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Preparation of an enteric-soluble solid-state emulsion using oily drugs

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Abstract

To improve the patient's compliance and enhance the stability of oily drugs in the gastric fluid, an enteric-soluble solid-state emulsion (ESE), was developed. The ESE was prepared by spreading liquid o/w-emulsions on a flat glass and drying at the oven maintained at 40 °C. Aerosil 200 was applied as solid carrier and emulsifier. And Eudragit® L30D-55 was used as enteric coating material. The influence of various preparation parameters on the residual volatile oil and the release behavior was investigated. Droplet size distribution of the primary emulsions and the emulsion after reconstitution of zedoary turmeric oil (ZTO) ESE in the phosphate buffer were also measured. When ZTO ESE was immersed into phosphate buffer (pH 6.8), the stable emulsion was formed in 20 min, but the release was obviously suppressed when it was exposed to the gastric fluid. It was concluded that preparation of enteric-soluble solid-state emulsion by the present method for oral oily drug was feasible.

Keywords: Solid-state emulsion; Zedoary turmeric oil; Enteric-soluble

1. Introduction

There are a lot of oily drugs, which have strong therapeutic activity, such as oleum fructus bruceae (Ma et al., 2004), evening primrose oil (Ping, 2001) and zedoray turmeric oil (Li et al., 2002). However, they have not been widely used due to their liquid state and unpleasant odor. From a practical point of view, oily drugs or liquid-dosage form (oral liquid emulsion, suspension), are comparative difficult to manipulate because of their low physicochemical stability and they often should be stored in special conditions.

To date there have been several attempts, such as adsorption, solid-state emulsion, to prepare solid preparations from oily drugs. Silica gel is a popular adsorbent due to its large porosity and huge specific surface area. At present much surface-modified silica gel has been produced to improve its affinity to oily drugs (Otsuka et al., 2000). However, the higher drug adsorption ability leads to the lower drug release in vivo resulting in low bioavailability. Another alternative popular preparation is the solid-sate emulsion, which would form emulsion upon the addition of an aqueous phase. It is prepared by removing water from an ordinary emulsion containing a water-soluble or water-insoluble solid carrier, through rotary evaporation (Myers and Shively, 1992), lyophilisation (Molina and Cadorniga, 1995) or spray drying (Takeuchi et al., 1992; Christensen et al., 2001). At present solid-state emulsion has attracted wide attention because it eliminates the shortcomings of liquid emulsion, physical instability and the difficulty to operation, but retains its advantages, high bioavailability. However, with regard to the volatile oily drug or the drug, which is susceptible to acidic or enzymatic degradation in the stomach, each of the previous preparations mentioned above does not fit. Because during the operation of rotary evaporation or spray drying, long drying time or high temperature was needed. Although lyophilisation is a suitable method to prepare solid-state emulsions for the volatile medicine, during storage the medicine would easily volatile due to its loose architecture and a porous to hollow structure (Steckel and Brandes, 2004). To date no sustained solid-state emulsion or enteric-soluble solid-state emulsion has been investigated.

Zedoary turmeric oil (ZTO), extracted from the dry rhizome of *Curcuma zedoaria Rosscoe*, has been used for thousands of years in China. A series of studies on ZTO shows that it has strong pharmacological actions including suppression of tumor cells and thrombosis, anti-bacterial, anti-virus and so on by pharmacological and clinical studies (Li et al., 2002; Wei et al., 2003). However, the disadvantage properties, uncomfortable odor, disagreeable taste, chemical instability and volatility, limits its clinical application. Up to now, Only zedoray turmeric

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oil and glucose injection is used in clinical and no per oral preparation has been permitted by the SFDA of People's Republic of China (PRC).

Here, a novel solid dosage form, an enteric-soluble solid-state emulsion was presented by an easily method, manual grinding, with the aid of Aerosil 200 and Eudragit® L30D-55, using water-insoluble and easily volatile oily drug, zedoray turmeric oil, as a model drug. In this preparation, no additional emulsifying agents or organic solvent was employed, so common ecological, toxicological, and manufacturing safety concerns are not problematic.

The purpose of this study was to investigate the effects of various materials and the amounts on the residual volatile oil, on the release behavior and on the particle size distribution of the reconstruction the solid-state enteric-soluble emulsion.

2. Materials and methods

2.1. Chemicals and reagents

ZTO was obtained from Jiangxi Tongren Natural Perfume Co. (Jiangxi, China); Aerosil 200 was purchased from Röhm Pharma Co. (Germany). Eudragit® L 30D-55 was donated by Röhm Pharma Co.; Tween 80 was of analytical trade and provided by Shandong Yuwang Chemical Plant (Shandong, China).

2.2. Preparation of an enteric-soluble solid-state ZTO emulsion

A novel and simple method was developed to prepare enteric-soluble solid-state ZTO emulsion. The flowchart of the preparation procedure for the ZTO ESE was illustrated in Fig. 1. ZTO (0.5 g) and Aerosil 200 (0.2, 0.3, 0.4, 0.5 g) were mixed uniformly. Then Eudragit® L30D-55 (3.0, 4.0, 5.0, 6.0 mL) mixed with some plastisizer was added under continuous grinding until a viscous semi-solid emulsion was achieved. The resultant semi-solid emulsion was spread on a flat glass plate with the thickness of about 0.5 mm. Then it was dried at the oven, the temperature of which was maintained at $40 \pm 1\,^{\circ}C$ for about 4 h to get a semi-transparent dry film. Then the dried film was cooled down at room temperature. It was triturated to powders with suitable particle size. The powders were sieved and particles of $-24 + 50$ mesh (355–855 μm) were collected for further investigation.

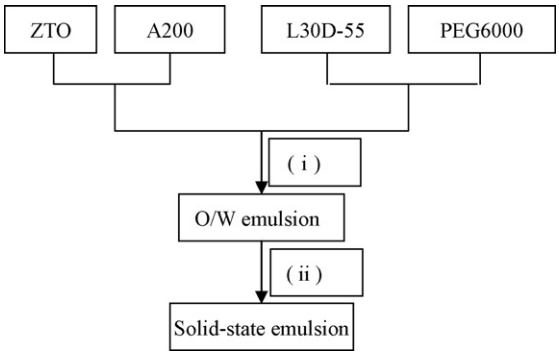

Fig. 1. Flowchart of preparation procedures for enteric-soluble solid-state emulsion. (i) Mixing with continuous grinding and (ii) spreading on the flat glass and drying at 40 °C.

2.3. Determination of ZTO content and the residual efficiency of ZTO in ESE

The content of ZTO in ESE was measured by the method described in the *Chinese Pharmacopoeia* (Ch. P. 2005) (NPC, 2005; Wang et al., 2001). The weighed amount of ZTO ESE was dissolved in ethanol, ultrasonic until the polymers dissolved and passed through 0.8 μm membrane filter. Then 1 mL of the filtrate was uniformly blended with 9 mL 0.2% vanillin sulfuric acid solution (50%). After 1 h, the blended solution was assayed at 520 nm using a spectrophotometer (Mode 752, The Third Analytical Instrument Plant, Shanghai, China). From this result, the drug loading percentage (w/w, ZTO content per dry ZTO ESE) was determined. Each sample was assayed in triplicate. ZTO residual efficiency in ZTO ESE was expressed by comparing the actual ZTO loading with the theoretical ZTO loading.

2.4. Measurement of micromeritic properties of microspheres

Bulk density was measured by filling the powder in a 10-ml measuring cylinder with a funnel. The angle of repose of ZTO ESE was also measured by powder pouring methods.

2.5. In vitro release studies

As specified in the method II for enteric dissolving preparations in Ch. P. 2005 ed., the release test was carried out. Firstly, ESE containing 100 mg of ZTO was incubated in 750 mL dissolution medium which is composed of artificial gastric fluid (pH 1.2, without enzyme) containing 0.1% Tween-80 maintained at $37 \pm 0.5\,^{\circ}C$ with continuous stirring with a paddle at 100 rpm for 2 h. The release tests were then continued for another 2 h after adding 250 mL sodium phosphate solution (0.2 M) containing 0.1% Tween-80 to adjust the pH and the volume of the dissolution medium to 6.8 and l000 mL, respectively. Aliquots (5 mL) of the solution were withdrawn at appropriate intervals, and fresh dissolution medium was simultaneously replaced in the apparatus to maintain a constant volume. The withdrawn sample was passed through a 0.8 μm membrane filter. The ZTO concentration of the samples was determined by the method described above.

2.6. Reconstitution of liquid emulsion and droplet size distribution analysis

A small amount of primary semi-solid emulsion or ZTO ESE was dispersed in the phosphate buffer (pH 6.8) under gentle stirring, respectively. After the polymer dissolved, the emulsion was allowed to stand for an appropriate period (5 min and 24 h) to investigate its physical stability, and an aliquot (0.5 mL) was sucked up through a syringe at the middle point of the emulsion. The stability coefficient was express by comparing the content of ZTO in emulsion at 5 min and 24 h. In addition, the emulsion

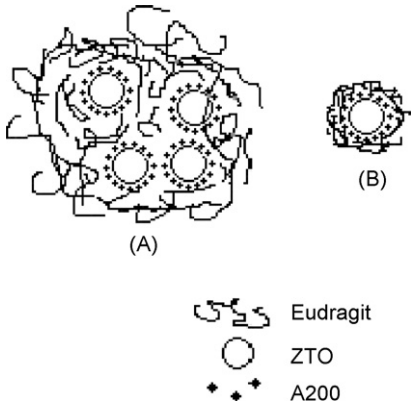

Fig. 2. Models of ZTO in ESE (A) and in resultant emulsion (B).

drop size was measured by laser diffractometry using a Beckman Coulter LS230 laser sizer. The drop size was expressed as the volume mean diameter.

3. Results and discussion

It has been well established that solid particles of colloidal size could be employed to kinetically stabilize emulsions. They are irreversibly anchored at the oil-water interface and develop strong lateral interactions providing a mechanical barrier against coalescence (Arditty et al., 2004). Hydrophilic polymer is a common coemulsifier to improve the emulsion stability. It has been reported that Aerosil with a hydrophilic polymer would make emulsication easier and the emulsion more stable (You et al., 2005). Through the preliminary experiment, Aerosil 200, a common solid state emulsifier and thickening agent was chosen as the best solid emulsifying agent and adsorbent, Eudragit® L30D-55 as the coemulsifier and the unique film-forming agent. Aerosil 200 has a mean typical diameter of 12 nm and its specific surface area is high up to 224.38 m^2 determined by a surface area analyzer (SA3100, Beckman CoulterTM, USA). It was easily surrounding on the surface of the oil droplets, and kept the oil exiting in the architecture of Eudragit® L30D-55 due to the high compatibility of Aerosil 200 to Eudragit® L30D-55. The models of ZTO in ESE and in resultant emulsion were shown in Fig. 2. Here, A200 surrounded on the surface of ZTO emulsion as an emulsifying agent and adsorbent, while Eudragit acted as a carrier material and coemulsifier.

3.1. Effect of plasticizer on the ZTO ESE

It is well known that plasticizer plays an important role on the coating process of Eudragit® L30D-55. Coating layer with different weigh gain of the plasticizer showed different gastric fluid resistance ability. In order to investigate the effects of plasticizers on the property of ZTO ESE, two common plasticizers suitable for Eudragit® L30D-55 were selected and their effect on the release behaviors of ZTO ESE in the gastric fluid was investigated. The amount of oil, Eudragit® L30D-55 and A200 were fixed at 0.5 g, 4.0 mL and 0.3 g, respectively.

It is apparent from Table 1 that ZTO ESE without plasticizer shows the fastest release behavior and the ZTO ESE using different weight of triethyl citrate as plasticizer shows no obviously variation on the release behavior in the gastric fluid. This could be easily explained that without plasticizer the latexes of Eudragit® L30D-55 could not form continuous film. While triethyl citrate would immigrate into the oil phase; little was retained in the latexes of Eudragit® L30D-55 acting as plasticizer due to its highly lipophilic. As can be seen from Table 1, approximately, 15% weight of PEG6000 (based on dry polymer weight) could achieve a suitable gastric resistance. When the weight of PEG6000 was higher than 20% or lowers than 10%, the cumulative release percentage was over 10% at 2 h in the gastric fluid. This could be easily understood that low quantity of plasticizer could not exert enough plasticizing effect on the enteric polymer film, while higher quantity of plasticizer was used, PEG6000 would dissolve in the gastric fluid resulting in a porous film structure to accelerate the release of ZTO due to the high hydrophilicity of PEG6000.

3.2. Effect of amount of aerosil 200 on the ZTO ESE

To investigate the effect of Aerosil 200 on the property of ZTO ESE, the amount of Aerosil 200 was varied between 0 and 0.5 g for the preparation of the ZTO ESE and the amount of oil, Eudragit® L30D-55 and plasticizer (PEG6000) were fixed at 0.5 g, 4.0 mL and 0.18 g, respectively. According to Table 2, when the amount of Aerosil 200 was less than 0.2 g, no ZTO ESE was obtained. In fact, no primary emulsion could be gained; this could be easily understood that there was not enough emulsifying agent. When the amount of A200 exceeded 0.2 g, good ZTO ESE would be gained. When the amount of Aerosil 200

Table 1
Effect of plasticizer on the property of ZTO ESE ($n = 3$, $\bar{x} \pm$ S.D.)

Plasticizer	Content[a] (%)	Drug loading (%)	Residual efficiency (%)	Bulk density (g/mL)	Angle of repose (°)	Cumulative release[b] (%)
None	0	21.88 ± 0.46	87.5 ± 1.85	0.428 ± 0.012	27.6 ± 2.1	33.10 ± 1.62
Trietnyl citrate	10	21.16 ± 0.55	89.7 ± 2.34	0.397 ± 0.017	38.4 ± 1.8	16.52 ± 1.03
	15	20.69 ± 0.27	90.2 ± 0.99	0.401 ± 0.010	35.7 ± 1.6	14.52 ± 0.50
	20	19.96 ± 0.42	89.4 ± 1.80	0.374 ± 0.013	37.8 ± 2.1	14.02 ± 0.40
PEG	10	21.32 ± 0.27	90.4 ± 1.14	0.417 ± 0.014	27.6 ± 1.9	16.39 ± 0.39
	15	20.71 ± 0.32	90.3 ± 1.41	0.433 ± 0.010	28.7 ± 2.3	8.73 ± 0.34
	20	20.01 ± 0.32	89.6 ± 1.45	0.439 ± 0.010	28.7 ± 1.6	11.17 ± 0.33

[a] Based on dry polymer weight.
[b] Cumulative release percentage at 2 h in gastric fluid.

Table 2
Effect of the amount of Aerosil 200 on the ZTO ESE ($n = 3$, $\bar{x} \pm$ S.D.)

Aerosil 200 (g)	Drug loading (%)	ZTO residual efficiency (%)	Bulk density (g/mL)	Angle of repose (°)	Cumulative release[a] (%)
0.1	–	–	–	–	–
0.2	20.66 ± 0.49	85.94 ± 2.04	0.387 ± 0.013	34.6 ± 1.9	8.09 ± 0.19
0.3	20.71 ± 0.32	90.29 ± 1.41	0.433 ± 0.014	28.7 ± 2.3	8.73 ± 0.34
0.4	19.82 ± 0.19	90.38 ± 0.87	0.412 ± 0.010	26.2 ± 1.2	10.24 ± 0.59
0.5	18.13 ± 0.21	86.30 ± 1.00	0.425 ± 0.006	26.7 ± 1.6	12.64 ± 0.32

[a] Cumulative release percentage at 2 h in gastric fluid.

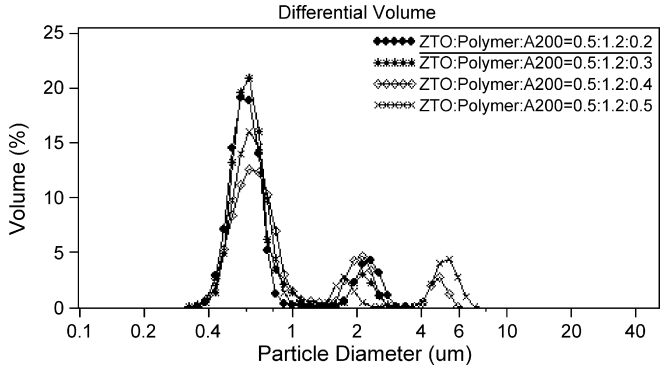

Fig. 3. Effect of Aerosil 200/Eudragit ration on the particle size distribution. Aerosil 200:Eudragit = 0.2:1.2 (♦);0.3:1.2 (*); 0.4:1.2 (◊); 0.5:1.2 (×).

increased from 0.2 to 0.5 g, the cumulative release percentage in gastric juice in 2 h increased from 8.1 to 12.6%, correspondingly. While the drug release in the intestinal fluid shew no obviously changes. It was believed to be due to the high hydrophilic of Aerosil 200. When ZTO ESE was poured into the gastric fluid, some Aerosil 200 was dispersed into the medium and a porous structure was formed to accelerate the release of ZTO. However, with the amount of Aerosil 200 increased, the loading was slightly decreased, but the ZTO residual efficiency was firstly increased, and then decreased slightly. It suggests that ZTO residual efficiency was depended on the balance of the affinity between ZTO-Aerosil 200 and Aerosil 200-H_2O. When the amount of Aerosil 200 was increased, the surface adsorbed ZTO was increased, meanwhile the surface contacting the water increased resulting that the time needed to dry the emulsion was prolonged. Fig. 3 illustrates that when the ratio of Aerosil 200: Eudragit® L30D-55 was 0.2:1.2 or 0.3:1.2 the distribution of the resultant emulsion was bimodal, one population around 600 nm and another population around 2 μm. However, when the ration increased to 0.4:1.2, a new population around 5 μm was obtained. This would be due to the congregation of redundant A200 in the resultant emulsion.

3.3. Effect of the amount of eudragit® L30D-55 on the ZTO ESE

The amount of Eudragit® L30D-55 was varied between 0.9 and 1.8 g (dry polymer weight) for the preparation of the ZTO ESE and the amount of oil, A200 and plasticizer (PEG6000) were fixed at 0.5 g, 0.3 g and 15% (dry polymer weight), respectively. As shown in Table 3, the cumulative release percentage of ZTO in ESE decreased with the amount of Eudragit® L30D-55 increasing. Although when the amount of Eudragit® L30D-55 was lower than 1.2 g, the emulsion (primary emulsion or reconstitution of the ZTO ESE) could be produced, the release in gastric juice was over 10% in 2 h. When the polymer was higher than 1.2 g, the cumulative release percentage of ZTO in gastric fluid shows no obviously change, which was not in accordance with enteric coated pellets. This could be attributed to the special architecture of ZTO ESE. In ZTO ESE, ZTO was dispersed uniformly in the structure formulated by Aerosil 200 and Eudragit® L30D-55. While in coated pellets, enteric materials were only spread on the surface of pellets; when the enteric coating material increased, the release of the drug would be obviously suppressed in gastric juice. But with the increase of Eudragit® L30D-55 quantity in the formulation, the cumulative release percentage of ZTO in ZTO ESE in the phosphate buffer was slightly slower down in 20 min. After 45 min, 90% ZTO in different formulations was released. This could be attributed to the unique characteristic of Eudragit® L30D-55 that it did not form viscous gel layer when it dissolved in the phosphate buffer.

The particle size distributions of the ZTO emulsion release from ZTO ESE were shown in Fig. 4. It indicates that with the different contents of Eudragit® L30D-55, the distribution of ZTO emulsion was varied. When the ratio of Eudragit® L30D-55:Aerosil 200 was 0.9:0.3, the distribution was trimodal, one population around 600 nm, one population around 2 μm and the last one around 5 μm. When the quantity of Eudragit® L30D-55 was increased to 1.2 g, the bimodal distribution was obtained and the largest size distribution around 5 μm vanished. While

Table 3
Effect of the amount of Polymer on the property of ZTO ESE ($n = 3$, $\bar{x} \pm$ S.D.)

ZTO:Eudragit:A200 (g/g/g)	Drug loading (%)	ZTO residual efficiency (%)	Bulk density (g/mL)	Angle of repose (°)	Cumulative release[a] (%)
0.5:0.9:0.3	24.69 ± 0.42	90.61 ± 1.53	0.375 ± 0.015	35.7 ± 2.7	12.30 ± 0.19
0.5:1.2:0.3	20.71 ± 0.32	90.29 ± 1.41	0.433 ± 0.014	28.7 ± 2.3	8.73 ± 0.34
0.5:1.5:0.3	18.09 ± 0.28	91.35 ± 1.41	0.417 ± 0.010	26.4 ± 1.2	7.27 ± 0.15
0.5:1.8:0.3	15.98 ± 0.22	91.73 ± 1.27	0.412 ± 0.013	26.4 ± 1.2	7.14 ± 0.36

[a] Cumulative release percentage at 2 h in gastric fluid.

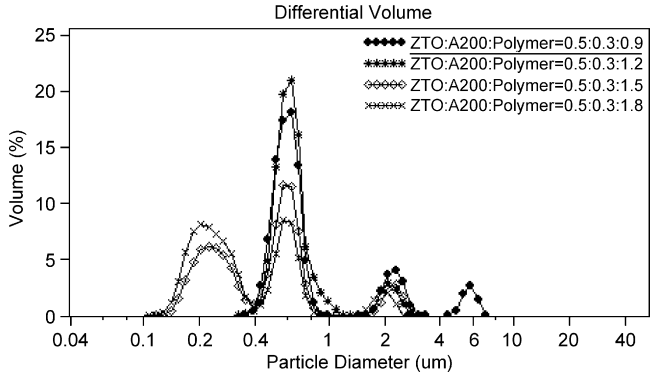

Fig. 4. Effect of polymer/Aerosil 200 ration on the particle size distribution. Eudragit:Aerosil 200 = 0.9:0.3 (♦); 1.2:0.3 (*); 1.5:0.3 (◊); 1.8:0.3 (×).

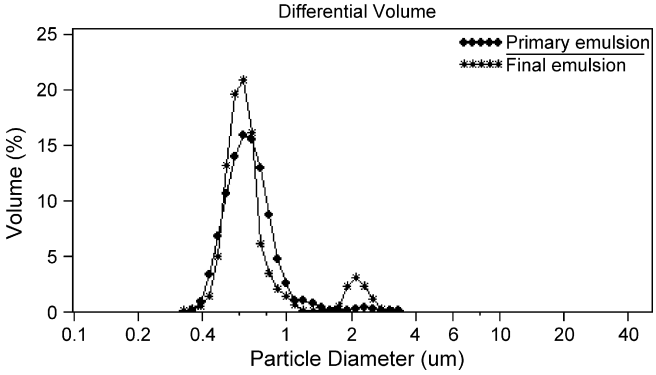

Fig. 5. Particle size distribution of the primary liquid emulsion (×) and the reconstitution emulsion from ZTO ESE (●).

the quantity of Eudragit® L30D-55 was raised to 1.5 g, a novel size distribution around 186 nm appeared and a new trimodal size distribution was obtained. This unsatisfactory result could be explained that, preferred by the author, titration by hand could not create adequate shear to get a uniform emulsion, nevertheless it reminded us that Eudragit® L30D-55 would be a good microemulsion stabilizer with Aerosil 200.

3.4. Droplet size distribution of the primary emulsion and after reconstitution of ZTO ESE in the phosphate buffer

According to the factors investigated above, an optimal formulation, ZTO:Eudragit® L30D-55:A200:PEG6000 = 0.5:1.2:0.3:0.18, was determined.

The physical stability study of the reconstruction emulsion in the following 24 h showed that the emulsion had a good physical stability, no sedimentation or oil float was observed, and the concentration of ZTO in the middle of the final emulsion in 24 h had no obviously variation (date not shown).

According to Fig. 5, we could conclude that the particle size distribution of the reconstitution emulsion from ZTO ESE has a larger distribution than the primary liquid emulsion and an obviously bimodal size distribution was gained. It indicated that some emulsion coalescence had happened during the drying process or the reconstruction procedure.

4. Conclusion

In this study, a novel solid dosage form, enteric-soluble solid-state emulsion containing water-insoluble and easy volatile ingredient ZTO, was first prepared with the aid of Aerosil 200 and Eudragit® L30D-55. The release of ZTO from ZTO ESE in the gastric juice was obviously suppressed but when it was introduced into the phosphate buffer (pH 6.8) under gentle agitation the emulsion was formed immediately.

This preparation was convenient to operation and no special instrument was needed. So enteric-soluble solid-state emulsions prepared with Aerosil 200 and Eudragit® L30D-55 would be an alternative promising oral preparation for the solidification of liquid oil drugs.

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