Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Preparation and Characterization of Voriconazole Solid Lipid Nanospheres

SOMAYEH BRAHIMI[1] AND TAYEBEH TOLIYAT[2*]

[1]International Campus, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Pharmaceutical Sciences, Tehran, Iran

ARTICLE DETAILS

Article history:
Received on 17 September 2017
Modified on 18 October 2017
Accepted on 25 October 2017

Keywords:
Voriconazole
Solid Lipid Nanospheres
Physicochemical Characterization
In vitro Release Study

ABSTRACT

Voriconazole is an antifungal drug used for treatment of various conditions caused by yeast or fungi. Voriconazole is changed form of flouconazole and it is improved potency and spectrum. In this study, we prepared voriconazole as solid lipid nanoparticles (SLN) using the melting method. Stearic acid, palmitic acid and glyceryl monostearate were selected as lipid carriers based on drug solubility and partitioning behaviour. Poloxamer and soya lecithin were the choice for surfactant. The particle sizes of the SLNs determined by zeta sizer. The in vitro release study of SLNs exhibited a sustained-release property of the drug. The effect of various lipids on capture volume, particle size and drug release of these particles were studied. The results show that the presence of glyceryl monostearate as lipid phase has significant effects on the size of particles. In Vitro release performed in phosphate buffer (pH=7.4) by using dialysis bags. It can be assumed that drug release from SLNs is following biphasic model and the first phase is followed the first order equation.

INTRODUCTION

Voriconazole is an antifungal drug used for treatment of various conditions caused by yeast or fungi. Voriconazole binds and inhibits ergosterol synthesis by inhibiting cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alphamethylsterols correlates with the subsequent loss of ergosterolin the fungal cell wall and may be responsible for the antifungal activity. Voriconazole is available as powder for infusion, oral suspension, and tablet on the market [1].

Solid lipid nanoparticles (SLN) have attracted increasing attention during recent years [2, 3]. Colloidal drug carriers prepared from solid lipid have been presented as promissing alternative to polymer nanoparticles [4-6]. The use of solid lipid nanoparticles as a matrix material for drug delivery is well known from various reports on lipid pellets for oral drug delivery [7].

Author for Correspondence:
Email: toliyat@tums.ac.ir

Proposed advantages include: possibility of controlled release and drug targeting, increase drug stability, high drug payload, incorporation of lipophilic and hydrophilic drugs feasible, no problems with respect to large scale production and sterilization [8]. Some studies showed increased bioavailability and prolonged plasma levels have been described after peroral administration of drug containing lipid nano dispersion to animals [9, 10]. Higher amounts of drug were also found in the brain after iv injection, suggesting the potential use of SLN as a brain delivery of drugs such as doxorubicin, tobramycin, not capable of crossing the blood brain barrier [11].

In the present investigation, the main aim was to develop a solidlipid-loaded formulation for voriconazole delivery.

MATERIALS AND METHODS

Materials

Voriconazole, stearic acid, palmitic acid, glyceryl monostearate, Tween 80 were purchased from Merck, Germany. Soya lecithin 90% was purchased from Applichem, Germany.Poloxamer 188 was purchased from GERADO Chemie, Germany.

Table 2: Characterization of SLNs

SA (g)	GMSO (mg)	PA (g)	CH (mg)	Probsonicator time(min)	Particle size(nm)	pdI	Zeta potential (mv)	Drug in participant%	Drug in supernatant %
-	0.441	1.029	-	3	1100	0.8	-10	20(indirect)	80
1.33	0.147	-	-	3	460.9	0.6	-15	3.7	43.9
1.176	0.294	-	-	3	329.7	0.5	-12	9.975	94.4
1.029	0.441	-	-	3	351.8	0.4	-20	5.7	91
0.882	0.588	-	-	3	318.1	0.5	-18	5.145	97.6
1.176	0.147	-	-	3	406	0.4	-12	7.35	54
-	0.441	1.029	-	30	130	0.6	-21	5/38±0/4	68
-	0.441	1.029	-	30	182	0.2	-17	5/38±0/4	52
-	0.441	1.029	-	30	177	0.2	-19	5/38±0/4	52
-	-	1.029	-	30	158		-20	5/38±0/4	85
-	-	1.029	0.441	3	1041	0.3	-13	7/46±1/4	42

Preparation of SLNs

SLNs were prepared by melting technique. At the beginning, solid lipids were heated at 60C because of melting. Since, voriconazole was added and stirred up to make a clear solution. This solution makes our lipid phase, in the other hand the aqueous phase is produced by adding lecithin and tween80 to 10cc water. Finally the aqueous phase and lipid phase were homogenized (Heidolphhemogenizer) for 5 minutes to from an emulsion. Then water is added quickly to the emulsion and vortexed (KIKA) to obtain a suspension. This suspension was put on the stirrer under hood for 30 minutes to remove the organic solvents. Final sample was sonicated for 30 minutes.

Physicochemical Characterization of SLNs

The average diameter, polydispersity index and z-potential were determined by photon correlation spectroscopy (PCS) (Zetasizer Nano ZS, Malvern Instrument. UK).

HPLC Analysis

Reverse phase-HPLC were used to determine the amount of voriconazolein the different samples. Chromatographic separation was carried out in a C18 column Eurosphere, length, 250: inner diameter, 4.6mm) using a mixture of acetate buffer (pH=3.5)-acetonitrile (88:12, v/v) as the mobile phase at a flow rate of 1ml/min, with UV detection at 251 nm.

Entrapment Efficiency (%EE) and Drug Loading (%DL)

Five ml of SLN dispersion were dissolved in 5 ml methanol. The drug content in the supernatant after centrifugation (15000 rpm for 30 min, Sigma, Germany) was measured by HPLC (drug content in whole dispersion of SLN).

$$\%\boldsymbol{EE} = \frac{\text{amount of drug in nanoparticles}}{\text{amount of drug added}} \times 100$$

$$\%\boldsymbol{DL} = \frac{\text{amount of drug in nanoparticles}}{\text{amount of drug added + amount of excipent added}} \times 100$$

***In vitro* Release Study**

The drug release from SLN containing was performed in phosphate buffer (pH=7.4), respectively using the dialysis bag method. The dialysis bag retains nanoparticles and allows the free drug into the dissolution media at 37°C. At appropriate intervals, 5 ml sample was collected and 5ml buffer was added. The amount of drug was determined by HPLC. Experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Initial experiment was intended to define the optimal conditions for the production of nanoparticles by melting method.

Table 1: The compositions of oil phase and water phase in the preparation process

Phase	Materials
Aqueous phase	Tween 80
	Poloxamer 188
	Water
	PVA
Oil phase	Voriconazole
	Lecithin
	Palmitic acid (PA)
	Stearic acid (SA)
	Cholesterole (CH)

Influence of Lipid

Characterization of SLNs were prepared with different lipids were showed at Table 2. Stearic acid or palmitic acid SLNs had a large size with a high PdI. When glyceryl monostearate added to these formulations the size of particles decreased to 180 nm with a polydispersity index of 0.2.

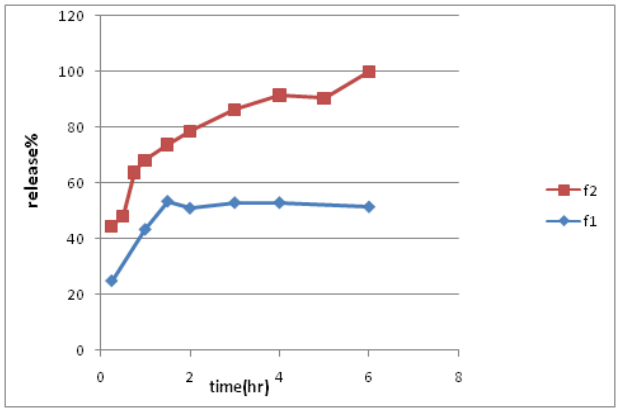

Figure 1: The release of voriconazole from SLNs (F1: PA +GMSO and F2: CH+ GMSO)

***In Vitro* Release Study**

Figure 1 illustrate *in vitro* release behavior of nanoparticles in phosphate buffer solution. A biphasic drug release pattern was observed, that was a rapid drug release at the initial stage followed by sustained release at a constant rate. The drug release profiles from the SLN prepared by this method in aqueous system proved linear relationships for Higuchi plotting after the burst of the drug. During the later stage, drug release was continuous and slow, indicating that the drug release rate was determined by the diffusion of the drug from the rigid matrix structure. With the definite percentages of burst followed by prolonged release, the burst can be exploited to deliver an initial dose when desired.

CONCLUSION

The present study highlighted the successful development and characterization of voriconazole SLNs. The optimized batch (F1 and F2) exhibited the desired size range with a sustained delivery profile.

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