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Formulation and physicochemical characterisation of a novel self-microemulsifying delivery system as hydrotropic and solubilising agent for penfluridol

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Abstract

As a poorly water-soluble chemical, penfluridol is used as a maintenance drug for individuals with chronic schizophrenia. A novel self-microemulsifying drug delivery system has been successfully developed to benefit the solubility of penfluridol. Pseudo-ternary phase diagrams were constructed to investigate the phase behaviour and to assess the effects of different co-surfactants and the mass ratios of surfactant to co-surfactant (K_m) on the phase regions. Optimal compositions of the formed systems were screened via viscosity studies and microemulsion droplet size tests. The optimal formulation of penfluridol-loaded self-microemulsion consists of penfluridol 5.0%, oil (MCT) 15.8%, surfactant (cremophor EL) 52.8%, co-surfactant (PEG-400) 26.4%, with the average particle size at approximately (53.5±4.3) nm. Transmission electron microscopy (TEM) revealed the spherical nature and size homogeneity of the microemulsion droplets. No significant variations (droplet sizes and penfluridol contents) in microemulsion were observed over a period of 30 days at 4 °C and 25 °C, respectively. The developed self-microemulsion proved to be a potential candidate to enhance the solubility of penfluridol.

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Keywords: penfluridol; self-microemulsifying drug delivery system; phase behaviour

1 Introduction

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As a highly lipophilic oral neuroleptic, penfluridol can be released at a slow pace from the tissues following ingestion. A single oral dose of penfluridol results in a long duration of activity[1]. Despite this remarkable long-term effect, its peak blood levels are achieved at 4 to 6 h, more typically at 6 h[2] after administration. The retarded dissolution of penfluridol brings about its slow response to schizophrenia.

As a novel drug delivery system, self-emulsifying drug delivery systems (SMEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug[3, 4]. SMEDDS offer numerous advantages such as spontaneous formation, thermodynamic stability, improved bioavailability and feasibility for preparation. Enhanced solubility and improved bioavailability are amongst the main advantages of SMEDDS[5, 6].

The objectives of our present study were to formulate penfluridol-loaded self-microemulsion and assess its physicochemical characterisation. The solubility of penfluridol was determined in various vehicles. To sieve out the optimal formulation, the viscosity studies and microemulsion droplet size tests were conducted. The spherical nature and size homogeneity of the microemulsion droplets were revealed by transmission electron microscopy.

2 Materials and methods

2.1 Materials

The chemicals are described as follows: penfluridol (Jiangsu Nhwa Pharmaceutical Co., Ltd., Jiangsu, China), soybean oil and medium chain triglyceride (MCT) (Tieling Beiya Pharmaceutical Oil Co., Ltd., Tieling, China), polyethylene glycol 400 (PEG-400) and polysorbate 80 (Qingdao Tianliyuan Biotechnology Co., Ltd., Qingdao, China), propylene glycol and glycerol (Jiangxi Ipsen Pharmaceutical Co., Ltd., Jiangxi, China), cremophor EL (BASF, Ludwigshafen, Germany), and methanol of HPLC grade (Merck KGaA, Darmstadt, Germany). All the other chemicals were of reagent grade.

2.2 HPLC analysis of penfluridol

The concentration of penfluridol was determined by HPLC method. The system consists of Agilent 1100 series with a UV detector. All samples were analysed using a platinum C_{18}-EPS column (5 μm, 4.6×250 mm) with the thermostat set at 25 °C. The mobile phase was methanol/0.2% triethylamine (70: 30, v/v) with pH adjusted to 2.5 by phosphoric acid and delivered at a flow rate of 1.0 ml/min. A volume of 20 μl was injected into the system to determine the concentration of penfluridol at 219 nm.

2.3 Solubility studies

To sieve out the appropriate oil (soybean oil, MCT), surfactants (polysorbate 80, cremophor EL) and co-surfactants (propylene glycol, glycerol and PEG-400) of self-microemulsion, the solubility of penfluridol in various vehicles was investigated by HPLC method. Each vehicle (10 ml) was permitted addition of an excess amount of penfluridol in a sealed flat-bottomed flask and ultrasonic wave (300 w, 5 min) was employed to facilitate the solubility. The resultant mixture was reciprocally agitated at 25 °C for 72 h in a water bath, followed by centrifugation at 14000 rpm for 10 min. The supernatant was filtered through a membrane filter (0.45 μm) to remove the residual insoluble penfluridol. Subsequently, 0.1 ml supernatant was obtained for penfluridol quantification by spectrophotometry at 219 nm following dilution to 10 ml with methanol. The concentration of penfluridol in the filtrate was quantified by high performance liquid chromatography (HPLC).

2.4 Construction of pseudo-ternary phase diagrams

On the basis of the solubility studies, pseudo-ternary phase diagrams were constructed with water titration method to obtain the o/w microemulsion region, within which the concentration range of the components was identified. The weight ratio of surfactant to co-surfactant (K_m) was varied as 1:2, 1:1, 2:1. For each pseudo-ternary phase diagram at a specific K_m, the ratio of oil to the surfactant/co-surfacant mixture was varied form 9:1 to 1:9 at 10% increments. The mixture of oil, surfactant and co-surfactant at certain weight ratio was titrated with double-distilled water dropwise under proper magnetic stirring at 25 °C. When the mixture became transparent at a certain time point, the concentrations of the components were recorded to complete the pseudo-ternary phase diagrams. Subsequently, co-surfactants were screened on the basis of the range of o/w microemulsion obtained from their pseudo-ternary phase diagrams.

2.5 Preparation and selection of penfluridol-loaded self-microemulsion

The contents of oil, surfactant, co-surfactant and water at defined weight ratios were screened to optimise the microemulsion. Briefly, MCT (1.0 g) and S_{mix} were mixed at the weight ratios of 1:4, 1:5, 1:6, 1:7 and 1:8. Then, the formulations (M_1 to M_5) were prepared as aforementioned and were checked for the viscosity as well as the mean droplet size to screen the optimal formulation. Based on the results of formulation screening, microemulsion formulations at the desired component ratio were prepared (with penfluridol loaded or unloaded). Subsequently, the resulting self-microemulsions were sealed in ampoules for physicochemical characterisation.

2.6 Viscosity measurements

The microemulsions (M_1 to M_5) were determined with a digital viscometer (Shanghai Precision and Scientific Instrument Co., Ltd., China) at 25±1 °C. The viscosity behaviour of each disperse system was evaluated at 30 rpm, with the results recorded for formulation selection.

2.7 Dynamic light scattering measurements

Dynamic light scattering was employed to determine the droplet sizes of selected microemulsions. The measurements were performed with a Zetasizer 3000 HS (Malvem Instruments, Worcestershire, UK). Light scattering was measured at a scattering angle of 90° at 25 °C, with polystyrene beads as the criterion. A cumulant-based algorithm that fitted a single exponential to the correlation function was designated for the mean droplet diameter and an estimate of the droplets size distribution.

2.8 Transmission electron microscopy (TEM)

As a visualising aid, the morphology of the optimal blank and penfluridol-loaded self-microemulsion was observed under a transmission electron microscope (TEM) (H600, Hitachi, Japan). Formvar/ Carbon-coated 200 mesh copper grids were glow discharged and samples were diluted with distilled water (1:50). One drop of diluted samples was dripped on a film-coated copper grid and dried down. 30 µl saturated staining solution of uranyl acetate was added and the mixture was immediately dried down with filter paper to rid excess colorant, followed by imaging of the dried specimens by TEM.

2.9 Stability studies

The stability of the optimised penfluridol-loaded microemulsion sealed in ampoules was assessed in temperature and centrifugation tests[7], wherein samples were subjected to different temperatures (4, 25 and 60 °C), withdrawn in triplicate on 0, 15th and 30th day, and evaluated for their physical stability, including the macroscopic appearance of the samples, droplet size of the internal phase of the microemulsion within 100 nm and viscosity of the disperse system. In the centrifugation test, the samples were submitted to a centrifuge at 14,000 rpm for 20 min and assessed for their macroscopic appearance.

3 Results and discussion

3.1 HPLC analysis of penfluridol

The method was demonstrated for accuracy, precision, specificity and solution stability for penfluridol detection. The linear range was between 4.0 and 32.0 μg/ml, and the mean calibration curve was obtained by the equation:

$$y = 0.04498\,x + 0.0338 \quad (1)$$

With a correlation coefficient, r^2=0.9998, where y represents area under the curve and x represents the concentration of penfluridol in microgram per millilitre.

3.2 Solubility studies

Solubility of penfluridol in nine vehicles was presented in Tab. 1. The solubility of penfluridol in MCT, cremophor EL and PEG-400 was up to 192.97 mg/ml, 166.30 mg/ml and 132.79 mg/ml. Due to the improvability of oil phase on drug entrapment in the self-microemulsion, of 2 tested oils (MCT and soybean oil), MCT exhibited better solubility of penfluridol. Hence, MCT was designated as the oil phase. Meanwhile, cremophor EL served as the surfactant on the basis of the higher solubility of penfluridol.

3.3 Phase behaviour studies

To investigate the phase behaviour of the identified surfactant/co-surfactant, oil and water mixture and identify the optimum microemulsion area, pseudo-ternary phase diagrams were constructed, consisting of MCT, cremophor EL, distilled water and different co-surfactants as described in Fig. 1, which showed the effects of different co-surfactants and weight ratios of surfactant to co-surfactant (*Km*) on the phase regions. A co-surfactant is an amphiphilic molecule that substantially accumulates with the surfactant at the interfacial layer. The presence of co-surfactant allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of compositions[8]. In our study, the largest o/w microemulsion region was obtained with a *Km* value of 2:1 in the MCT/cremophor EL/PEG-400. Therefore, it was reasonable to designate PEG-400 as the co-surfactant. Furthermore, clear isotropic microemulsions of the selected system were formulated for further characterisation with the weight ratios of S_{mix} to oil (MCT) set at 3:1, 4:1, 5:1, 6:1, 7:1 (M_1 to M_5) and a total microemulsion weight of 20.0 g (Table 2).

3.4 The optimal formulation selection by measurements of droplet size and viscosity

The droplet sizes and viscosities of the microemulsions (M_1 to M_5) are presented in Tab. 2. The droplet sizes of microemulsions (M_1 to M_3) significantly diminished with the increasing concentrations of the surfactant, but increased in M_4 and M_5. Structurally, the dispersed phase of microemulsion consists of

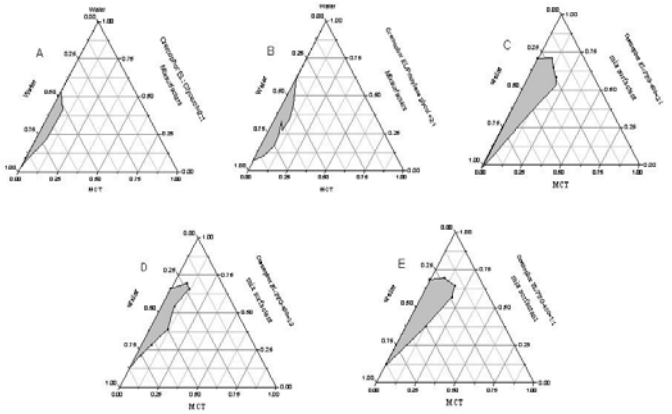
microstructures of oil-entrapped pockets stabilised by surfactant/ co-surfactant accumulation on the oil/water boundary. Furthermore, the addition of surfactants caused the interfacial film to stabilise and condense. Thereby, the droplet sizes of microemulsions (M_1 to M_3) decreased with the increasing surfactant concentrations. However, the structures of microemulsion coexist in equilibrium, with their relative abundance determined by the proportions of different components. Owing to the relatively small percentages of oil in prescription, M_4 and M_5 were adjacent to the liquid crystalline phases, *i.e.*, viscoelastic gels, which were not sufficiently emulsified and had increased particle sizes.

Tab. 1. Solubility results of penfluridol at 25 °C in various vehicles (mean ± S.D.; n = 3)

Vehicles	Soybean oil	MCT	Polysorbate 80	Cremophor EL	Propylene glycol	Glycerol	PEG-400
Solubility (mg/ml)	117.38±0.09	192.97±0.03	126.27±0.21	166.30±0.29	126.95±0.11	119.60±0.18	132.79±0.07

Tab. 2. Calculation of percentage of oil, S_{mix} and water used in the optimal formulation selection based on the viscosity and droplet size (mean ± S.D.; n = 3)

Formulation code	Oil (%)	S_{mix} (%)	penfluridol (%)	Viscosity (mPa·s)	Droplet size (nm)
M_1	23.75	71.25	5.0	10.4	89.4±6.9
M_2	19.0	76.0	5.0	19.0	75.1±5.5
M_3	15.8	79.2	5.0	26.8	53.5±4.3
M_4	13.6	81.4	5.0	49.8	60.7±7.3
M_5	11.9	83.1	5.0	60.7	71.7±9.8



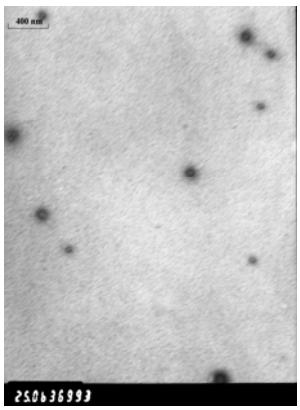


Fig. 1. Pseudo-ternary phase diagrams of microemulsion. (A) MCT/Cremophor EL/ Glycerol (Km = 2:1). B, MCT/Cremophor EL/ Propylene glycol (Km = 2:1). C, MCT/ Cremophor EL/ PEG-400 (Km = 2:1). D, MCT/ Cremophor EL/PEG-400 (Km = 1:2). E, MCT/Cremophor EL/PEG-400 (Km = 1:1).

Fig. 2. TEM photographs of penfluridol-loaded self-microemulsion

As presented in Tab. 2, the results also showed an increase in the values of viscosity coupled with the rise of S_{mix} content. These results could be attributed to the increased proportion of surfactant relative to co-surfactant. Furthermore, there are reports that surfactants and co-surfactants can be toxic at high doses, so they may be limited in their daily and per-dose intake level[9]. As mentioned above, a high concentration (over 80%) of S_{mix} is thus inappropriate for the formulations. Besides, the relative ratio of surfactant to co-surfactant has modified effects on the droplet size when S_{mix} to oil reaches the suitable weight ratio. Consequently, M_3 (MCT 15.8%, cremophor EL 52.8%, PEG-400 26.4%) with penfluridol (5%) was selected as the optimal self-microemulsion.

3.5 Transmission electron microscopy (TEM) and droplet size distribution measurement of the optimal microemulsion

Morphological characterisation of the optimal self-microemulsion was presented by TEM (Fig. 2). The droplet on the microemulsion appears black with the white surrounding. TEM photographs confirmed that the droplets were well-dispersed with no aggregation or cluster formation, spherical in shape, uniform and appreciably homogeneous with particulate sizes. The size distribution of the blank and the penfluridol-loaded self-microemulsion by dynamic light scattering technique was depicted. The blank formulation had an average droplet size of 29.7 nm, whereas the penfluridol-loaded microemulsion had an average droplet size of 53.5 nm. On the one hand, the addition of penfluridol caused an increase in size of larger droplets at the expense of smaller droplets[10]. On the other hand, as the preconcentrated microemulsion is diluted, the structure might transform from small to large droplets[11].

3.6 Stability tests

Evaluations of temperature stability of self-microemulsions suggested that the optimal self-microemulsions were still stable under all conditions except a temperature of 60 °C on account of opacity on their macroscopic appearance at the end of the experiment. It was probably due to both the temperature-induced oxidation of the MCT and the gradual increase of particle sizes of the microemulsions. Self-microemulsions submitted to the centrifugation test appeared stable, for no stratification phenomenon was observed at the end of the study.

4 Conclusions

A novel self-micromeulsifying drug delivery system of penfluridol was formulated and physicochemically characterised by *in vitro* parameters such as viscosity, particle size, stability tests and morphology characterisation. An optimal self-micromeulsifying drug delivery system consists of MCT as oil phase, cremophor EL as surfactant, and PEG-400 as co-surfactant. The combination of all the three components, *i.e*., oil/surfactant/co-surfactant in the ratio of 1.5: 4: 2, formulates SMEDDS with a lower particle size of 53.5 nm. The optimised SMEDDS showed good solubilisation of penfluridol. Our study illustrated the application potential of self-microemulsifying drug delivery system to enhance the solubilisation of penfluridol.

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