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In vitro controlled release of sodium ferulate from Compritol 888 ATO-based matrix tablets

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Abstract

A controlled release matrix formulation for freely water-soluble drug of sodium ferulate (SF) was designed and developed to achieve a 24 h release profile. Using Compritol 888 ATO as an inert matrix-forming agent to control the release of SF, formulation granules containing the physical mixtures or solid dispersions were investigated. The matrix tablets for these formulations were prepared by direct compression and their *in vitro* release tests were carried out. The solid dispersion based tablets were found to be more effective than those compressed from physical mixtures in retarding the release of SF. Drug release from the matrix tablets containing physical mixtures nearly completed within 12 h, while that from the solid dispersion formulations lasted for over 24 h. Images of the tablet surface and cross-section were characterized by scanning electron microscopy to show the formed pores and channels in the matrices. These might provide the release pathway for the inner embedded drugs. Drug released fast from the matrix tablets with the release-enhancer of lactose. The addition of surfactants was also found to increase the release rate of SF effectively. Moreover, the co-mixing of polyethylene glycol 6000 (PEG 6000) in the waxy matrices played a meaningful role in controlling the drug release for 24 h. The drug release from the novel formulation might be attributed to the diffusion-controlled mechanism.

Keywords: Sodium ferulate; Compritol 888 ATO; Solid dispersion; Controlled release matrix tablet; Drug release *in vitro*

1. Introduction

Ferulic acid is the most abundant hydroxycinnamic acid initially extracted from Angelica sinensis, Cimicifuga heracleifolia, Lignsticum chuanxiong, and other plants. The synthesized sodium ferulate (SF) or 3-methoxy-4-hydroxy-cinamate sodium has antithrombotic, platelet aggregation inhibitory and antioxidant activities in animals and humans (Ju et al., 1990; Ogiwara et al., 2002; Mathew and Abraham, 2004; Wang and Ou-Yang, 2005). It has been used in traditional Chinese medicine and approved by State Drugs Administration of China as a drug for the treatment of patients with cardiovascular disease and cerebrovascular disorder clinically. The results of recent studies showed that SF might be a potential agent against hepatic fibrosis (Liu et al., 2002; He et al., 2005). It has a short elimination half-life of less than 2 h (Zhang et al., 2005; Xu et al., 2005) *in vivo*, and requires to be administrated frequently (thrice daily) to maintain the therapeutic effect for necessary long-term therapy. The sustained-release systems can achieve effective drug concentration therapeutically in the systemic circulation over an extended period of time. For the improvement of compliance to patients, however, it is desirable to develop a sustained-release oral dosage form for SF.

Erosion/swelling matrix or coating measures have been usually taken to retard the drug release. In the previous work (Li and Hu, 2004a), we have used the water-swellable hydrophilic material of hydroxypropyl methylcellulose (HPMC) to delay the release of SF for 12 h *in vitro*. For the development of sustained-release dosage forms, the drug solubility is one of the important factors to be considered. Since SF is a freely water-soluble compound, of which solubility in water is about 120 mg/ml, it is often difficult to control the drug release at the required rate (Zeng, 2004).

Drug release behavior could be modified with the implication of solid dispersion technique. The diffusion and release properties of insoluble active compound were improved significantly to obtain enough solubility and release rate for desired bioavailability (Craig, 2002; Vippagunta et al., 2002; Shin and Kim, 2003;

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Li and Hu, 2004b). Recently, sustained or controlled release of water-soluble active ingredient can be realized by utilizing the solid dispersion coating procedure with inert retarded materials. As the characteristics of water-insoluble and non-swellable, waxy materials have major applications in sustained-release systems, especially for freely water-soluble drugs. Glyceryl behenate is a waxy material, originally introduced as a lubricant for tablets, which has recently had a wide application as a sustained-released excipient (Sutanata et al., 1995). Barthelemy et al. (1999) had investigated the use of glyceryl behenate as a hot-melt coating agent to prolong the release of theophylline. Their study confirmed a satisfactory coating potential by this agent and a potential in sustaining the release of theophylline over an extended period of time.

Comprital 888 ATO is composed of glyceryl behenate, with low fusion point, has been utilized as retard material for sustained-release dosage forms (Barthelemy et al., 1999; Faham et al., 2000; Mirghani et al., 2000). Unlike HPMC, which work by swelling in water, and eventually, disintegration of the matrix, the Comprital 888 ATO-based inert matrices might provide another solution for the controlled release of those freely water-soluble drugs needed to be formulated into sustained or controlled drug release system.

In this study, Compritol 888 ATO was used as the waxy retardant material, and SF was chosen as the model of freely water-soluble drug. The matrix tablets of SF were prepared by direct compression of granules composed with solid dispersions or physical mixtures of SF and Compritol 888 ATO. The release behaviors of SF from the matrix tablets were studied *in vitro*. And the imaging of scanning electron microscopy was used to inspect the porosity and morphology of the drug-released tablets. The effects of release-enhancer and surfactant on the release of SF were also investigated. Further more, the hydrophilic material of polyethylene glycol 6000 (PEG 6000) was incorporated into the waxy matrices to regulate the SF release profiles.

2. Materials and methods

2.1. Materials

Sodium ferulate with the particle size range of 50–90 μm (Limin Pharmaceutical Factory of LiZhu Group, China), Compritol 888 ATO (Gattefossé S.A., Saint Priest, France) and Lactose 450 mesh (DMV International, The Netherlands) were needed. Polysorbate-80, poloxamer 188 and PEG 6000 were purchased from the Chemical Agent Station, Medicine Group of China. All other chemicals were of reagent grade and used as received.

2.2. Methods

2.2.1. Preparation of solid dispersions by hot fusion method

Compritol 888 ATO was melted in porcelain evaporating dish by water bath at 75 °C. SF was added with continuous stirring (glyceryl behenate and the drug were used in the required ratios for each preparation) to get a homogeneous dispersion. Then, the molten mass with SF presented in its solid form was allowed to cool down and solidify. Subsequently, the mass was ground, pulverized and passed through a 60-mesh sieve (less than 300 μm). The obtained powders were stored in a desiccator at room temperature until use.

In order to study the effect of lactose and surfactant on the release of the drug from tablets with such matrices, other solid dispersions were prepared with the addition of lactose or surfactants (such as polysorbate-80 and poloxamer 188) at specified ratios listed in Table 1. PEG 6000 was also used as a matrix-forming agent to compose the mixed fusion matrices (Table 1).

2.2.2. Preparation of physical mixtures by mechanical blending

Particles of physical mixtures for tablets were prepared to compare and elucidate the sustained-release effect of solid dispersion matrices. Different ratios of SF to Compritoll 888 ATO were mixed directly in a mortar until the homogeneous mixtures were obtained. The resulting mixtures were sieved through a 80-mesh sieve (less than 210 μm) and then stored in a desiccator at room temperature until use.

2.2.3. Manufacture of Compritol 888 ATO-based matrix tablets

The physical mixture or solid dispersion was directly compressed using a 19-station rotary tablet machine (Tianxiang Jiantai Machinery Drug Making Co., Shanghai, China) fitted with 9 mm diameter normal biconcave punches and die sets. Relatively constant tablet hardness was held around 8 kg (measured on a 78X-2 multifunctional determinator for tablet, Shanghai,

Table 1
The compositions of the sodium ferulate solid dispersion formulations investigated

Formulation	Ratio of SF to Compritol (w/w)	Ratio of SF to lactose (w/w)	Surfactant used (2.0%, w/w)	PEG 6000 (%, w/w)
1	1.5:1	–	–	–
2	1:1	–	–	–
3	1:1	3:1	–	–
4	1:1	5:1	–	–
5	1:1	15:1	–	–
6	1:1	–	Poloxamer 188	–
7	1:1	–	Polysorbate-80	–
8	1:1	15:1	Polysorbate-80	5
9	1:1	15:1	Polysorbate-80	10

Huanghai, China) for compression. The tablets, having luminous surfaces, were stored in a plastic container until use.

2.2.4. Release studies in vitro

The release tests of the prepared tablets were performed according to the rotating basket method, which was employed to overcome the problems due to floating of the tablets onto the surface. A ZRS-8 intelligent dissolution apparatus (Tianjin University, China) was employed with a stirring rate of 50 rpm. In order to hold sink conditions also in this case, 900 ml of freshly distilled water, maintained at $37 \pm 0.1\,^{\circ}C$ were used as the dissolution medium. At predetermined time interval, aliquots volumes of 5 ml samples were withdraw from the dissolution medium and immediately replaced by the same volume of fresh dissolution medium. The samples were filtered, and the concentrations of SF were measured spectrophotometrically at 320 nm using an ultraviolet spectrophotometer (UV-2201, Shimadzu, Japan). It is worth noting that none of the additives used in the matrices interfered with the assay. The results were expressed as the percentage of released drug as a function of time.

2.2.5. Scanning electron microscopy (SEM) analysis

The morphology of tablets might reflect the pathway and mechanism for drug release. So, SEM was used to image the tablet surfaces and cross-sections before or after the drug released. Samples were sputter coated with gold–platinum, and then imaged on an S-520 scanning electron microscope (Hitachi, Japan) at an accelerating voltage of 20 kV. SEM analysis of the tablet internal structure was also made after splitting the sample.

3. Results and discussion

3.1. The effects of wax levels and matrix formation methods on drug release

The amount of drug in the formulated tablet was held constant at 150 mg, while the wax level varied. Fig. 1 shows the release profiles for matrices made from the physical mixtures or solid dispersions. In either case, both of these matrices will be highly hydrophobic and would be expected to release the drug at a very slow rate, as indeed was found to be the case. The release rates of SF from Compritol 888 ATO-based matrix were retarded effectively.

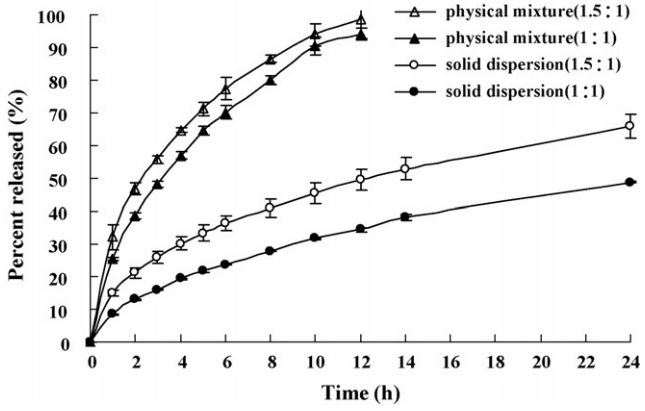

Fig. 1. *In vitro* profiles of SF released from sustained-release tablets made by direct compression of the particles of physical mixtures and solid dispersions. The ratios represent SF to Compritol 888 ATO by weight.

Although the drug release from these matrices is torpidity and sustained, it was higher from the matrices prepared with physical mixtures than from tablets with solid dispersions. As shown from Fig. 1, Almost 90% of the drug released after 12 h for those tablets based upon the mechanic mixtures of SF and the wax material. But for the solid dispersion compressed tablets, less than 20% of SF was released at the first 2 h. And the tablets prepared with 40% Compritol 888 ATO (drug wax ratio of 1.5:1, w/w) released nearly 60% of the drug, while tablets containing 50% Compritol 888 ATO (drug wax ratio of 1:1, w/w) released only 48% of the drug after 24 h. Therefore, increasing the ratio of Compritol 888 ATO in the matrices resulted in a further decrease in the drug release rate.

The slower release from the solid dispersion matrices is due to almost complete coating of the drug particles by Compritol 888 ATO melted in the process of hot fusion. In this case, it is expected that the penetration of the dissolution medium into the matrix will be low compared with matrices prepared by mechanical mixtures, and hence, the dissolution and release of the drug occurs at a slower rate.

Inspection of the appearance of the tablets, at the end of the dissolution test, revealed that all tablets containing Compritol 888 ATO remained intact without any significant change in their shape. This indicated that the Compritol 888 ATO used in the tablet formulation created an inert matrix. It seems that the water-soluble active substance diffused across the waxy matrix.

3.2. SEM imaging of the tablets before/after drug release

Imaging technique of scanning electron microscopy (SEM) can offer useful information about the surface characterization of the tablet surface (Seitavuopio et al., 2003). The microstructures of tablet transverse and longitudinal sections might reflect the pathway for drug release. So, SEM was used to image the tablet surfaces and cross-section before and after the drug released.

Representative SEM images of surface and cross-section of the matrix tablets are shown in Fig. 2. It can be seen from Fig. 2b, the surface was full of pinholes, which might be due to the dissolution and diffusion of the drug particles at the surface of the matrices, and allow the inner drug to release through the established mini-channels. The cross-section of the drug-released tablet also had large quantities of cracks on its cut surface, which might reflect the multiplicity of porosity (Fig. 2c and d). These features revealed the internal mini-tunnels with multiple voids resembling a microbore-network structure.

These observations support our conclusion that the drug release is mainly due to diffusion through the channels formed in the matrix. These channels were caused by the rapid dissolution of the water-soluble drug particles on the surface of the matrix. Then, the aqueous medium would penetrate into these channels

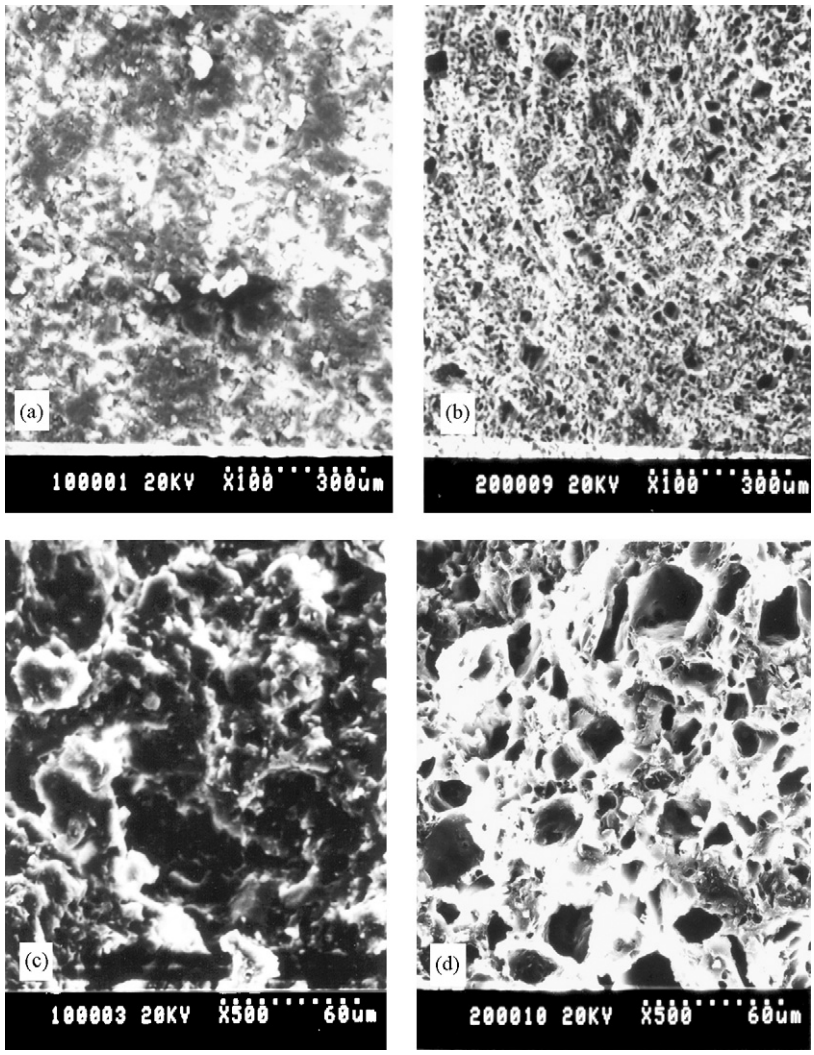

Fig. 2. SEM micrographs of the surfaces and cross-sections of the matrix tablets compressed from the solid dispersions of SF and Compritol (1:1, w/w). (a) Surface of tablet before release test; (b) surface of the drug-released tablet; (c) transverse section of tablet before release test; (d) transverse section of the drug-released tablet.

for more dissolution of the drug presented in the deeper sites of the matrix.

3.3. Influence of lactose in solid dispersions on the release of SF from matrix tablets

Since drug release from the compressed matrix tablets was very slowly, the release-enhancer of lactose was added into the waxy matrices to increase the release rate. Different ratios of lactose were used to investigate their effect on the drug release properties. In this experiment, SF amount and the ratio of drug to Compritol 888 ATO were kept constant, while the ratios of SF to lactose varied (Table 1).

As it can be seen from Fig. 3, increasing the amount of lactose in the matrix resulted in a little increase in the release of the drug. At the drug to lactose ratio of 15:1 (w/w), the cumulative drug release percent could be increased to about 70% within 24 h. Because of its rapid and high solubility in water, lactose could participate and help to produce pores and channels in the matrix. This function might interpret the speed up of drug dissolution rate with the addition of lactose.

3.4. Influence of surfactant in solid dispersions on the release of SF from matrix tablets

As for the yielded matrix tablets, there may be three types of interactions that can affect the drug-release rate: (1) elec-

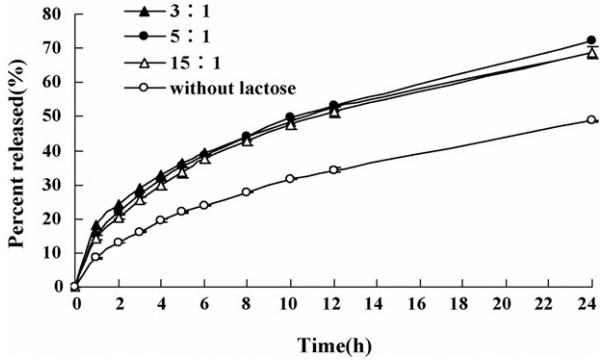

Fig. 3. Effect of lactose on the release profiles of SF from the matrices tablets prepared by compression of solid dispersions. The ratios represent SF to lactose by weight.

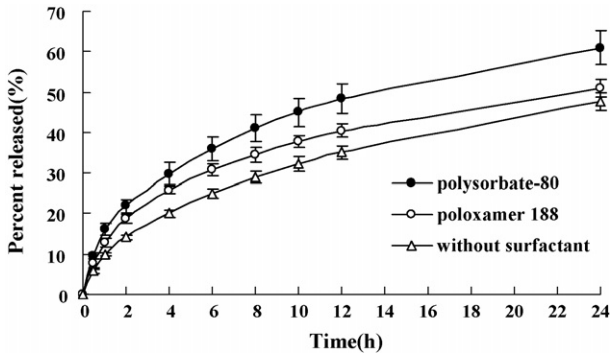

Fig. 4. Effect of surfactants of polysorbate-80 and poloxamer 188 on the release profiles of SF from matrix tablets containing solid dispersions.

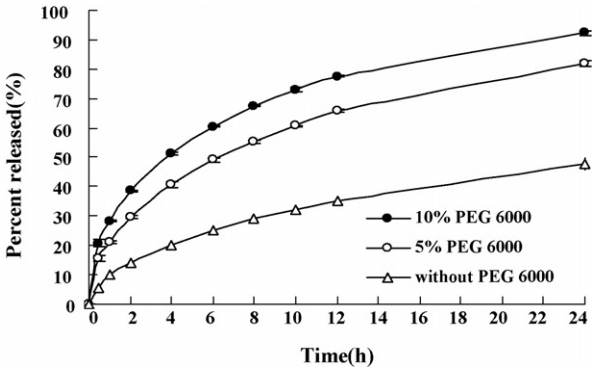

Fig. 5. Effect of PEG 6000 mixed into the waxy solid dispersion system on the release profiles of SF from matrix tablets.

trostatic interactions; (2) hydrogen bonding; (3) hydrophobic interactions. The electrostatic attraction and hydrogen bonding are not as important as the hydrophobic interactions and the textural properties of the matrices (Wu et al., 2005). The interface between hydrophobic wax carrier and hydrophilic water-soluble drug might hinder the further completely release of the drug. Surfactant can balance the hydro-lipid property of the releasing environment. So the drug concentration gradient could be bridged and maintained continuously with the existence of surfactant.

By including a surfactant in the formulation, the release rate could be further increased since hydrophobic interactions between the drug and matrix might be adjusted. Fig. 4 demonstrated that the drug release was obviously increased by the addition of the surfactant, such as polysorbate-80 or poloxamer 188. Tablets formulated with 2.0% (w/w) polysorbate-80 had relatively high release rate with about 60% drug released within 24 h, while the release of SF is slightly promoted by the addition of poloxamer 188. And the increased drug release rate caused by polysorbate-80 might also be explained by the better solubility of polysorbate-80 in the lipid matrix than that of the too hydrophilic poloxamer 188. The ability of surfactants to accelerate the *in vitro* release of drug from waxy matrix might be attributed to the diffusion aid for the dissolved drugs out of hydrophobic pores or channels.

3.5. Effect of the combined use of hydrophilic material in waxy carrier on the drug release rate

It is thus evident that these highly hydrophobic matrices of Compritol 888 ATO would retard the drug at a very slow release rate. PEG 6000 can be often used as hydrophilic material for solid dispersions to give an increased drug dissolution rate (Li et al., 2002). So, matrix tablets contained with different amount of PEG 6000 were prepared to examine the accelerated release rate of SF. As it can be seen from Fig. 5, the combined use of PEG 6000 had increased the release of the drug from Compritol 888 ATO matrices significantly. The release rate of the tablets was higher compared with matrices without PEG 6000. Within 24 h, more than 90% drug could be released from the matrix tablets contained with 10% PEG 6000 (w/w), lactose and surfactant of polysorbate-80. The time required for 50% drug released from the formulation was about 6 h.

This result was expected due to the uniformly dispersion of water-soluble PEG 6000 into the coating wax of Compritol 888 ATO. The dissolve of PEG 6000 will induce high porosity and produce even more channels in the matrix, which will facilitate the dissolution medium to penetrate the matrix and dissolve the drug more rapidly. After the prophase release, drugs embedded inside the matrices could be released through the formed porous waxy networks completely.

The data of drug release were fitted to the Higuchi's square root of time model. A good fitness was obtained to describe the release kinetics of the drug from the matrix tablets, and this seemed not affected by the compression force or the amounts of different ingredients in the inert matrices (Obaidat and Obaidat, 2001). The release of SF from Compritol 888 ATO matrices appeared to be an operative diffusion-controlled mechanism.

4. Conclusion

This study showed that Compritol 888 ATO is an appropriate waxy material that can be utilized as a matrix-forming agent to control the release of a freely water-soluble drug sodium ferulate. Matrix tablets prepared from solid dispersions were more effective than those from physical mixtures in controlling the drug release rate. However, it was possible to adjust the release characteristics by employment of other ingredients including release-enhancer, surfactant and hydrophilic PEG 6000. The prepared 24 h controlled-release matrix tablets would provide an extended duration of therapeutic effect of SF with minimum potential for side-effects.

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