Bulletin of Faculty of Pharmacy, Cairo University xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Bulletin of Faculty of Pharmacy, Cairo University

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

Original Article

Formulation of risperidone loaded proniosomes for effective transdermal delivery: An *in-vitro* and *in-vivo* study

Sharda Sambhakar[a,*], Sarvesh Paliwal[a], Swapnil Sharma[a], Bishambar Singh[b]

[a] Department of Pharmacy, Banasthali University, Rajasthan 304022, India
[b] PHTI Department, SMS Medical College, Rajasthan 302017, India

ARTICLE INFO

Keywords:
Risperidone
Proniosomes
Transdermal systems
Atypical antipsychotic
Relative bioavailability

ABSTRACT

In the present investigation, proniosomes of risperidone were formulated, optimized and evaluated for effective transdermal delivery in order to overcome the bioavailability issues of orally administered risperidone. The proniosomes were prepared using various sorbitan esters with cholesterol and soya lecithin and were evaluated for *in-vitro* parameters, *ex-vivo* permeation and *in-vivo* performance. Results indicated that the vesicles were spherical in shape, their size ranged from 284.00 nm to 941.40 nm and they had high zeta potential. The entrapment efficiency for spans was higher compared to tweens. DSC and IR studies confirmed the absence of chemical interactions between the risperidone and proniosome components. *In-vitro* release study showed that formulations with spans exhibit controlled release profile and followed the Higuchi model. No significant change in vesicle size and entrapment efficiency was observed when the proniosomes were stored at 4 ± 1 °C and 25 ± 2 °C for three months. Proniosomes with span 60 showed no signs of erythema or edema and has highest flux across the rat skin (169.851 ± 2.13 μg cm^{-2} h^{-1}). The relative bioavailability was 92% after transdermal administration of proniosomes and the t_{max} was increased to 8 h. So we conclude that the developed proniosome formulation would be a promising alternative to improve the bioavailability problems of risperidone.

1. Introduction

Transdermal drug delivery system (TDDS) is among the most widely employed system to overcome the issues associated with oral route. TDDS increases the therapeutic efficacy of many drugs by preventing their conversion to undesirable metabolites and also helps in maintaining uniform plasma levels *in-vivo*. TDDS offers two advantages firstly, self-administration and secondly of termination of drug exposure at any point of time, if required [1]. Due to which it exhibits high level of patient compliance with low levels of intra and inter-patient variability. FDA successfully approved TDDS of various psychotropic drugs like selegiline, rivastigmine, methyphenidate [2].

Stratum corneum is one of the major barriers in TDDS [3]. Among various strategies, vesicular systems like niosomes exhibits substantial potential to overcome such barrier. These vesicles interact with the horny layer and improve the permeability of drug across stratum corneum. It also acts as drug reservoir and provides the controlled release of drug. Further, the release rate can be adjusted by either changing the composition or by surface modification. However, sedimentation, aggregation or fusion and leakage of vesicles are one of the common drawbacks associated with niosomal preperations [4,5].

Proniosomes was introduced to overcome such problems as it provides ease of transportation, distribution, storage and dosing. Proniosomes are usually dry powder or gel, which can be hydrated just before use resulting in the formation of niosomes. Proniosome gel when applied to skin under occlusive conditions, they get hydrated with the skin moisture and converted to niosomes [6].

Risperidone is a potent benzisoxazole derivative used in the treatment of schizophrenia and other psychiatric disorders and is commercially available as tablets, oral solutions, long acting parenterals [7–9]. Risperidone belongs to Biopharmaceutics Classification System (BCS) class II drug, i.e. bears low solubility and high permeability. It has low molecular weight of 410.49 Daltons with Log P about 2.5 (sufficiently lipophilic). One of major drawback associated with risperidone therapy, is its low oral bioavailability due to its extensive hepatic first pass metabolism mediated via Cytochrome P-450 enzymes [10–12]. Keeping this fact in mind, present study was designed to formulate risperidone proniosomes and evaluate its efficacy as transdermal drug delivery systems.

Peer review under responsibility of Faculty of Pharmacy, Cairo University.
* Corresponding author.
E-mail address: ssambhakar@yahoo.co.in (S. Sambhakar).

http://dx.doi.org/10.1016/j.bfopcu.2017.09.003
Received 9 August 2016; Received in revised form 28 August 2017; Accepted 9 September 2017

Please cite this article as: Sambhakar, S., Bulletin of Faculty of Pharmacy, Cairo University (2017), http://dx.doi.org/10.1016/j.bfopcu.2017.09.003

Table 1
Proniosome formulations their compositions, encapsulation efficiency, vesicle size, polydispersity index and zeta potential.

Code	SAA type	Composition (mg)			% EE ± SD	MVS ± SD (nm)	PDI	ZP ± SD (mV)
		SAA	SL	Ch				
PS-20	Span 20	1800	1800	200	85.23 ± 3.45	486.40 ± 3.84	0.246	−56.2 ± 7.67
PS-40	Span 40	1800	1800	200	92.43 ± 2.76	941.40 ± 3.23	0.297	−52.7 ± 7.91
PS-60	Span 60	1800	1800	200	94.13 ± 4.76	858.30 ± 2.42	0.310	−47.3 ± 7.63
PS-80	Span 80	1800	1800	200	89.17 ± 3.46	716.80 ± 4.37	0.209	−48.5 ± 5.60
PT-20	Tween 20	1800	1800	200	52.45 ± 7.89	338.80 ± 6.43	0.281	−41.3 ± 6.37
PT-60	Tween 60	1800	1800	200	58.13 ± 4.34	342.90 ± 5.35	0.293	−40.9 ± 5.44
PT-80	Tween 80	1800	1800	200	62.43 ± 5.67	284.00 ± 5.43	0.284	−37.4 ± 7.68
PS-L	Span 60	900	1800	200	90.23 ± 7.99	821.85 ± 7.89	0.134	−45.6 ± 3.42
PS-H	Span 60	2700	1800	200	94.78 ± 3.76	899.74 ± 6.84	0.243	−47.8 ± 4.16
PL-L	Span 60	1800	900	200	89.45 ± 4.87	999.00 ± 6.34	0.231	−49.9 ± 7.62
PL-H	Span 60	1800	2700	200	96.13 ± 9.45	1084.00 ± 9.45	0.245	−51.4 ± 11.9
PC-L	Span 60	1800	1800	100	82.45 ± 3.45	842.20 ± 2.67	0.048	−55.1 ± 9.73
PC-H	Span 60	1800	1800	300	88.43 ± 1.54	1289.00 ± 4.30	1.000	−52.3 ± 7.71

* Each formulation containing risperidone 50 mg.
* SAA: surfactant, SL: Soya lecithin, Ch: Cholesterol, %EE: Percent encapsulation efficiency, MVS: Mean vesicle size, PDI: Polydispersity index, ZP: Zeta potential, SD: Standard deviation (n = 3).

2. Materials and methods

2.1. Materials

Risperidone was received as a gift sample from Torrent Research Centre (Ahmedabad, India). Sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate and polysorbate (tweens) 20, 40, 80, cholesterol, stearylamine and soya lecithin were purchased from SD Fine Chemicals (Mumbai, India). All other chemicals and solvents used were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Preparation of proniosomes

Risperidone proniosomes were prepared by Coacervation phase separation method, reported by Vora et al. [13]. The non-ionic surfactant, cholesterol, soya lecithin and risperidone were taken in appropriate amount as shown in Table 1. All the components were taken in a wide mouth glass tube and absolute ethanol (1 ml) was added to it and warmed on water-bath at 65 ± 3 °C, to dissolve all the ingredients. While heating, tube was covered with lid to prevent the loss of solvent. After that phosphate buffer pH 7.4 (1 ml) was added and heated again till a clear solution was obtained. The mixture was cooled overnight at room temperature so as to achieve complete gel formation.

2.2.2. Fabrication of transdermal patch

The proniosome formulation was fabricated into transdermal patch, as described by Thakur et al. [14] An adhesive tape of 25 cm^2 was taken. To this, a circular aluminium foil of diameter 2.5 cm was attached. On this aluminium foil, a plastic ring 2.0 cm internal diameter and 0.1 cm thickness was stuck with adhesive. The proniosome gel was spread uniformly over this area, which was then covered with tracing paper (liner).

2.3. Evaluation of proniosomes

2.3.1. Entrapment efficiency

Initially 1 g of the proniosomes were hydrated using 10 ml phosphate buffer (pH 7.4) followed by heating the vial in water bath for 10 min at 60–70 °C. The percentage entrapment efficiency of risperidone in hydrated proniosomes was determined by centrifugation technique [15]. The eppendorff containing hydrated proniosome was centrifuged at 14,000 rpm, at 4 °C for 30 min (Pico 21 centrifuge, Thermo Scientific HERAE US). The supernatant containing unentrapped drug was withdrawn and analysed at 280 nm against phosphate buffer, pH 7.4 (with 30% v/v ethanol) as blank. The entrapment efficiency was calculated by the following formula:-

$$\%EE = \frac{\text{Total amount of drug added} - \text{free drug in supernatant}}{\text{Total amount of drug added}} \times 100$$

2.3.2. Vesicle size and size distribution analysis

For all the batches of proniosomes vesicle size analysis was carried out using Malvern Zetasizer Nano ZS (Malvern Instruments, UK). The freshly prepared hydrated niosomes were dispersed in double distilled water (DDW) and was used to characterize the vesicle size. Polydispersity Index (PDI) was also determined as a measure of homogeneity. Zeta potential of the niosome formulations was determined to estimate stability of the formulations.

2.3.3. Morphology

Morphology of prepared niosomes (PS-60) was analysed using transmission electron microscopy (Tecnai 200 kV, Fei Electron Optics, USA) at AIIMS Delhi. The sample was prepared by mixing the formulation; with 1% of phosphotungstic acid. A drop of the above mixture was placed on carbon coated grid and excess of the sample was drawn out using filter paper. After drying for two minutes, samples were processed for TEM.

2.3.4. Differential scanning calorimetry (DSC)

DSC experiments were performed using DSC instrument (Netzsch, DSC-204 F1 Phoenix, Germany). About 5 mg of risperidone, span 60, soya lecithin, physical mixtures, blank and risperidone loaded proniosome sample (PS-60) were individually capped in aluminium crucible. The crucible was kept under a dynamic atmosphere of nitrogen (50 ml/min) and a heat flow rate of 10 °C/min from 30 to 200 °C and the corresponding spectra between heat flow (w/g) on Y-axis and temperature on X-axis were obtained.

2.3.5. Fourier transform infra red (FTIR) spectroscopy

Infrared spectroscopy of risperidone, span 60, soya lecithin, physical mixtures, blank and risperidone loaded proniosome samples (PS-60) were analysed by ALPHA-T (Brucker) FTIR Spectrophotometer and the spectra were recorded in the region of 3500–1000 cm^{-1}.

2.3.6. In-vitro release study

In-vitro drug release study of proniosome formulations was performed using locally fabricated Franz diffusion cells with diffusional area of 2.011 cm^2. An egg membrane was placed between donor and