and the drug release was also slower.



**Fig. 2:** Effect of different ratios of drug resin complex to coating material on the dissolution of venlafaxine hydrochloride  
Dissolution of venlafaxine hydrochloride from microencapsulated ion-exchange resin beads with different ratios of drug-resin complexes to coating material. The ratios tested were 15:01 (—◆—), 10:01 (—■—), 8:01 (—▲—) and 5:01 (—●—)

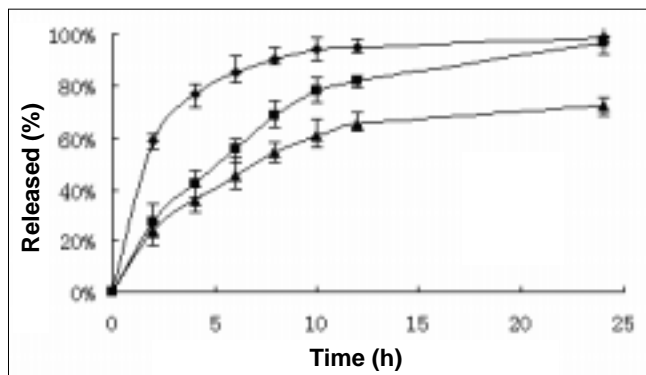


Fig. 3: Effect of concentration of coating material on the dissolution of venlafaxine hydrochloride

Dissolution of venlafaxine hydrochloride from microencapsulated ion-exchange resin beads with different concentrations of coating materials in acetone; 1% (—◆—), 3% (—■—) and 5% (—▲—).

The effect of ratio of plasticity agent, PEG 400, to coating material on drug release was presented in fig. 4. The results showed that drug release rate decreased with increasing the amount of plasticity agent. When the ratio was 0%, the drug release was very fast, this was perhaps because the microencapsulating process could not form the film. When the ratio of the plasticity-agent to coating materials was increased to 20%, the drug released much more slowly, indicating the formation of complete film.

From the individual factor investigations, it was concluded that the ratio of plasticity agent PEG 400 to Eudragit RS100, the concentration of coating material in acetone and the ratio of drug-resin complexes to coating materials had a marked effect on drug

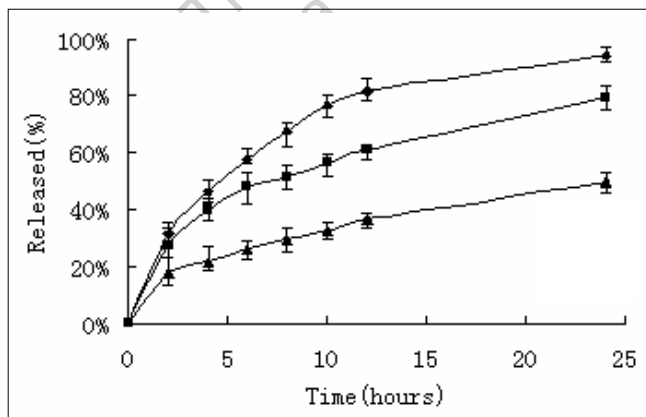


Fig. 4: Effect of different amounts of plasticity agent on dissolution of venlafaxine hydrochloride from microencapsulated ion-exchange resin beads

Dissolution of venlafaxine hydrochloride from microencapsulated ion-exchange resin beads containing different concentrations of plasticity agent; 0% (—◆—), 10% (—■—) and 20% (—▲—).

release. So these factors were chosen to carry out the orthogonal experiment.

The cumulative percent drug release at 2, 6, and 12 h was investigated. The cumulative percent drug release at 2, 6 and 12 h was converted into a single index for analysis of the results. The cumulative percentage drug release at 1 h was used to see if the drug was released too fast, and 30% was used as the best cumulative percentage drug release, the weight coefficient was 1. In addition, the cumulative percentage drug release at 6 h was used to see if enough drug release had been achieved, and 50% was used as the best cumulative percentage drug release, the weight coefficient was 1. Also, the cumulative percentage drug release at 12 h was used to see if complete drug release had been achieved, while 80% was used as the best cumulative percent drug release, the weight coefficient was 1, i.e. the index  $L$ , at the lower score, the level of the factor was better.  $L=(L1-30\%)+(L2-50\%)+(L3-80\%) \dots (1)$ . The orthogonal experiment was carried out according to Table 1, and the results are presented in Table 2.

The ANOVA was used to examine the results of the orthogonal experiment, and to identify the best experimental conditions. The results showed that while all factors A, B and C influenced the result significantly; factor C influenced the result most, followed by factor A, and finally, factor B. The best level of each factor was chosen. The analytical results are given in Table 3. The best prescription for the coating solution was found to be  $A_2B_2C_1$ , i. e., the ratio of drug-resin complexes to coating materials was 8:1, the concentration of coating material in acetone was 3% and the ratio of plasticity agent, PEG 400, to coating material was 5%.

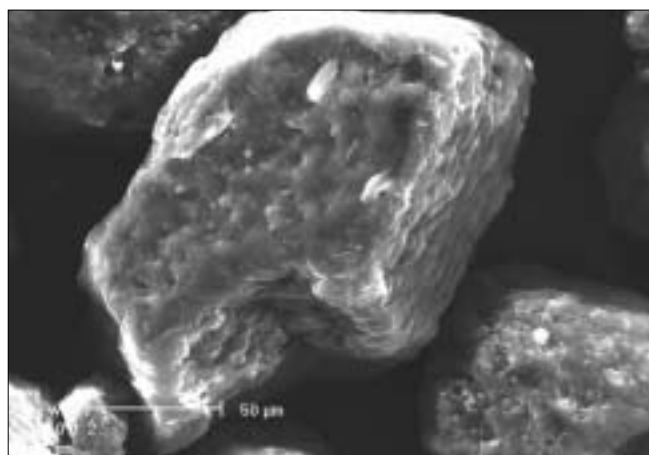
Scanning electron micrographs of microencapsulated ion-exchange resin beads containing venlafaxine hydrochloride prepared by optimum formula are

TABLE 2: THE RESULTS OF THE ORTHOGONAL EXPERIMENT

No.	2 h	6 h	12 h
1	33.5	60.9	83.1
2	37.9	61.9	83.1
3	36.4	59.6	82.2
4	37.6	61.7	84.8
5	31.4	55.5	78.1
6	27.9	54.7	71.3
7	27.5	45.2	61.3
8	28.2	46.5	67.3
9	26.3	43.9	55.9

**TABLE 3: ANALYSIS ON RESULTS OF THE ORTHOGONAL EXPERIMENT**

No.	A	B	C	D	L
	Ratio of drug-resin complexes to coating materials	Concentration of coating material	Ratio of PEG400, to coating material	Error	
1	1(5:1)	1(1%)	1(5%)	1	10.8
2	1	2(3%)	2(10%)	2	36.5
3	1	3(5%)	3(15%)	3	43.7
4	2(8:1)	2	3	1	33.3
5	2	3	1	2	5.8
6	2	1	2	3	28.4
7	3(10:1)	3	2	1	42.8
8	3	1	3	2	23
9	3	2	1	3	12.2
Ij	59.9	68.9	52.3	61.5	
IIj	48.4	49.7	80.9	64.4	
IIIj	77.9	67.6	53	60.3	
SSj	147.389	76.749	177.429	2.962	
F	49.756	25.909	59.897		
P	0.01<p<0.05	0.01<p<0.05	0.01<p<0.05		

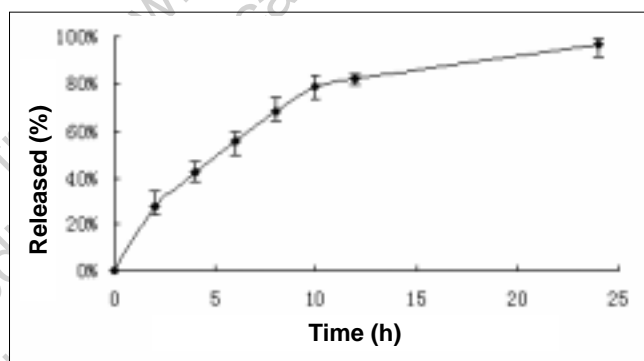


**Fig. 5: SEM of microencapsulated ion-exchange resin beads of venlafaxine hydrochloride**

Scanning electron micrographs of microencapsulated ion-exchange resin beads containing venlafaxine hydrochloride prepared by the optimum formulation.

shown in fig. 5. The micrographs show that the particle size of microencapsulated ion-exchange resin beads was about 100 μm, the microcapsule size was similar to the size of the ion-exchange beads, and the microcapsules were predominately mononucleated. Also, the surface of microcapsules in the figure was not very smooth, and the film was not very tight. This was perhaps the reason that complete drug release from the microcapsules was achieved by the optimum formula at the end of the release test.

The release of venlafaxine hydrochloride from the microencapsulated ion-exchange resin beads made using the optimized formula was shown in fig. 6. The drug released in a sustained manner for about 2 h, then gradually for about 6 h, with 90% being achieved at the end of the release period. These



**Fig. 6: Dissolution of venlafaxine hydrochloride from optimized microencapsules**

Dissolution of venlafaxine hydrochloride from the microencapsules made by the optimum formulation.

results showed that the microencapsulated ion-exchange resin beads containing venlafaxine hydrochloride exhibited sustained release characteristics and were completely released when prepared by the optimum microencapsulation formula.

The mononucleated microencapsulated ion-exchange resin beads containing venlafaxine hydrochloride with sustained release characteristics and exhibiting complete release were successfully prepared by the optimum microcapsule formulation. By means of the orthogonal experiment, the optimum prescription for the microencapsulation process was found to involve the ratio of plasticity-agent, PEG 400, to coating material was 5%, the concentration of coating material was 3% and the ratio of drug-resin complexes to coating materials was 8:1.

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