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Intranasal haloperidol-loaded miniemulsions for brain targeting: Evaluation of locomotor suppression and in-vivo biodistribution

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ABSTRACT

Haloperidol is a commonly prescribed antipsychotic drug currently administered as oral and injectable preparations. This study aimed to prepare haloperidol intranasal miniemulsion helpful for psychiatric emergencies and exhibiting lower systemic exposure and side effects associated with non-target site delivery. Haloperidol miniemulsions were successfully prepared by spontaneous emulsification adopting 2^3 factorial design. The effect of three independent variables at two levels each namely; oil type (Capmul®-Capryol™90), lipophilic emulsifier type (Span 20–Span 80) and HLB value (12–14) on globule size, PDI and percent locomotor activity inhibition in mice was evaluated. The optimized formula (F4, Capmul®, Tween 80/Span 20, HLB 14) showed globule size of 209.5 ± 0.98 nm, PDI of 0.402 ± 0.03 and locomotor inhibition of 83.89 ± 9.15% with desirability of 0.907. Biodistribution study following intranasal and intravenous administration of the radiolabeled ^{99m}Tc mucoadhesive F4 revealed that intranasal administration achieved 1.72-fold higher and 6 times faster peak brain levels compared with intravenous administration. Drug targeting efficiency percent and brain/blood exposure ratios remained above 100% and 1 respectively after intranasal instillation compared to a maximum brain/blood exposure ratio of 0.8 post intravenous route. Results suggested the CNS delivery of major fraction of haloperidol via direct transnasal to brain pathway that can be a promising alternative to oral and parenteral routes in chronic and acute situations. Haloperidol concentration of 275.6 ng/g brain 8 h post intranasal instillation, higher than therapeutic concentration range of haloperidol (0.8 to 5.15 ng/ml), suggests possible sustained delivery of the drug through nasal route.

1. Introduction

Haloperidol, the dopamine D2 receptor antagonist is one of the most frequently prescribed antipsychotic drugs for the treatment of schizophrenia, mania and other psychiatric disorders (Mutschler et al., 1995; Dold et al., 2015). It is currently available as oral and injectable preparations. These formulations release haloperidol to the systemic circulation resulting in limited drug uptake across the blood brain-barrier and drug distribution to non-targeted sites (Misra et al., 2003). In addition, approximately 50–60% of perorally administrated haloperidol is metabolized in the liver resulting in low bioavailability (Yun et al., 2005).

Intranasal route offers an attractive alternative to parenteral and oral routes since it provides non-invasive painless drug delivery and avoids gastrointestinal and hepatic first-pass metabolism (Serralheiro et al., 2014). Recently, intranasal administration has received a great attention as a reliable route for direct nose to central nervous system/brain delivery of therapeutic substances via the olfactory pathway bypassing blood brain barrier (Serralheiro et al., 2014; Costantino et al., 2007; Abdelbary and Tadros, 2013; Li et al., 2000) and reducing drug delivery to non-targeted sites (Vyas et al., 2005). Also, the large surface area of the nasal mucosa provides a rapid uptake in brain, thus enables successful application in the psychiatric emergencies (treatment of acute agitation or psychoses) (Costantino et al., 2007; Li et al., 2002).

Haloperidol meets desirable properties necessary to intranasal-brain delivery including; small molecular weight; high potency, with a dose lower than 20 mg; and sufficient lipophilicity to permit crossing biologic membranes (Costantino et al., 2007). Very recently, two published articles investigated the potential of lecithin functionalized PEG-PLGA nanoparticles (Piazza et al., 2014) and PAMAM dendrimer (Katare et al., 2015) for brain targeting of haloperidol. In our work we investigated the utility of colloidal nanocarrier (miniemulsion) prepared by low energy spontaneous emulsification process for the potential intranasal brain delivery of haloperidol.

Miniemulsions are fine oil-in-water near thermodynamically stable dispersions, having droplets covering the size range of 100–600 nm (Nakajima, 1997; Tadros Th et al., 2004). Miniemulsions by virtue of

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their appropriate lipophilic nature and low globule size are investigated as a delivery system to enhance the uptake across nasal mucosa (Lawrence and Rees, 2000). Addition of mucoadhesive agents helps to overcome the nasal mucociliary clearance resulting in a longer residence time in the nasal cavity (Sinswat and Tengamuay, 2003).

The objectives of this work were to develop nose to brain haloperidol miniemulsions; helpful for psychiatric emergencies and exhibiting lower systemic exposure and side effects associated with non-target site delivery, employing factorial design, to evaluate the effect of the developed miniemulsions on locomotor activity in mice and finally to perform comparative biodistribution study following intravenous and intranasal administration of optimum miniemulsion to mice to explore its potential for brain targeting.

2. Materials and methods

2.1. Materials

Haloperidol (El-kahira Pharmaceutical Co., Cairo, Egypt); Capmul® MCM EP (Glyceryl caprylate caprate, Abitec Corp., USA); Capryol™ 90 (Propylene glycol monocaprylate, Gattefosse, France); Methanol (Analar, India); Sorbitan monolaurate (Span 20) and Sorbitan monooleate (Span 80) (Sigma-Aldrich Co., USA); Polyoxyethylene sorbitan monooleate (Tween 80), Triethanolamine and Ethanol (Adwic, El-Nasr Pharmaceutical Chemicals Co., Cairo, Egypt); Transcutol (Diethylene glycol monoethyl ether, Merck Co., Hohenbrunn, Germany); Pemulen™ TR-2 (C10–30 Alkyl Acrylate Crosspolymer, gift from Luna Pharmaceutical Co., Cairo, Egypt: Lubrizol Advanced Materials Inc., USA); Hydroxypropyl methylcellulose (HPMC K15M, Colorcon, England). Whatman No. 1 paper chromatography (Whatman International Ltd., Maidstone, Kent, UK). Technetium-99m eluted as $^{99m}TcO_4^-$ from $^{99}Mo/^{99m}Tc$ generator (Gentech, Turkey).

2.2. Spectrophotometric studies

Direct spectrophotometric determination of haloperidol through its spectrum was not possible due to the interference of the spectra of the oily phases (Capryol 90, Capmul MCM), surfactants mixtures (Tween 80/Span 20 or Tween 80/Span 80) and the co-solvent (Transcutol). The development of spectroscopic techniques combined with multivariate calibration proved to be fast, direct and relatively less expensive methods for the determination of drugs in mixtures where there is a great overlap between the spectra of the components. Partial least squares is among the most widely applied multivariate calibration methods employed to solve data analysis problems (El-Gindy et al., 2006; El-Gindy et al., 2007; Espinosa Mansilla et al., 1993; Ghasemi and Niazi, 2005; Hadad et al., 2008).

A Partial least squares chemometric method was used for the determination of haloperidol in the presence of the interfering substances in the prepared formulae. Multilevel multifactor design (Halland and Thomas, 1988) was used for the preparation of 25 mixtures containing drug, oily phases, surfactants and co-solvent with different expected concentrations (Table 1). The spectra of the prepared mixtures were recorded from 200 to 280 nm. Haloperidol stock solution of 1 mg/ml was prepared in ethanol and the working standard solution of 100 μg/ml was prepared by dilution using the same solvent. All stock and working standard solutions of the additives were prepared in ethanol.

A partial least squares model was built using a calibration set formed of 15 mixtures of haloperidol with the expected concentrations of the oily phases, surfactants and co-solvent. The cross validation method, leaving out one sample at a time was used to select the optimum number of latent variables where seven latent variables were selected for building the model. The built model was validated to predict the concentration of haloperidol in ten validation mixtures, where good recoveries were obtained (Table 2). The suggested model was then used to predict haloperidol concentration. Spectrophotometric measurements were carried out on a dual beam UV-Spectrophotometer (Shimadzu, model UV-1650 PC, Kyoto, Japan) and the spectral data were exported to excel and further manipulated using partial least squares tool box version 2.5 under MATLAB 7.0 (The Mathworks, Natick, USA).

Table 1
Concentrations of haloperidol, oil phase, surfactants and co-solvent in the calibration and validation sets[a].

Mixture no.	Drug	Capryol	Capmul	Tween80	Span 80	Span 20	Transcutol
1	10.0	100.0	100.0	180.0	75.0	112.5	100.0
2	10.0	0.0	0.0	285.0	30.0	195.0	100.0
3	5.0	0.0	200.0	135.0	120.0	112.5	50.0
4	5.0	200.0	50.0	285.0	75.0	45.0	50.0
5	15.0	50.0	200.0	180.0	30.0	45.0	120.0
6	7.5	200.0	100.0	135.0	30.0	150.0	150.0
7	15.0	100.0	50.0	135.0	100.0	195.0	120.0
8	10.0	50.0	50.0	265.0	120.0	150.0	100.0
9	7.5	50.0	187.5	285.0	100.0	112.5	150.0
10	7.5	187.5	200.0	265.0	75.0	195.0	150.0
11	12.5	200.0	187.5	180.0	120.0	195.0	0.0
12	15.0	187.5	100.0	285.0	120.0	0.0	120.0
13	12.5	100.0	200.0	285.0	0.0	150.0	0.0
14	10.0	200.0	200.0	0.0	100.0	0.0	100.0
15	15.0	200.0	0.0	265.0	0.0	112.5	120.0
16	15.0	0.0	187.5	0.0	75.0	150.0	120.0
17	5.0	187.5	0.0	180.0	100.0	150.0	50.0
18	12.5	0.0	100.0	265.0	100.0	45.0	0.0
19	5.0	100.0	187.5	265.0	30.0	0.0	50.0
20	10.0	187.5	187.5	135.0	0.0	45.0	100.0
21	10.0	187.5	50.0	0.0	30.0	112.5	0.0
22	10.0	50.0	0.0	135.0	75.0	0.0	0.0
23	7.5	0.0	50.0	180.0	0.0	0.0	150.0
24	5.0	50.0	100.0	0.0	0.0	195.0	50.0
25	7.5	100.0	0.0	0.0	120.0	45.0	150.0

The concentration is in (μg/ml).
[a] The grey mixtures were used for calibration set and the white mixtures for the validation set.

2.3. Determination of haloperidol solubility in different excipients

The solubility of haloperidol in Capryol 90 and Capmul MCM as oils, Tween 80, Span 20, and Span 80 as surfactants as well as Transcutol as co-solvent was determined. An excess amount of haloperidol was added in to different oils, surfactants or co-solvent separately and kept under moderate stirring for 24 h to reach equilibrium at 25 ± 0.5 °C in a thermostatically controlled shaking water bath (Model 1083, GLF Corp., Burgwedel, Germany). A sample from each mixture was centrifuged (Megafuge1.0R, Heraeus, Germany) at 15,000 rpm for 20 min (Kelmann et al., 2007), an aliquot of the supernatant was diluted with ethanol and haloperidol content was assayed spectrophotometrically as under the previous section.

Table 2
Haloperidol percentage recovery for the validation set mixtures.

Mixture no.	Haloperidol concentration (μg/ml)		
	Nominal	Found	% recovery
1	10	9.99	99.87
2	10	10.23	102.34
3	5	4.66	93.20
21	10	9.98	99.76
22	10	9.28	92.81
23	7.5	7.40	98.67
24	5	4.92	98.30
25	7.5	7.38	98.34