International Journal of Pharmaceutics 365 (2009) 136–142

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Optimization and *in situ* intestinal absorption of self-microemulsifying drug delivery system of oridonin

Ying Liu, Ping Zhang, Nianping Feng*, Xin Zhang, Shan Wu, Jihui Zhao

School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai 210203, PR China

ARTICLE INFO

Article history:
Received 8 May 2008
Received in revised form 20 July 2008
Accepted 9 August 2008
Available online 20 August 2008

Keywords:
Self-microemulsifying drug delivery system
Central composite design
Optimization
Oridonin
Desirability function

ABSTRACT

The objective of this study was to optimize and characterize an oridonin self-microemulsifying drug delivery system (SMEDDS) formulation. A central composite design (CCD) was used to investigate the influence of factors (oil percentage and surfactant to co-surfactant ratio (Sur/Co-s ratio)) on the responses including droplet size, polydispersity, equilibrium solubility and *in situ* intestine absorption rate. Furthermore, the desirability function approach was applied to obtain the best compromise among the multiple responses. It was found that oil percentage played a significant role on the droplet size and polydispersity. The drug equilibrium solubility was mainly contributed to oil percentage and less to Sur/Co-s ratio. The *in situ* intestinal absorption was influenced by both of the two factors, whereas the oil percentage played a more important role in absorption. The practical response values under the optimized formulation were in good accordance with the predicted values. Our results demonstrate CCD is of value in optimizing the SMEDDS formulation and understanding the effects of formulation compositions on SMEDDS properties.

1. Introduction

In recent years, self-microemulsifying drug delivery systems (SMEDDS) have attracted growing interest as promising means for the delivery of poorly water-soluble drugs. SMEDDS have gained this popularity largely due to their excellent efficiency in improving the drug solubility, increasing the dissolution rate, promoting oral absorption for poorly water-soluble drugs and simplicity of preparation (Constantinides and Scalart, 1997; Hauss et al., 1998; Kommura et al., 2001; Holm et al., 2003; Wu et al., 2006a,b). SMEDDS are isotropic mixtures of oil, surfactant, co-surfactant and drug substance. Oil, surfactant, and co-surfactant are essential components in view of solubilizing the poorly water-soluble drug and forming fine microemulsion droplets after being introduced into the aqueous media under gentle agitation. Basically, type of each composition in SMEDDS formulation can be determined by solubility studies and phase behavior investigations (Kim et al., 2000; Kang et al., 2004). In addition, the weight percentage of oil in the preparations (oil percentage) and the ratio of surfactant to co-surfactant (Sur/Co-s ratio) seem to be closely related to the qualities of SMEDDS (Zidan et al., 2007). In this regard, it is necessary to know exactly how the preparation compositions determine the formulation characteristics; particularly how the formulation characteristics are influenced by the formulation factors and potential interactions between them. Therefore, an appropriate method is needed to analyze this issue and furthermore find the optimum formulation of SMEDDS achieving a required property.

Generally, the impact of each variable can be assessed by varying each variable while keeping others constant. However, it fails to take into account the interactions between these factors. Response surface methodology (RSM) is a suitable experimental design strategy to overcome this problem. Using RSM, the influence of the selected variables on the subject responses in a defined experimental region can be predicted by constructing mathematical models. The goodness of fit of the obtained mathematical models can be checked by statistical analysis. Therefore, RSM is a combination of mathematical and statistical techniques to analysis models and achieve the goal of optimizing the responses. Basically, the RSM can be classified into two categories: Box–Wilson central composite designs (CCD) and Box–Behnken designs. CCD is composed by the factorial experiment, axial points and center point. This structure makes it have a better prediction capability than the Box–Behnken design. CCD has been successfully used to optimize the technology or production conditions for drug delivery systems such as sustained-release tablets, liposomes, microspheres, nanoparticles in recent years (McCarron et al., 1999; Billon et al., 2000; Gløgård et al., 2002; Gil et al., 2006; Wu et al., 2006a,b). Furthermore, if conflict among the multiple responses occurred, it is difficult to optimize

* Corresponding author. Tel.: +86 21 51322197; fax: +86 21 51322197.
E-mail address: npfeng@hotmail.com (N. Feng).

0378-5173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2008.08.009

Table 1
Composition of preparations used in central composite design

No.	Oil percentage, X_1 (%)	Sur/Co-s ratio, X_2
1	48.41	3.56
2	48.41	1.44
3	16.59	3.56
4	16.59	1.44
5	55.00	2.50
6	10.00	2.50
7	32.50	4.00
8	32.50	1.00
9–13	32.50	2.50

Table 2
Factor levels and the correspondent values

Factor	Level				
	$-\alpha$	−1	0	+1	$+\alpha$
X_1 (oil percentage)	10.00	16.59	32.50	48.41	55.00
X_2 (Sur/Co-s ratio)	1.00	1.44	2.50	3.56	4.00

$\alpha = 1.414$.

all the responses simultaneously. A desirability function approach was commonly employed to find the best compromise condition (Ficarra et al., 2002; Pizarro et al., 2006).

In a previous study, we developed a SMEDDS for delivering oridonin, an active compound isolated from the Chinese herb *Raddosia rubescens* (*Hamsl.*) *Hara*. The formulation consisted of Maisine 35-1 and Labrafac CC (1:1, w/w), Cremophor EL and Transcutol P. The system exhibited the potential for increasing the bioavailability of oridonin, which provided a promising approach to the delivery oridonin by the oral route (Zhang et al., 2008).

The aim of the present study was to acquire a clear understanding of the influence of formulation compositions on the properties of SMEDDS and obtain an optimal formulation for oridonin SMEDDS. CCD was used to study the effect of formulation variables (oil percentage and Sur/Co-s ratio) on the response variables including droplet size, polydispersity, equilibrium solubility and intestinal absorption rate. Furthermore, the desirability function approach was used to simultaneously optimize the responses. The optimal preparation was characterized by morphological observation and *in vitro* release test besides the evaluation of properties shown in CCD experiments.

2. Materials and methods

2.1. Materials

Oridonin (purity 98.2%) was purchased from Nanjing Qingze Medical Technology Development. Co., Ltd. (Nanjing, China). Polyoxyethyleneglycerol triricinoleate 35 caster oil (Cremophor® EL) was a gift from BASF, Germany. Glyceryl monolinoleate (Maisine® 35-1), caprylic/capric triglyceride (Labrafac CC), and diethylene glycol monoethyl ether (Transcutol® P) were supplied by Gattefosse, France. All other chemicals used were of analytical grade.

2.2. Preparation of SMEDDS

Table 1 presents all of the formulation compositions used in the central composite design experiment. All the formulations contain the same level of oridonin (0.5% (w/w) of the vehicle) except those for equilibrium solubility studies. The oridonin SMEDDS was prepared as described previously (Zhang et al., 2008). Briefly, each formulation was prepared by dissolving oridonin in the mixture of Transcutol P and Maisine 35-1 at 50 °C in an isothermal water bath, followed by the addition of Cremophor EL and Labrafac CC. Then, the components were mixed by gentle vortexing until a transparent preparation was obtained. An optimized formulation was prepared with the same method.

2.3. Experimental design

2.3.1. Central composite design

The oil percentage or content in the formulation (oil%, w/w), the ratio of surfactant to co-surfactant (Sur/Co-s ratio) as well as the drug content were reported to affect the properties of SMEDDS (Wu et al., 2006a,b; Zidan et al., 2007). The drug content in this study is capable of meeting the needs of medical use, therefore we kept the drug content as a fixed concentration. Based on the preliminary experiments and our previous studies, two formulation parameters, the oil percentage and Sur/Co-s ratio, were identified as key factors responsible for the properties of SMEDDS. In view of the feasibility of SMEDDS formation at the extreme values, the ranges of the two factors were determined as follows: oil percentage (X_1): 10–50%; Sur/Co-s ratio (X_2): 1–4. Four responses include droplet size (Y_1), polydispersity index (PI) (Y_2), equilibrium solubility (Y_3), and intestinal absorption rate (Y_4) since they are generally regarded as significant factors for assessing the qualities of SMEDDS. A two-factor, five-level CCD was undertaken to investigate the main effects and the interactions of the two factors on the four responses (Table 2). The design consists of 9 runs (4 factorial points, 4 star points and 1 center point) and 4 replicated runs (center points) yielding 13 experiments in total (Table 3). The purpose of the replication was to estimate experimental error and increase the precision.

The data obtained for the four responses in each trial were fitted to classical second-order polynomial model and third-order quadratic model. The mathematical models were expressed as

Table 3
Experimental responses and result of central composite design

No.	Particle size (nm)	Polydispersity index (PI)	Solubility (mg/ml)	Intestinal absorption rate constant (h^{-1})	D
1(+1, +1)	34.2	0.018	15.28	0.177	0.180
2(+1, −1)	42.1	0.089	22.66	0.256	0.241
3(−1, +1)	20.3	0.084	35.94	0.199	0.383
4(−1, −1)	22.3	0.127	39.56	0.562	0.545
5(+α, 0)	42.0	0.057	9.87	0.390	0.141
6(−α, 0)	19.0	0.144	36.56	0.388	0.230
7(0, +α)	25.5	0.027	23.74	0.274	0.500
8(0, −α)	29.7	0.033	24.89	0.587	0.670
9(0, 0)	25.9	0.060	20.43	0.651	0.629
10(0, 0)	25.5	0.043	20.35	0.671	0.667
11(0, 0)	26.5	0.017	18.48	0.638	0.653
12(0, 0)	25.9	0.032	19.01	0.622	0.642
13(0, 0)	26.8	0.020	18.04	0.635	0.638