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Preparation of roxithromycin-polymeric microspheres by the emulsion solvent diffusion method for taste masking

Yan Gao, Fu-de Cui *, Ying Guan, Lei Yang, Yong-sheng Wang, Li-na Zhang

Department of Pharmaceutics, Shenyang Pharmaceutical University, No. 103 Wenhua Road, Shenhe District, Shenyang City, Liaoning Province 110016, China

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Abstract

Microspheres of roxithromycin with Eudragit S100 and silica were prepared by the emulsion solvent diffusion method to mask the bitter taste of the antibiotic. The effect of different polymers and drug–polymer ratios on the taste masking and the characteristics of the microspheres were investigated. It was found that Eudragit S100 was the best for masking the unpleasant taste of roxithromycin among the six kinds of polymers investigated. The results of DSC, X-ray diffraction and IR showed that there were several combinations of roxithromycin and Eudragit S100. The influence of other formulation factors, i.e. dichloromethane–acetone ratios and silica–polymer ratios on the properties of the microspheres were also examined. In conclusion, the results of the present study will be helpful for the preparation of oral forms of roxithromycin with an acceptable taste.

Keywords: Roxithromycin; Eudragit S100; Microspheres; Emulsion solvent diffusion method; Taste masking

1. Introduction

As every pharmacist knows, many pharmaceutical drugs have an unpleasant taste, often very bitter. The major consequence of the bitter taste is to restrict greatly the further development of oral preparations and clinical applications of these drugs. Along with the continuing improvement in the social standard of living, it is no longer acceptable for useful medicines to taste bitter. People wish to take effective drugs that have a nice taste and can be administered easily. Accordingly, it is important to mask the unpalatable taste of a drug in order to improve the product quality. This will also increase the value of the finished product as well as patient compliance, especially where infants, children and elderly are concerned.

In order to achieve more pleasant dosage forms, various masking techniques have been described in the literature (Shou and Chen, 2002; Zhang and Hou, 2003). The simplest method is to add flavors or sweeteners. However, in most cases, these are rather limited and may not be effective enough to mask the unpleasant taste of some drugs. A number of more useful approaches have been tried, including capsule formulations, coating with water-insoluble polymers or pH-dependent water-soluble polymers (Yajima et al., 1996), absorption to ion-exchange resin (Jaskari et al., 2001; Vuorio et al., 2003), microencapsulation with various polymers (Sjoqvist et al., 1993; Gouin, 2004; Nii and Ishii, 2005), inclusion complexes with cyclodextrins (Duchene et al., 1999; Loftsson and Masson, 2001), chemical modification such as turning drugs into their milk-toast prodrugs without any reduction in bioavailability.

Generally speaking, the mechanisms of all the masking methods listed above may be summarized as follows. The first is to mask the distasteful sensation by the addition of flavors and sweeteners. The second is to avoid the bitter drugs coming into direct contact with patients' taste buds and the third is to reversibly anaesthetize patients' taste buds temporarily. In addition, chemical methods have been used such as altering the chemical structure of the drug itself to remove the bitter taste. In this regard, a lot attention must be paid to preventing any loss of bioavailability after such modification.

Microencapsulation techniques have become more and more popular in the last few decades because they offer significant advantages as far as taste masking is concerned. Furthermore,

* Corresponding author. Tel.: +86 24 23986355; fax: +86 24 23986355.
E-mail address: cuifude@163.com (F.-d. Cui).

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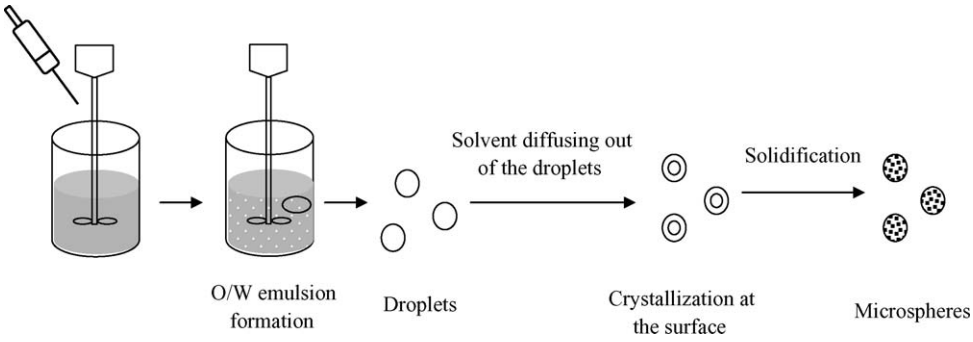

Fig. 1. Mechanism of the emulsion solvent diffusion method.

the materials used to coat the drug particles create a physical barrier and thereby enhance the stability of the particles. In this study, roxithromycin microspheres were prepared by a novel technique, called the emulsion solvent diffusion method, which was proposed by Kawashima et al. (1989a,b). It is a process in which spherical agglomeration occurs simultaneously during drug crystallization (Kawashima, 1989). As shown in Fig. 1, the water-insoluble drug and polymer are dissolved in a solvent system mixed with a good solvent and a bridging liquid. The drug solution is poured slowly into an aqueous medium (as a poor solvent) under constant stirring, and the o/w emulsion droplets are formed as soon as they meet each other. The droplets solidify gradually while the good solvent diffuses out of the droplets into the aqueous medium and finally forms microspheres. This new method has gained worldwide attention due to its simplicity, low cost and lack of need for special equipment. In addition, polymeric microspheres can be produced by coprecipitation of the drug and polymer in droplets, and then conglomerate into microspheres.

The macrolide antibiotic, roxithromycin, is active against a wide spectrum of pathogens, and is particularly effective in the treatment of respiratory and genital tract infections (Ronald, 1989; Markham and Faulds, 1994; Barreto, 1996; Ferrara et al., 1996). In this study, in order to mask the bitter taste of roxithromycin, we tried to prepare drug microspheres with different water-insoluble polymers using the emulsion solvent diffusion method. All the polymers used here were not regarded as materials for controlling drug release, but simply as taste-masking agents. The influence of various materials on taste-masking and some formulation variables on microsphere characteristics were examined here. The drug release rate from the microspheres was monitored by an in vitro release test in accordance with the China Pharmacopeia.

2. Materials and methods

2.1. Materials

Roxithromycin (Beijing Kang Di Ni Pharmaceutical Factory, China) was used as a water insoluble model drug with a very bitter taste. Its standard was purchased from National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Eudragit E100, Eudragit L100-55, Eudragit L100 and Eudragit S100 were a kind gift from Degussa Chemical Co. Ltd., Shanghai agency of Röhm Pharma. Hydroxypropylmethylcellulose phthalate (HP-50, HP-55) was generously supplied by Shin-Etsu Chemical Ind. Co. Ltd., Japan. Silica (Guangzhou People Chemical Plant, China) was used as a dispersing and anti-adhesion agent. Polyvinyl alcohol (PVA) was purchased from Shanghai Dong Cang International Trading Co. Ltd. Methanol, acetonitrile and tetrahydrofuran of HPLC-grade were obtained from Concord Tech. Co. (Tianjin, China). All other chemicals were of analytical reagent grade and used as received.

2.2. Preparation of microspheres

All microspheres were obtained by the emulsion solvent diffusion method using distilled water as an external phase, in which 1% of PVA was dissolved as an emulsifier. The internal phase consisted of a good solvent and a bridging liquid involving roxithromycin, polymer and silica.

At first, the drug and polymer were co-dissolved in an organic solvent mixture that was composed of ethanol, acetone (good solvent) and dichloromethane (bridging liquid). The drug solution was slowly injected via a syringe into the external water phase (poor solvent) under agitating. The system was stirred continuously for about 1 h. Along with the good solvent diffusing into the poor solvent, the droplets gradually solidified and formed microspheres. Then, the system was filtered to separate the microspheres from the preparation system. The resultant product was washed with distilled water and dried in an oven at 40 °C for 12 h. The whole process was carried out at room temperature.

2.3. Assessment of the bitter taste of the microspheres

2.3.1. Standard solution for evaluation of the bitter taste threshold of roxithromycin

The bitter taste threshold value of roxithromycin was determined based on the bitter taste recognized by six volunteers (three females and three males). A series of roxithromycin aqueous solutions were prepared at different concentrations as standard solutions, i.e. 4.95, 9.90, 19.8, 29.7, 39.6, 49.5 μg/ml, respectively.

The test was performed as follows: 1 ml of each standard solution was placed on the center of the tongue, it was retained

in the mouth for 30 s, and then the mouth was thoroughly rinsed with distilled water. The threshold value was correspondingly selected from the different roxithromycin concentrations as the lowest concentration that had a bitter taste.

2.3.2. Estimation of the bitter taste of microspheres in vitro

Microspheres containing about 50 mg roxithromycin were put into a test-tube containing 10 ml distilled water. The mixture was immediately vibrated for 30 s and then filtered. Five milliliters of filtrate and 5 ml sulfuric acid solution (75 ml sulfuric acid was added to 100 ml distilled water exactly) were combined and allowed to react for 30 min to produce a color, then the solution was analyzed in an spectrophotometer (Mode 752, Shanghai the Third Analytical Instrument Plant, China) at 482 nm to determine the dissolved drug concentration in water, which was then compared with the threshold value (Fu and Yang, 2000). The calibration curve between absorbance (A) and concentration (C) was $A = 0.0078C + 0.0901$ ($r = 0.9990$, $n = 5$), the linear relation was well fit when the drug concentration was within 4.95 and 59.4 μg/ml.

2.4. Methods of characterization and evaluation of the microspheres

The dried microspheres were sieved to determine their size distribution and mass median diameter (D_{50}) using the standard sieves stipulated in the Chinese Pharmacopeia 2005ed.

DSC patterns of the samples were obtained using a differential scanning calorimeter (DSC-60, Japan Shimadzu Co.). Each sample was heated from 30 to 350 °C at a scanning rate of 10 °C/min.

An X-ray diffractometer (D/max-2500pc, Rigaku Co., Japan) was employed to study the crystalline form of the drug in the microspheres. The X-ray copper target tube was operated at 60 kV and 250 mA. The scan time was 5°/min and the step size was 0.05.

Samples were crushed to make KBr tablets (0.5%, w/w) and then their IR (IFS55, BRUKER, Switzerland) spectra were recorded over the region 400–4000 cm^{-1}. The production yield was defined by Eq. (1). The drug loading and the incorporation efficiency of the microspheres were determined using HPLC (PU-980, Jasco Co., Japan) with an ultraviolet detector (UV-975, Jasco Co. Japan) set at a wavelength of 210 nm and calculated from Eqs. (2) and (3), respectively. An external standard method was used during the process. In the HPLC analysis, under condition of a Diamonsil™ C18 column (Dikma Technologies, 250 mm × 4.6 mm, 5 μm particle size) and a mixture of 0.067 mol/l $NH_4H_2PO_4$–acetonitrile–tetrahydrofuran (65:20:15, v/v/v) as the mobile phase (Liu, 1996; Wang et al., 1998; Li et al., 1999), the calibration curve was $A = 3 \times 10^6 C + 36458$ ($r = 0.9999$, $n = 5$). It was showed that the absorbance was linear to the roxithromycin concentration within 100 and 2800 μg/ml:

$$\text{production yield} = \frac{\text{total mass of microspheres}}{\text{total mass of raw materials}} \times 100\% \quad (1)$$

$$\text{drug loading} = \frac{\text{actual drug content}}{\text{weight of microspheres}} \times 100\% \quad (2)$$

$$\text{incorporation efficiency} = \frac{\text{actual drug content}}{\text{theoretic drug content}} \times 100\% \quad (3)$$

2.5. In vitro drug release studies

The drug release testing of the microspheres was conducted by the quality standard of Roxithromycin Granules specified in the Chinese Pharmacopeia 2005ed (paddle method). It was carried out for 2 h with 600 ml hydrochloric acid solution (1 → 1000) which was maintained at 37 ± 0.5 °C and agitated at 100 rpm. The selected test microspheres were under 180 μm in size and the amount of the microspheres was chosen to be equivalent to 50 mg roxithromycin. Six milliliters of dissolution medium was sampled and filtered at regular intervals to determine the percentage drug release. The drug concentration was determined by the same method as for estimation of the bitter taste in vitro. The calibration curve was $A = 0.0077C + 0.0393$ ($r = 0.9987$, $n = 5$). The linear relation between absorbance (A) and roxithromycin concentration (C) was well fit within 20–100 μg/ml region in hydrochloric acid solution (1 → 1000).

2.6. Effect of formulation factors

2.6.1. Taste-masking ability of various polymers

In the first place, a series of polymers including Eudragit E100, Eudragit L100-55, Eudragit L100, Eudragit S100, HP-50 and HP-55 were chosen to study their ability to mask the bitter taste of roxithromycin. The ratio of drug to polymer was kept constant at 1:3.

2.6.2. The influence of drug–polymer ratio, dichloromethane–acetone ratio and silica–polymer ratio on the properties of the microspheres

Eu S100 is effective in masking the bitter taste of roxithromycin. Several higher ratios of drug to polymer (1:0.65, 1:0.75, 1:0.85, 1:1) were employed to determine their effect on taste-masking and the drug dissolution properties from the microspheres. In each formulation, the solvent volume and the amount of polymer were fixed. The amount of roxithromycin was regulated in terms of the drug–polymer ratios.

To investigate the effect of the dichloromethane–acetone ratio on the properties of the microspheres, the total amount of the organic solvent and the amount of ethanol were kept constant. In addition, the ratio of dichloromethane to acetone was varied between 0:1and 5:1 for the preparation of the microspheres.

Silica was used as a dispersing and anti-adhesion agent. The ratio of silica to polymer was also examined to identify the optimal amount. The ratio of silica to polymer was varied between 0:8.5 and 3:8.5, while the drug to polymer ratio was fixed at 1:0.85.

3. Results and discussion

3.1. The bitter threshold of roxithromycin

The bitter threshold of roxithromycin recognized by the volunteers was between 19.8 and 29.7 μg/ml roxithromycin. If the drug concentration dissolved in 10 ml water from the microspheres after vibration for 30 s was below the threshold value, no bitter taste could be identified the taste buds. Accordingly, the bitter taste of roxithromycin was masked successfully by the polymers.

3.2. Taste-masking ability of various polymers

It may be that different polymers have different abilities to mask the unpleasant taste of different drugs. This is likely to be related to the different ingredients of the polymers. In order to find out the best one for masking the unpleasant taste of roxithromycin, six kinds of polymers were used to prepare microspheres with roxithromycin, and then the microspheres were taken at the same dose by six volunteers (three females and three males) and retained in their mouths for at least 30 s. In addition, the in vitro testing of the bitter taste of the microspheres was carried out for quantitative analysis. Except in the case of Eudragit S100 (Eu S100), the concentration of drug released from all the polymeric microspheres exceeded the bitter threshold of roxithromycin. The results are shown in Table 1. Obviously, Eu S100 was exactly what we needed.

As far as the taste-masking mechanism of Eu S100 is concerned, it is still one of the key points that need investigation. As we know, Eu S100 is an anionic copolymer based on methacrylic acid and methacrylic acid esters. The ratio of carboxyl groups to ester units is about 1:2. A great number of carboxyl groups are free in the molecules. Roxithromycin is an alkaline drug with a hydroxyimino and a tertiary amine group in its molecular structure. So, it is supposed that some unknown reactions may take place between them.

In fact, some researchers have studied the possible interactions between drugs and different kinds of Eudragit. For example, interactions were observed when the active agent had acid–base properties opposite to those of the Eudragit used. Warfarin and piroxicam, which are weak acids, exhibit interactions when associated with Eudragit E that contains basic groups; however, no interaction was reported with the anionic Eudragit S100 (Lin et al., 1994, 1996). Also, morphine base, when co-precipitated with Eudragit L, produced an intermolecular association between the polymer and the drug, consisting of two different hydrogen bonds (Alvarez-Fuente et al., 1994). It can be concluded that in the present case, a similar combination occurred.

Table 1
Taste masking ability of various polymers

Polymers	Drug:polymer	Taste	Concentration[a] (μg/ml)
Eudragit E100	1:3	Bitter	34.64 ± 6.13
Eudragit L100-55	1:3	Bitter	33.17 ± 4.36
Eudragit L100	1:3	Bitter	29.48 ± 5.00
Eudragit S100	1:3	Insipid	6.43 ± 1.29
HP-50	1:3	Bitter	48.11 ± 5.73
HP-55	1:3	Bitter	45.69 ± 6.57

[a] Drug release concentration in 10 ml distilled water over 30 s.

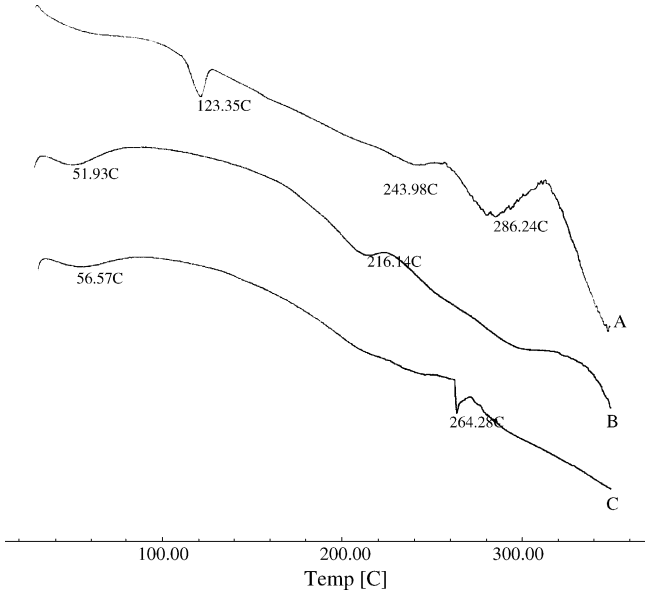

Fig. 2. DSC curves of roxithromycin, Eu S100 and the microspheres prepared from them. (A) Roxithromycin, (B) Eudragit S100 and (C) microspheres with roxithromycin and Eu S100 (1:0.85).

To further confirm our hypothesis, DSC graphs of roxithromycin, Eu S100 and the microspheres were obtained (Fig. 2). As shown in Fig. 2C, the endothermic peak of roxithromycin disappeared compared with Fig. 2A. This implied that the drug might be dispersed uniformly in the microspheres in an amorphous state. When Fig. 2C was compared with Fig. 2B, differences were also noted.

The result of X-ray diffraction showed that the pure drug (Fig. 3A) exhibited crystalline property, while Eu S100 and the microspheres (Fig. 3B and C) displayed amorphous pattern. All

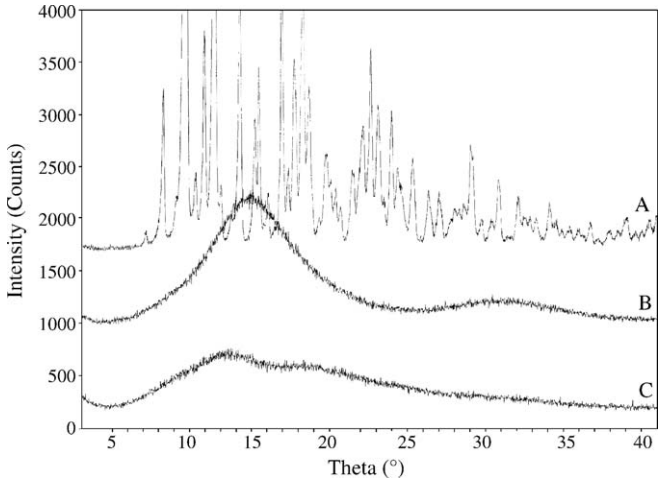

Fig. 3. X-ray diffractograms of roxithromycin, Eu S100 and the microspheres. (A) Roxithromycin, (B) Eudragit S100 and (C) microspheres with roxithromycin and Eu S100 (1:0.85).

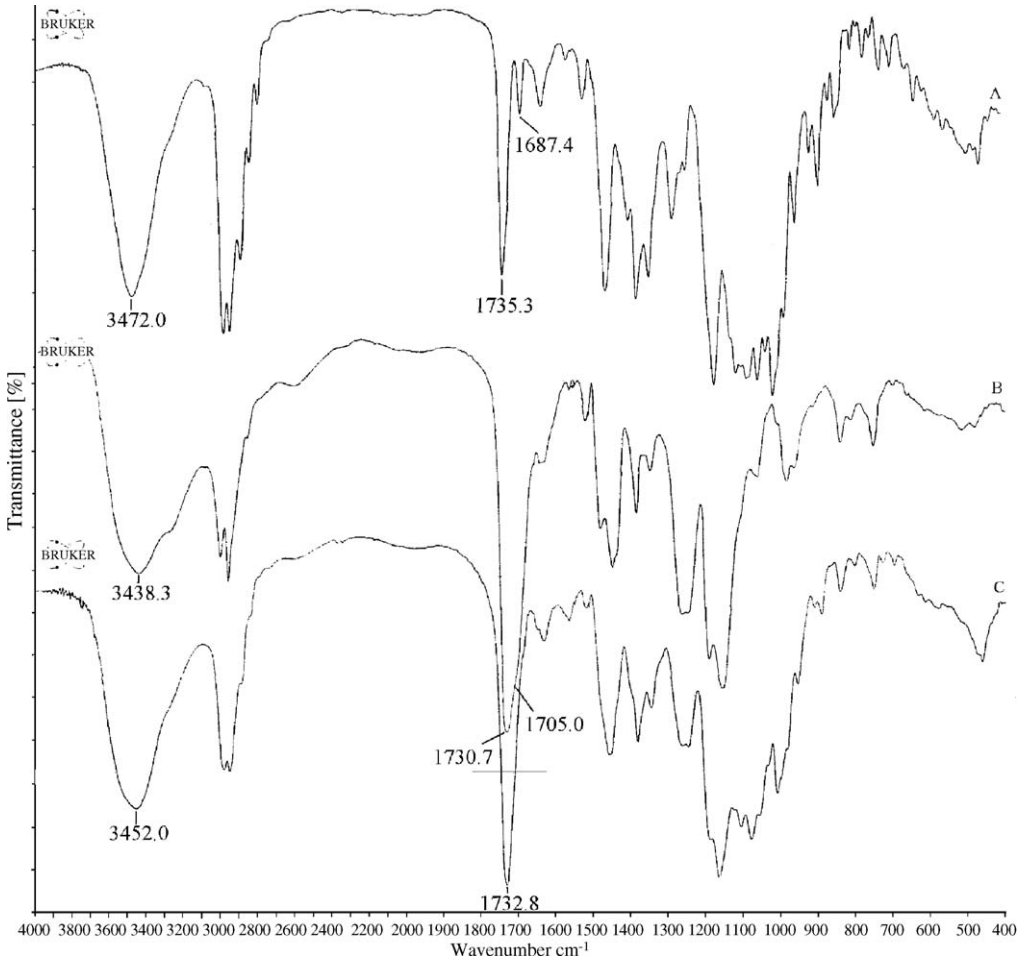

Fig. 4. IR spectra of roxithromycin, Eu S100 and the microspheres. (A) Roxithromycin, (B) Eudragit S100 and (C) microspheres with roxithromycin and Eu S100 (1:0.85).

the peaks of roxithromycin were absent in case of the microspheres. It proved the drug was changed into amorphous form after the preparation process of microspheres.

The IR spectra also provided powerful evidence to support our hypothesis (see Fig. 4). The IR spectrum of roxithromycin (Fig. 4A) exhibits three characteristic absorption peaks at 3472, 1735 and 1687 cm^{-1}, attributed to the stretching vibrations of O–H, C=O and C=N, respectively. In the IR spectrum of Eu S100 (Fig. 4B), an intense peak at 3438 cm^{-1} was evident due to the O–H stretching vibration. The C=O vibration band of the carboxylic groups presents as a shoulder at 1705 cm^{-1}; while the peak at 1730 cm^{-1} is attributed to the esterified carboxyl groups. However, in Fig. 4C which is the IR spectrum of the microspheres, the peaks of C=N at 1687 cm^{-1} in Fig. 4A and C=O at 1705 cm^{-1} in Fig. 4B have disappeared. The marked change shows that there are indeed interactions between the drug and Eu S100. During the process of preparing the microspheres, the C=N of roxithromycin is converted to C–N and this bonds with the carboxylic hydroxyl groups in the polymer molecules. The peak intensity at about 1730 cm^{-1} is increased markedly in Fig. 4C owing to the superimposition of the esterified carbonyls in both drug and polymer molecules, as well as the newly formed ones between them. All these interactions are considered to be useful for masking the bitter taste of the drug. More research is currently being performed.

3.3. The influence of the drug–polymer ratio

The ratio of drug to polymer was varied as reported in Table 2. The effect of the taste masking gradually improved as the ratio decreased. When the ratio of the drug to polymer was 1:1, the drug concentration released in the in vitro bitter taste test was below the bitter threshold value. However, correspondingly, the drug release rate from the microspheres fell to less than 70%. This was caused by the characteristics of Eu S100 which dissolved stepwise at a pH above 7.0, and the films formed by Eu S100 remained intact for a long time in acidic medium, thereby limiting the roxithromycin dissolution. In the drug release test over 2 h, the percentage drug released was over 70% in hydrochloric acid solution for other three formulations. All the results can be seen in Table 2 and Fig. 5.

3.4. The effect of the dichloromethane–acetone ratio

Acetone was used as a good solvent, which can dissolve drug and polymer, and can mix with bridging liquid. In the preparation

Table 2
The effect of drug to polymer ratio on the properties of roxithromycin microspheres ($n = 3$, $\bar{x} \pm$ S.D.)

Formulation code	Drug–polymer ratio	Bitter taste	Concentration[a] (μg/ml)	Production yield (% ± S.D.)	Drug loading (% ± S.D.)	Incorporation efficiency (% ± S.D.)	D_{50} (μm)
F1	1 : 1	−[b]	13.77 ± 4.51	92.23 ± 1.40	48.54 ± 0.41	97.07 ± 0.75	146 ± 19
F2	1 : 0.85	+[c]	22.63 ± 5.38	94.98 ± 1.08	52.86 ± 0.35	97.80 ± 0.64	151 ± 23
F3	1 : 0.75	++	26.19 ± 6.07	92.56 ± 1.14	55.68 ± 0.47	97.44 ± 0.82	138 ± 29
F4	1 : 0.65	++	30.37 ± 5.23	91.89 ± 1.35	59.22 ± 0.29	97.71 ± 0.48	124 ± 25

[a] Drug release concentration in 10 ml distilled water over 30 s.
[b] Insipid taste.
[c] Produces a bitter taste after a short time.

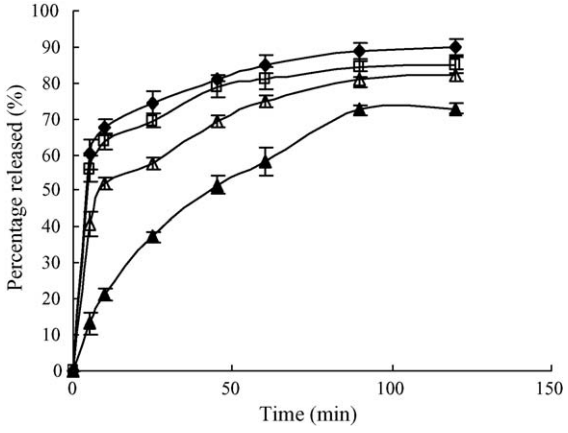

Fig. 5. Roxithromycin release profiles from the microspheres. with different ratios of drug to Eu S100 ($n = 3$). Roxithromycin:Eu S100 = 1:0.65 (□); 1:0.75 (♦); 1:0.85 (△); 1:1 (▲).

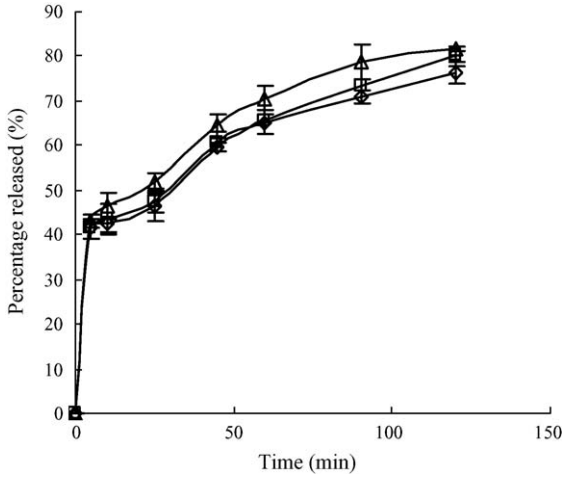

Fig. 6. Roxithromycin release profiles from the microspheres produced by different ratios of dichloromethane to acetone ($n = 3$). Dichloromethane: acetone = 3:1 (□); 4:1 (♦); 5:1 (△).

process of the microspheres, the diffusion of the good solvent from the emulsion droplets into the poor solvent promoted the coprecipitation of the drug and the polymer in the droplets, and the residual dichloromethane linked the sediments together to form microspheres. An unsuitable ratio of dichloromethane to acetone would affect the preparation processes, and the microspheres would not be produced successfully. In region of the efficient preparation ratio, the characteristics of the microspheres on the variation in the ratio were investigated. The results are given in Table 3 and Fig. 6. In this case, the ratio of the drug to polymer was fixed at 1:0.85. The addition of acetone had no significant effect on the drug release rate, the drug loading or the incorporation efficiency of the microspheres. It was found that the microspheres would conglutinate with each other by the addition of acetone. This may be one of the reasons why D_{50} increased slightly when the amount of acetone increased. And since the dissolution rate is directly proportional to the surface area to some extent, the percentage drug released in distilled water was reduced along with D_{50} increased. What's more, the internal structure of the microspheres may be influenced by the addition of acetone. It seems that acetone helps to mask the bitter taste to some extent. However, filiform and a few microspheres formed without dichloromethane as in the case of formulation F2-a.

3.5. The effect of the silica–Eu S100 ratio

Generally, highly sticky droplets were produced in the early period of the preparation process due to the semi-solid polymer, and resulted in the droplets gathering together. Silica has tremendous surface area, high porosity and unique adsorption property. It is an inorganic material which is insoluble in any organic solvents. During the preparation process of microspheres, silica

Table 3
The effect of dichloromethane to acetone ratios ($n = 3$, $\bar{x} \pm$ S.D.)

Formulation code	Dichloromethane–acetone ratio	Drug loading (% ± S.D.)	Incorporation efficiency (% ± S.D.)	Concentration[a] (μg/ml)	D_{50} (μm)
F2-a	0:1	–	–	–	–
F2-b	3:1	52.91 ± 0.38	97.88 ± 0.70	17.48 ± 4.10	161 ± 17
F2-c	4:1	52.86 ± 0.44	97.79 ± 0.81	20.03 ± 3.89	149 ± 21
F2-d	5:1	52.79 ± 0.32	97.66 ± 0.59	23.56 ± 5.44	142 ± 26

[a] Drug release concentration in 10 ml distilled water over 30 s.

Table 4
The effect of the Silica to S100 ratios ($n = 3$, $\bar{x} \pm$ S.D.)

Formulation code	Silica–S100 ratio	Drug loading (% ± S.D.)	Incorporation efficiency (% ± S.D.)	Concentration[a] (μg/ml)	D_{50} (μm)
F5	0:8.5	52.86 ± 0.35	97.80 ± 0.64	22.58 ± 4.77	139 ± 24
F6	1:8.5	50.00 ± 0.34	97.50 ± 0.66	26.96 ± 5.38	167 ± 11
F7	2:8.5	47.49 ± 0.42	97.36 ± 0.85	29.11 ± 6.07	174 ± 20
F8	3:8.5	45.26 ± 0.23	97.31 ± 0.49	34.37 ± 5.23	198 ± 18

[a] Drug release concentration in 10 ml of distilled water over 30 s.

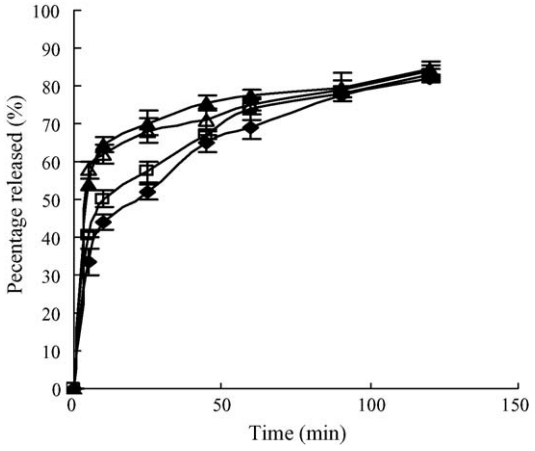

Fig. 7. Roxithromycin release profiles from microspheres produced with different ratios of silica to Eu S100 ($n = 3$). Silica:Eu S100 = 0:8.5 (□); 1:8.5 (♦); 2:8.5 (△); 3:8.5 (▲).

commixed with the polymer uniformly. The viscosity of the droplets was so reduced, which could prevent conglutination occurred between emulsified droplets and could improve the solidification of the droplets. It is a good anti-adhesion agent against the viscous characteristic of polymers. What is more, it was considered to be helpful to promote the dispersibility of the drug in the microspheres. Therefore, it would accelerate the drug release rate. On increasing the silica–Eu S100 ratio, both the size of the microspheres and the drug release concentration in distilled water increased. Obviously, the drug release rate rapidly increased when the ratio of silica to Eu S100 was greater than 1:8.5, although the total amount of drug released over 2 h was almost at the same level for all formulations (see Table 4 and Fig. 7).

4. Conclusions

Roxithromycin microspheres with polymers were prepared successfully by the emulsion solvent diffusion method. Among the polymeric microspheres, the most efficient in masking the bitter taste of roxithromycin were the microspheres produced with Eu S100. To our surprise, these microspheres tasted insipid even when the ratio of drug to Eu S100 was only 1:1. This may be helped by the combination between the drug and the polymer during the preparation process. The results of IR confirmed the possibility of such reactions. The DSC graphs and X-ray diffractograms showed that the drug was in an amorphous state in the microspheres. The formulation factors, i.e. drug–Eu S100 ratio, dichloromethane–acetone ratio and silica–Eu S100 ratio were found to have an effect on the characteristics and release behavior of the microspheres. It was obvious that microspheres masking the bitter taste of the drug could be incorporated into a suitable dosage form for oral application in the future. Further investigations are currently underway.

According to this study, the interactions between drugs and polymers help to mask the bitter taste of drugs. We suppose that the kinds of polymers could be picked out in the light of the molecule structure of the drug. It seems to be reasonable that the opposite electric groups between drug and polymer can take better effects on taste-masking with the interaction, but it must be considered that the chemical stability on the interaction between them, and whether the bitter taste was happened round the electric groups of the drug. As for neutral drugs, the situation is quite different. The bitter taste of them could not be masked by interactions between drug and polymer. Maybe the coating technique is the best candidate for masking the bitter taste of the drug. As a whole, different drugs possess diverse physical and chemical properties. The taste-masking studies should be performed in accordance with the characteristics of each drug. Only by experiments can we gain our expected ends.

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