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International Journal of Pharmaceutics 259 (2003) 103–113
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Preparation of sustained-release nitrendipine microspheres with Eudragit RS and Aerosil using quasi-emulsion solvent diffusion method

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Received 11 December 2002; received in revised form 14 March 2003; accepted 16 March 2003

Abstract

Sustained-release nitrendipine microspheres were prepared in liquid system by quasi-emulsion solvent diffusion method, in which the Aerosil was employed as an inert dispersing carrier to improve the dissolution rate of nitrendipine, and Eudragit RS as a retarding agent to control the release rate. The resultant microspheres were evaluated for the recovery, bulk density, average particle size, drug loading, and incorporation efficiency. And the factors affecting the formation of microspheres and the drug-release rate were investigated. It was observed by a scanning electron microscope (SEM) that the microspheres were finely spherical and uniform, and no entire nitrendipine crystals were observed visually. The results of X-ray diffraction indicated that nitrendipine in microspheres was disordered, suggesting that nitrendipine was highly dispersed in microspheres. The drug loading of microspheres was enhanced with increasing the ratio of drug to excipients, and the incorporation efficiency was always >90%. The formation of microspheres was mainly influenced by the amount of bridging liquid and sodium dodecyl sulfate (SDS) in poor solvent. The dissolution profiles could be modulated with adjusting the amount of retarding agent and dispersing carrier formulated.

Keywords: Nitrendipine; Sustained-release microsphere; Quasi-emulsion solvent diffusion method; Eudragit RS; Aerosil; Solvent deposition system

1. Introduction

The application of solvent deposition method has successfully increased the dissolution rate of the poorly water-soluble drugs such as griseofulvin, indomethacin, chlormaphenicol, prednisone, and prednisolone, etc. (Law and Chiang, 1990; Monkhouse and Lach, 1972; Liao and Jarowski, 1984). It is one of solid dispersion technique. The principle of this method is by deposition of the drug from a solvent onto the surface of an inert excipient, which has extensive surface, high porosity, and unique adsorption properties, to obtain a high surface area by reduction of particle size, since the dissolution rate is directly proportional to the surface area. The solvent deposition systems, however, usually have poor flowabilty and compressibility and required further particle designs such as being crushed, sieved, granulated, and compacted into tablet or filled into capsules.

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0378-5173/03/$ – see front matter
doi:10.1016/S0378-5173(03)00209-6

The quasi-emulsion solvent diffusion method of spherical crystallization technique has been accepted as a useful technique for particle design for pharmaceuticals (Cui et al., 1996). It could provide remarkable advantages over conventional microsphere preparation methods (Cui et al., 2001). In this process, drug and polymers are coprecipitated to form functional drug devices according to the polymer properties. For example, acrylic resin (Eudragit RS, Eudragit RL) and ethyl cellulose (EC) could be used to produce sustained-release microspheres (Kawashima et al., 1989a; Akbuga, 1989, 1991), HPMCP, Eudragit S100, and Eudragit L100 could be used to produce enteric dissolution microspheres (Cui et al., 2001; Akbuga, 1989) and DL-lactide/glycolide copolymer was used to prepare biodegradable nanospheres (Niwa et al., 1993) etc. However, further application of quasi-emulsion solvent diffusion method to produce solvent deposition system with poorly water-soluble drug to improve the dissolution rate has seldom been reported until now (Cui et al., 2001).

In this study, the principles of above two methods were combined to design the sustained-release microspheres having solid dispersion structure for poorly water-soluble drug. In this manufacturing process, the preparation of the microspheres and the solvent deposition system were combined into one step. Aerosil, an inert solid dispersing carrier, was introduced in this formulation to improve the dissolution rate of poorly water-soluble drug and the controlled-release polymer Eudragit RS PO was employed to bind the inert solid dispersing carrier into microsphere and control the drug-release rate. This method could simplify the traditional manufacturing processes for sustained-release preparation of poorly water-soluble drug, which usually consists of the preparation of solid dispersion, crushing, sieving, mixing with other excipients, being granulated for compacting into tablet and being coated with suitable coating materials if necessary. And it was indicated that the present method could also be used to improve the micromeritics properties of solvent deposition system with simple preparation process.

Nitrendipine, a dihydropyridines calcium antagonist (Mikus and Eichelbaum, 1987), which have a very low solubility in vitro, was used as a poorly water-soluble model drug to prepare the sustained-release microspheres in this work. The factors affecting recovery, micromeritic properties and drug-release behaviors of the sustained-release microspheres were investigated. The dispersion state of nitrendipine in microspheres was also analyzed.

2. Experimental

2.1. Materials

Nitrendipine was obtained from Nanjing Pharmaceutical Factory (China); the acrylic resins Eudragit RS PO (Eu RS) from Röhm Pharma (Germany); light anhydrous silicic acid (Aerosil, hydrophilic) from Guangzhou People Chemical Plant (China); and talc from Shandong Yuwang Chemical Plant (China). All other chemicals, such as sodium dodecyl sulfate (SDS), dichloromethane, acetone, etc. were of analytical grade.

2.2. Preparation of sustained-release nitrendipine microspheres

Nitrendipine (0.3 g) was dissolved with Eu RS (0.3–1.8 g) in a mixed solution of acetone (good solvent, 3.0–6.0 ml), and dichloromethane (bridging liquid, 2.0–4.0 ml). Then, Aerosil (0.3–1.8 g) was suspended uniformly in the drug–polymer solution under vigorous agitation. The resultant drug–polymer–Aerosil suspension was poured into 150 ml distilled water containing 0.02–0.15% of SDS (poor solvent) under agitation (400–700 rpm) and thermally controlled at 8–38 °C. After agitating the system for 20 min, another 150 ml of poor solvent was added slowly and agitation was continued for another 40 min till the translucent quasi-emulsion droplets turned into opaque microspheres. The solidified microspheres were recovered by filtration and washed with water. The resultant products were dried in an oven at 50 °C for 6 h.

To investigate the factors affecting recovery, micromeritics properties and drug-release behaviors of microspheres more easily, the general preparation condition of microspheres was employed as follows except mentioned especially. The amount of drug, Eu RS, and Aerosil in formulation was 0.3, 0.9, and 0.9 g. The volume of acetone and CH_2Cl_2 was 5 and 2.5 ml, respectively, and the concentration of SDS in distilled water was 0.08%. The agitation speed and temperature was 700 rpm and 20 °C.

The recovery of the microspheres was determined from the ratio of the amount of 280–900 μm microspheres to that of loaded powders. The X-ray diffractometer (D/max-r A type, Rigaku, Japan) was employed to investigate the dispersion state of nitrendipine in the microspheres produced at different ratios of the drug to excipients.

2.3. Measurement of micromeritic properties of microspheres

Size distribution and average mass median diameter (D_{50}) were determined by the sieving method using the standard sieve stipulated in the Ch. P. 2000 ed. The bulk density of the microspheres was measured by a tapping method. The shape, surface morphology, and internal structure of microspheres were observed by a scanning electron microscope (SEM, S-5200, Hitachi Co., Japan).

2.4. Determination of drug loading and incorporation efficiency of microspheres

The weighed amount of microsphere powder was dissolved in ethanol and the drug content was measured spectrophotometrically at 352 nm for nitrendipine. The drug loading and incorporation efficiency (%) were calculated by using Eqs. (1)–(2), respectively.

$$\text{Drug loading (\%)} = \left(\frac{M_{\text{actual}}}{\text{weighed quantity of powder of microspheres}}\right) \times 100 \quad (1)$$

$$\text{Incorporation efficiency (\%)} = \left(\frac{M_{\text{actual}}}{M_{\text{theoretical}}}\right) \times 100 \quad (2)$$

where M_{actual} is the actual nitrendipine content in weighed quantity of powder of microspheres and $M_{\text{theoretical}}$ is the theoretical amount of nitrendipine in microspheres calculated from the quantity added in the fabrication process. The means of three assays were reported.

2.5. Dissolution behavior of microspheres

The drug-release tests of the microspheres were carried out for 12 h under 100 rpm by the paddle method specified in Ch. P. 2000 ed. The temperature of the dissolution medium was controlled at 37 ± 0.5 °C. The microspheres were fractionated to −20 + 60 mesh (280–900 μm) and weighed to be equivalent to 20 mg of nitrendipine. The dissolution medium was 900 ml of distilled water containing 1.0% (w/v) of SDS to keep the sink condition for the drug. Five milliliters of the dissolution medium was sampled at certain intervals, and fresh dissolution medium was simultaneously replaced in the apparatus to keep the volume constant. The withdrawn sample was filtered with a membrane filter (0.8 μm), and the filtrate was assayed spectrophotometrically at 358 nm to determine the dissolved drug concentration using a spectrophotometer (Mode 752, Shanghai the Third Analytical Instrument Plant, China).

3. Results and discussion

3.1. Preparation process of the nitrendipine microspheres with Eu RS and Aerosil

When the drug–polymer–Aerosil suspension was poured into poor solvent with stirring, the finely dispersed gel-like emulsion droplets were formed immediately. Due to the good affinity of the polymer to the organic solvent, good solvent (acetone) and bridging liquid (dichloromethane) in the droplets could not be diffused into poor solvent at once. Because good solvent, which is discretionarily miscible with poor solvent, was diffused out from the quasi-emulsion droplets under the agitation, drug and polymer in the droplets were supersaturated, precipitated, and deposited on the Aerosil gradually. Consequently, the droplets were consolidated into microspheres by the linkage action of bridging liquid. The diffusion of good solvent into poor solvent can make a part of the bridging liquid in droplets diffuse into poor solvent to achieve diphase equilibrium between the droplets and poor solvent. After the process for 20 min, 150 ml of poor solvent was added into the system to promote the diffusion speed of good solvent and part of bridging liquid. Further solidification of the droplets led to production of the microspheres. The solidified microspheres was filtrated, washed, and dried to eliminate the residual organic solvent. The formation of the microspheres could be described in the following

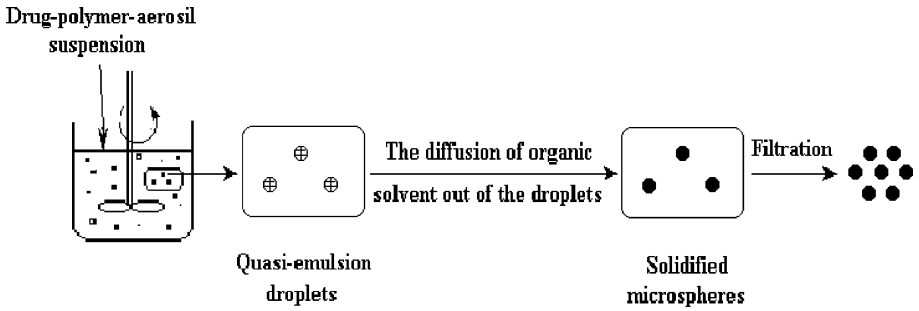

Fig. 1. Scheme of the preparation process and mechanism.

processes: the formation of quasi-emulsion droplets, the diffusion of the organic solvent and the solidification of the droplets. The scheme of the preparation process was illustrated in Fig. 1.

The preparation process of the present microspheres was almost similar with that of drug-Eudragit microspheres (Akbuga, 1989; Kawashima et al., 1989a), except that Aerosil was introduced in this microspheres formulation as an inert solid dispersing carrier to improve the dissolution rate of nitrendipine. Due to its large surface area, high porosity, and unique adsorption properties, Aerosil has been successfully used as a dispersing agent to increase the dissolution rate of sparingly soluble drugs (Sheth and Jarowski, 1990). At the same time, Aerosil was an effective antiadhesion agent, and it could accelerate the solidification of droplets and be packed in the microspheres well. These suggested that the higher recovery of microspheres could be obtained comparing with other conventional methods of microspheres.

In this formulation, Eu RS was used as a bond and retarding agent in order to bind the Aerosil into microspheres and control the release rate. In the previous researches (Akbuga, 1989; Kawashima et al., 1989a) for the preparation of microspheres with Eu RS using quasi-emulsion solvent diffusion method, a large ratio of drug to Eu RS and also a large amount of organic solvent had to be used, since the polymer was easy to be precipitated as a fibrous aggregate or adhere to the equipment because of its high viscosity. In this study, however, this problem could be avoided effectively due to the good antiadhesion property of Aerosil. And it was found that the microspheres having a good spherical shape were easy to form under strong agitation, though the plasticizer was not added in this formulation. It was indicated that Eu RS was one of the suitable polymers for the preparation of microspheres using this method due to its good plastic deformation property.

The surface morphology and internal structure of the microspheres were investigated using a SEM. As seen in Fig. 2, the microspheres were invariably spherical and exhibited porous surfaces with a large number of interstices, while no entire nitrendipine crystals were observed visually. The Aerosil particles and amorphous like polymers were commixed uniformly in dense texture, and macro-pores and voids were observed in the internal matrix. It was assumed that the coprecipitation of drug and polymers occurred on the surface of the quasi-emulsion droplets and then the film like a shell was formed on the outer surface of droplets. The cavity and micropores were formed inside the microspheres due to the further diffusion of the organic solvents out of the droplets.

3.2. Effect of the amount of CH_2Cl_2, acetone, and SDS on microsphere properties

The influence of the amount of CH_2Cl_2, acetone, and the concentration of SDS in distilled water on recovery, micromeritics properties of microsphere was shown in Table 1.

To investigate the effect of bridging liquid on the microspheres properties, the amount of acetone, and the concentration of SDS in distilled water was fixed at 5 ml and 0.08%, respectively. And the amount of dichloromethane was varied between 0 and 4 ml for the preparation of the microsphers. As can be seen in Table 1, without dichloromethane added, no microsphere was obtained after the drug–polymer–Aerosil

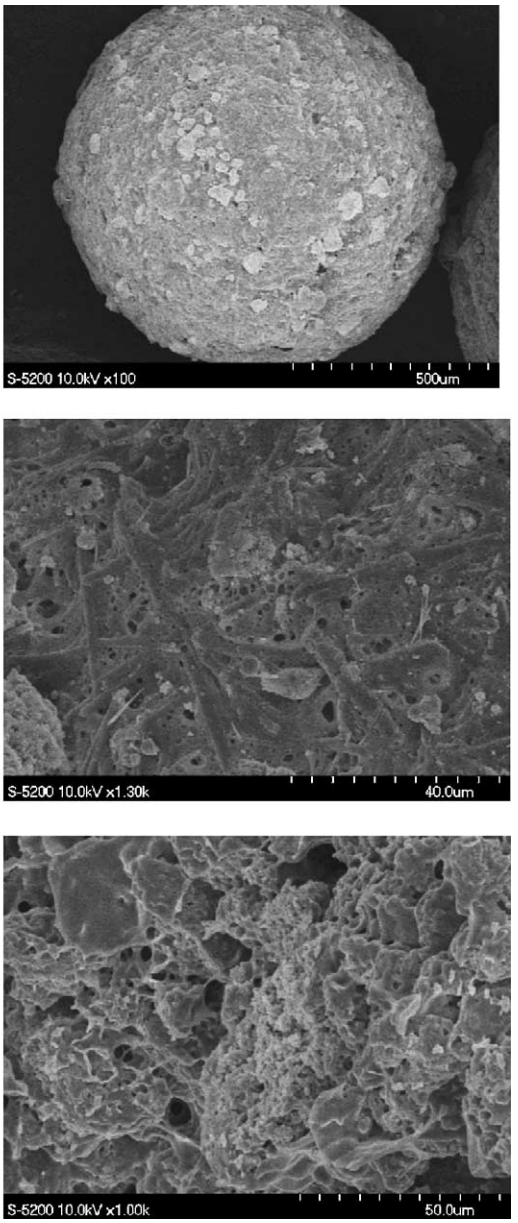

Fig. 2. Scanning electron microphotographs of microspheres. Key: A, whole image; B, surface; C, cross-section.

suspension was poured into poor solvent, because acetone was diffused into poor solvent so rapidly that no quasi-emulsion droplets could be formed. When the amount of dichloromethane was increased to 4 ml, the finely dispersed spherical quasi-emulsion droplets could be seen in poor solvent under the agitation. However, the emulsion droplets were adhered together and were turned into some big lumps immediately when the stirring was discontinued. Consequently, no microspheres could be recovered. It was believed to be due to the leaving superfluous CH_2Cl_2 in the droplets and the droplets were not solidified completely. Though a part of dichloromethane could be diffused into poor solvent, most of it remained in the droplets due to its limited solubility in poor solvent. The good microspheres were produced when 2 or 3 ml of dichloromethane was added. The recovery of microspheres was >70%. These suggested that the amount of dichloromethane should be controlled in an appropriate range to guarantee not only the formation of quasi-emulsion droplets at the initial stage of preparation but also the solidification of drug and polymer in droplets.

Good solvent was used in this process to increase the amount of soluble drug and polymer in the organic solution and to uniformly disperse the Aerosil in this organic solution. When the amount of dichloromethane and the concentration of SDS in distilled water was fixed at 2.5 ml and 0.08%, with increasing the amount of acetone from 3 to 6 ml, the recovery of microspheres was increased, but the bulk density and average particle size were decreased slightly (Table 1). The reduction of the particle size of microspheres was probably due to the decrease in the viscosity of polymer solution with increasing the amount of good solvent. The pores and interstices of the microspheres, which were formed after good solvent being diffused out of droplets, were increased with increasing the amount of acetone, leading to a decrease in the bulk density of microspheres. These indicated that the bulk density of microspheres could be increased by properly reducing the amount of good solvent. The increase of the recovery was probably due to the increasing dispersion of the quasi-emulsion droplets in poor solvent with an increase in the amount of acetone: the reduction of the conglutination of the polymer on equipment was observed in fact.

The emulsifier in poor solvent was also an important factor to affect the microspheres properties. Table 1 showed that the microspheres could not be obtained when the drug–polymer–Aerosil suspension was poured into poor solvent of low concentration of SDS (i.e. 0.02%, w/v). With an increase of SDS concentration, the recovery of the microspheres was

Table 1
Effect of the amount of CH_2Cl_2, acetone and the concentration of SDS in distilled water on microsphere properties ($n = 3$, $\bar{x} \pm$ S.D.)

CH_2Cl_2 (ml)	Acetone (ml)	SDS (%, w/v)	Recovery (%)	Bulk density (g/ml)	D_{50} (μm)
0	5	0.08	0	–	–
2	5	0.08	71.9 ± 4.2	0.29 ± 0.01	575 ± 10
3	5	0.08	72.5 ± 3.4	0.30 ± 0.02	650 ± 14
4	5	0.08	0	–	–
2.5	3	0.08	68.7 ± 3.7	0.31 ± 0.01	735 ± 23
2.5	4	0.08	70.9 ± 4.3	0.31 ± 0.02	690 ± 24
2.5	5	0.08	73.3 ± 3.4	0.29 ± 0.01	660 ± 16
2.5	6	0.08	76.4 ± 3.2	0.27 ± 0.01	585 ± 19
2.5	5	0.02	–	–	–
2.5	5	0.05	39.8 ± 5.8	0.30 ± 0.02	745 ± 30
2.5	5	0.08	73.3 ± 3.4	0.29 ± 0.01	660 ± 16
2.5	5	0.15	63.7 ± 2.6	0.27 ± 0.02	510 ± 9

increased, and average particle size was decreased. However, the recovery reached a maximum and then decreased slightly. This is probably due to the decrease in particle size of microspheres with increasing the concentration of SDS. Some small microspheres passed through 60 mesh sieve and could not be registered. These indicated that the SDS with a proper concentration made a contribution to the dispersed and stable formation of quasi-emulsion droplets in poor solvent. So, the presence of SDS was found to be indispensable for the formation of microspheres in this study.

3.3. Effect of agitation speed and temperature on microspheres properties

The agitation speed had evident influence on the particle size of the microspheres. As shown in Table 2, increasing the agitation speed decreases the mean diameter of the microspheres. The increased mechanical shear force, produced by increasing the agitation speed, divided the suspension of drug, polymer, and Aerosil into small droplets rapidly. On the other hand, the agitation speed had no detectable influence on the recovery and bulk density of the microspheres.

As shown in Table 2, the recovery and bulk density of microspheres is decreased with increasing the temperature, but the temperature has no obvious influence on the particle size. It was found in this test that the conglutination of polymer on the equipment was increased with increasing the temperature, which led to a decrease in recovery of microspheres. The bulk density of microspheres was reduced slightly probably due to swelling of the droplets with increasing the temperature of the system, resulting in the formation of more pores and interstices in droplets after the diffusion of organic solvent out of the droplets. Swelling of Eudragit RS has also been observed by Kawashima (Kawashima et al., 1989b) in preparation of microspheres using the emulsion-solvent diffusion method.

Table 2
Effect of agitation speed and temperature on recovery and micromeritic properties of the microspheres ($n = 3$, $\bar{x} \pm$ S.D.)

Agitation speed (rpm)	Temperature (°C)	Recovery (%)	Bulk density (g/ml)	D_{50} (μm)
400	20	68.4 ± 5.0	0.31 ± 0.02	840 ± 20
500	20	72.7 ± 4.1	0.31 ± 0.01	780 ± 13
700	20	73.3 ± 3.4	0.29 ± 0.01	660 ± 16
700	8	69.2 ± 3.4	0.29 ± 0.01	835 ± 25
700	18	72.8 ± 3.7	0.28 ± 0.01	660 ± 21
700	28	61.5 ± 5.1	0.26 ± 0.01	725 ± 15
700	38	49.1 ± 7.9	0.21 ± 0.02	840 ± 31

Table 3
Effect of feeding drug on drug loading and incorporation efficiency of microspheres ($n = 3$, $\bar{x} \pm$ S.D.)

Drug:Eu RS:Aerosil	Drug loading (%)	Incorporation efficiency (%)
0.5:3:3	7.06 ± 0.06	91.8 ± 0.75
1:3:3	13.47 ± 0.14	94.3 ± 0.98
1.5:3:3	18.94 ± 0.22	94.7 ± 1.10

3.4. Drug loading and incorporation efficiency of microspheres

Table 3 indicates the content of nitrendipine in microspheres and also drug loss. As seen in this table, microspheres with high drug loading were obtained. Incorporation efficiency was high since it always exceeded 90%. As increasing the ratio of drug to excipients, the drug loading of microspheres was increased. The high content of nitrendipine in microspheres was believed to be due to the poor solubility of drug in poor solvent. These suggested that the present method was suitable for the preparation of microspheres of a poorly water-soluble drug, such as nitrendipine.

3.5. Control of drug-release behavior of microspheres

The release rate of nitrendipine from the microspheres could be modulated with adjusting the ratio of Eu RS to Aerosil in the formulation. The influence of Eu RS on the release rate of nitrendipine was illustrated in Fig. 3. When the ratio of the amount of drug to Aerosil was fixed at 1:3, increasing the amount of Eu RS resulted in a marked decrease in drug release. It was evident that Eu RS was an efficient retarding agent to control the drug-release rate.

When the ratio of the amount of drug to Eu RS in the formulation was fixed at 1:3, the release rate of nitrendipine from microspheres was increased with increasing the amount of Aerosil in formulation (Fig. 4).

As shown in Fig. 4, the release rate of microsphere of drug:Eu RS:Aerosil = 1:3:3 was much faster than that of drug:Eu RS:Aerosil = 1:3:2. And there were relatively minor increase in the drug-release rate when the ratio of the amount of Aerosil to nitrendipine was increased from 3:1 to 6:1. These results could be explained from X-ray powder diffraction patterns of microspheres (Fig. 5).

As can be seen in Fig. 5, the crystalline peaks of nitrendipine in microspheres disappeared gradually

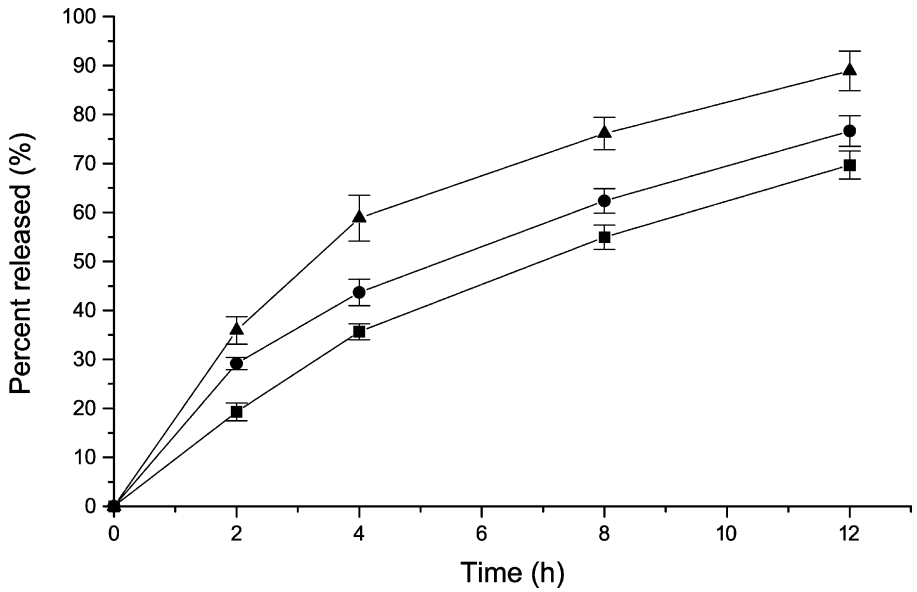

Fig. 3. Effect of Eu RS on the release profiles. Key: Nitrendipine:Eu RS:Aerosil = 1:2:3 (▲); 1:3:3 (●); 1:4:3 (■).

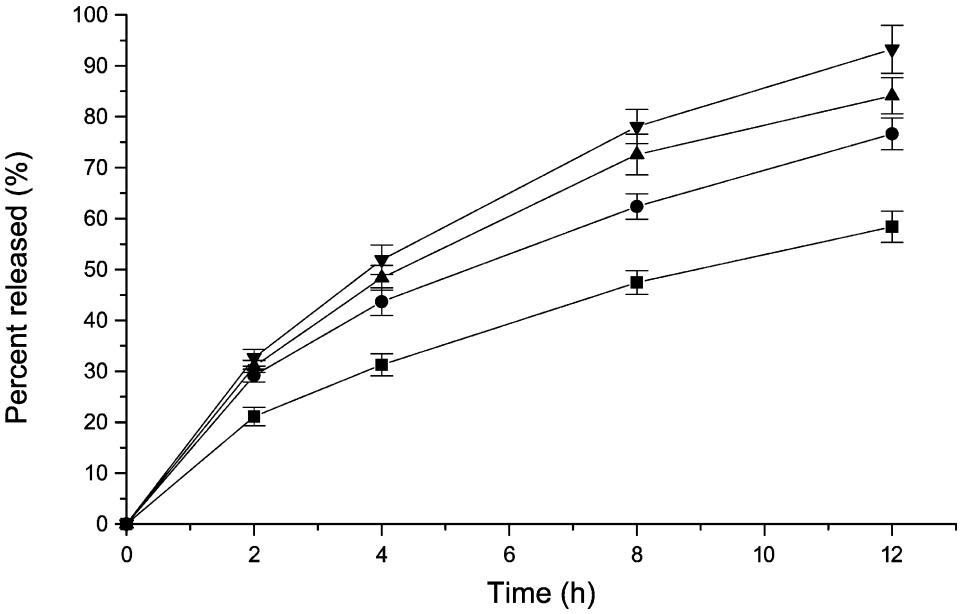

Fig. 4. Effect of solid dispersing carrier on release profiles. Key: Nitrendipine:Eu RS:Aerosil = 1:3:6 (▼); 1:3:5 (▲); 1:3:3 (●); 1:3:2 (■).

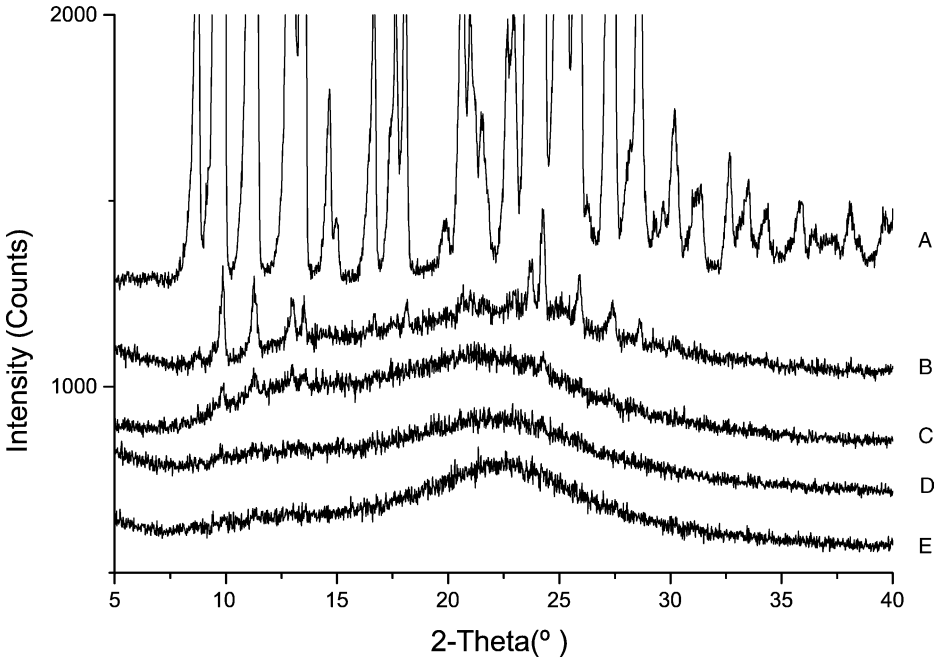

Fig. 5. X-ray powder diffractograms of nitrendipine, physical mixture and Aerosil-microspheres. Key: A, original crystals of nitrendipine; B, physical mixture (nitrendipine:Eu RS:Aerosil = 1:3:3); C, microspheres (nitrendipine:Eu RS:Aerosil = 1:3:2); D, microspheres (nitrendipine:Eu RS:Aerosil = 1:3:3); E, microspheres (nitrendipine:Eu RS:Aerosil = 1:3:6).

with increasing the ratio of Aerosil to nitrendipine in formulation. When the ratio of nitrendipine:Eu RS:Aerosil was 1:3:3, no crystalline peaks of nitrendipine was found in the microspheres, though the crystalline peaks were observed in the physical mixtures of the drug and excipients with the same formulation. Some small crystalline peaks of nitrendipine, however, could still be found in microspheres at the ratio of nitrendipine:Eu RS:Aerosil = 1:3:2. These indicated that nitrendipine had been disordered in microspheres at the ratio of the amount of Aerosil to drug = 3:1, suggesting that nitrendipine had been highly dispersed at this ratio, so as amorphous state.

As a dispersing carrier, Aerosil could improve the apparent solubility and dissolution rate of nitrendipine effectively. It was supported by the comparison test of dissolution rate of original nitrendipine powder and nitrendipine solvent deposition system (Fig. 6). This solvent deposition system was a solid preparation in which nitrendipine was deposited from a mixed solution of dichloromethane and acetone on the surface of Aerosil. This step was done by simple evaporation of the organic solution used for distribution of the drug onto the Aerosil. The method of preparation of solvent deposition system has been described in detail in previous papers (Monkhouse and Lach, 1972; Johansen and Møller, 1978). The dissolution rate tests were carried out in distilled water in order to eliminate other factors such as a surfactant influencing on dissolution rate of the drug.

As shown in Fig. 6, nitrendipine original powder has very low apparent solubility in distilled water. The dissolution rate of nitrendipine, however, was improved markedly after the drug was deposited on Aerosil and was also increased with increasing the ratio of Aerosil to drug.

It is very important to choose suitable inert dispersing carrier to improve the solubility and dissolution rate of poorly water-soluble drug using this method. Aerosil, used in this study, is known to be one of the most effective dispersing carriers (Monkhouse and Lach, 1972; Liao and Jarowski, 1984). To study the effect of inert dispersing carrier on the drug-release rate, talc was also chosen as a dispersing carrier to prepare the nitrendipine microspheres with Eu RS. And the drug-release profiles of this talc-microspheres were compared with that of the microspheres produced with Aerosil. The results were shown in Fig. 7.

Although the microspheres prepared with talc were as finely spherical and uniform as the microspheres prepared with Aerosil, there were significant differences in the drug-release rate. As seen in Fig. 7, the

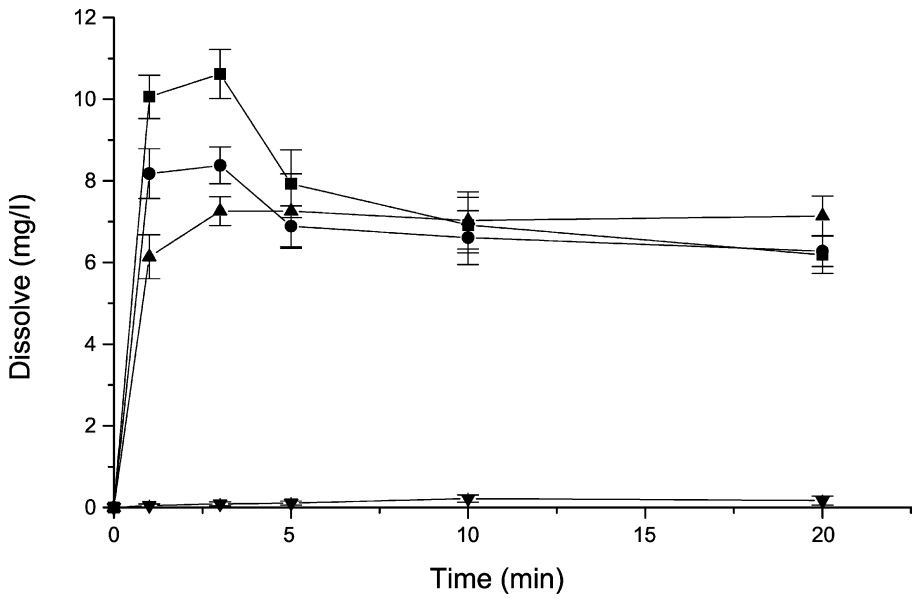

Fig. 6. Dissolution profiles of nitrendipine in distilled water. Key: Nitrendipine:Aerosil = 1:9 (■); 1:4.5 (●); 1:3 (▲); 1:0 (▼).

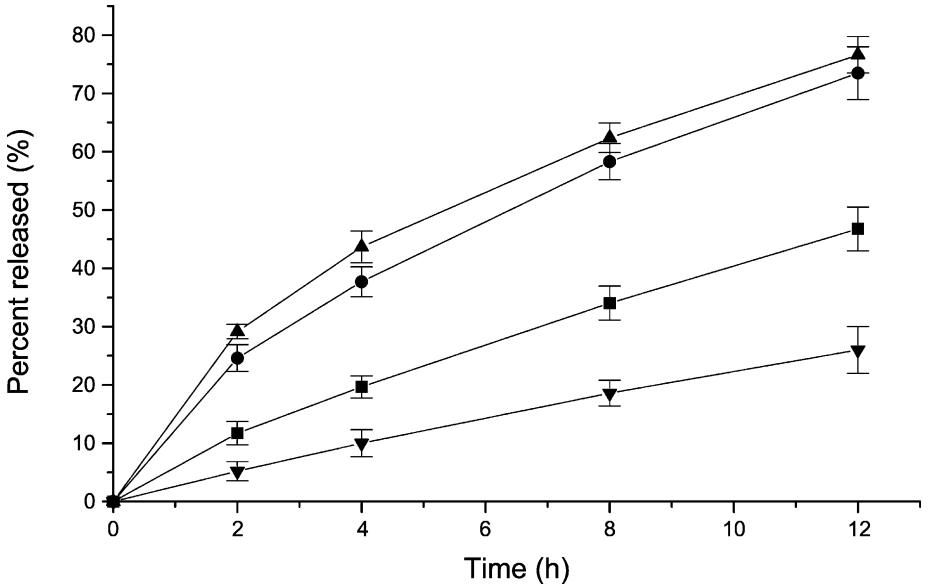

Fig. 7. Effect of different dispersion agents on release profiles of sustained-release microspheres. Key: Nitrendipine:Eu RS:Aerosil = 1:3:3 (▲); nitrendipine:Eu RS:talc = 1:3:15 (●); nitrendipine:Eu RS:talc = 1:3:6 (■); nitrendipine:Eu RS:talc = 1:3:3 (▼).

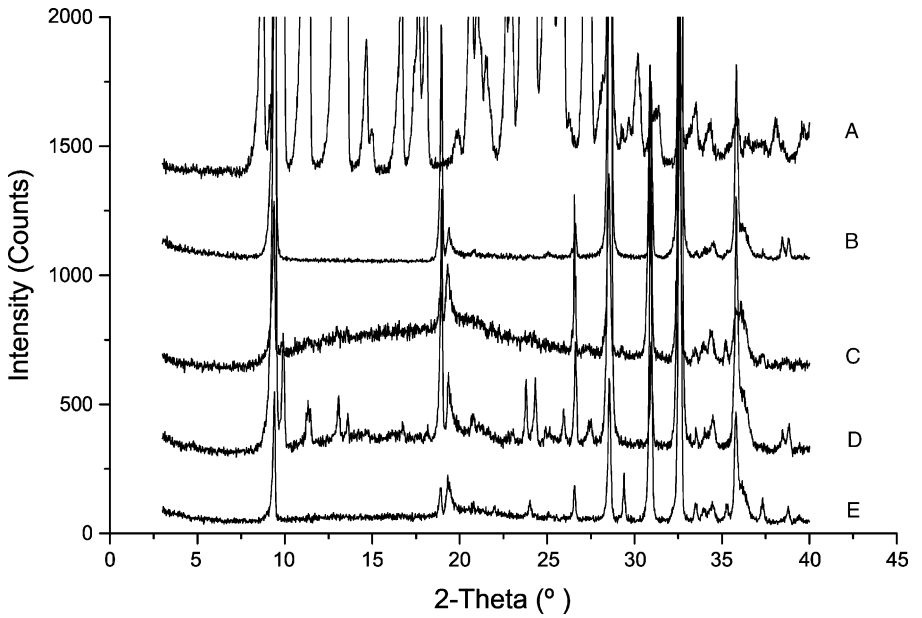

Fig. 8. X-ray powder diffractograms of nitrendipine, physical mixture and talc-microspheres. Key: A, original crystals of nitrendipine; B, original crystals of talc; C, microspheres (nitrendipine:Eu RS:talc = 1:3:6); D, physical mixture (nitrendipine:Eu RS:talc = 1:3:15); E, microspheres (nitrendipine:Eu RS:talc = 1:3:15).

drug-release rate of the microspheres formulated with the drug: Eu RS:talc = 1:3:15 was similar to that of the microspheres formulated with the drug: Eu RS:Aerosil = 1:3:3. The specific surface areas of the two kinds of carrier were determined using the BET method. It was found that the specific surface area of Aerosil (362.73 m^2/g) was much larger than that of talc (12.08 m^2/g).

And the crystal form of nitrendipine in talc-microspheres was also analyzed using X-ray diffraction. As illustrated in Fig. 8, although the crystalline peaks of drug in talc-microspheres had disappeared at the ratio of drug:Eu RS:talc = 1:3:6, its drug-release rate was more decreased than the Aerosil-microspheres of 1:3:3 (Fig. 7). These findings suggested that suitable dispersing carrier should be employed in the formulation of microspheres. And the effect of inert dispersing carrier on drug-release rate of microspheres should be further investigated.

4. Conclusion

Sustained-release nitrendipine microspheres with Eu RS and Aerosil was prepared using quasi-emulsion solvent diffusion method by a combination of the formation of microspheres and the solvent deposition system in one step. The resultant microspheres have the desired micromeritic properties. The release profiles of the microspheres were modulated with adjusting the ratio of the retarding agent to the dispersing carrier. The relatively high recovery and incorporation efficiency of microspheres also showed an advantage over the other conventional method of preparing microspheres.

This method could simplify the traditional manufacturing processes for sustained-release preparations having solid dispersion structure. And it was indicated that the present method was suitable for preparing the sustained-release microspheres for poorly water-soluble drug.

Acknowledgements

This work was funded by the ‘9.5’ National Science and Technology Foundation (China). The authors would like to thank professor Kawashima for useful advices for the study and also thank professor Sunada supporting for the measuring the micromeritic properties of inert dispersing carriers.

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