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FORMULATION AND CHARACTERIZATION OF PALIPERIDONE LOADED MUCOADHESIVE MICROEMULSION FOR INTRANASAL DELIVERY

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ABSTRACT

Paliperidone (PPD) is used for the treatment and management of schizophrenia. The present study demonstrates the potential of mucoadhesive microemulsion of PPD for nasal delivery. PPD-MME was prepared by water titration method, prepared formulations were subjected to physicochemical characterization, and evaluated for size, zeta potential, PDI, pH and stability studies. The microemulsion, containing 5% oleic acid (oil Phase), 40% surfactant mixture of Tween 80(surfactant): Transcutol HP (cosurfactant) (2:1) and 55% aqueous phase, that displayed globule size of 94.8±0.34nm, a PDI of 0.25±0.22 and zeta potential was 14.5±0.4 mV, chitosan was selected for the incorporation of polyelectrolytic polymer as the mucoadhesive component. The mucoadhesive microemulsion formulation of Paliperidone that contains 0.5 % by weight of chitosan.

KEY WORDS

Paliperidone; Microemulsion; pseudoternary phase diagram; solubility

INTRODUCTION:

Schizophrenia is a chronic condition and severe mental disorder having world-wide occurrence of 23 million people approximately. [1] It is associated with three types of symptoms which are positive symptoms (Hallucinations, delusions, thought disorder, movement disorders), negative symptoms (Inability to enjoy pleasure, abnormal emotions) and cognitive symptoms (Inability to focus or pay attention, inability to use learned skills). [2] Antipsychotic drugs are used for the treatment of both positive and negative and cognitive symptoms of schizophrenia [3]

Paliperidone (PPD) is a second-generation antipsychotic drug which appears to act as a dopamine type 2 (D2) and serotonin (5-HT)-2A receptor antagonist. [4] Paliperidone having broad efficacy and improves the symptoms of Schizophrenia. Paliperidone is practically insoluble in water.

Oral drug delivery is more convenient and well accepted. However, oral administration is inappropriate when drug undergoes degradation in the gastrointestinal tract or is metabolized to a high degree via the first pass effect in liver. [5] Presently, PPD oral formulation is available in a form of an extended release tablet which has oral bioavailability of 28%. [6] Disadvantages of oral dosage form includes poor bioavailability complex manufacturing, and slow transport along gastrointestinal tract. [7]

Hence, alternative routes of administration should be preferred. In recent years, the intranasal drug delivery system is emerging and an attractive delivery option for targeting to brain. It offers rapid absorption of drug, increase in bioavailability of drug, reduced in drug dose and avoidance of gastrointestinal or liver metabolism and anticipation of irritation of the GI membrane and improved patient compliance. [8,9,10,11] In recent

years microemulsion based delivery system in nose - brain targeting have been studied extensively. [12]

In the present study, we intend to make use chitosan (mucoadhesive agent) study its effect on enhancing mucoadhesion across nasal mucosa and help in achieving targeting the brain via intranasal route of administration.

MATERIALS:

Paliperidone was received from Hetero drugs Pvt limited (Hyderabad, India) as gift sample, Transcutol HP, Labrafil M 1944 CS, Cremophor RH 40 was received as free sample from Gattefose SAS (France), Oleic acid, Tween 80, Tween 20, PEG 200, Propylene glycol was purchased from Sd fine chemicals. Analytical grade solvents were used in the study.

Methods:

Screening of oil

The solubility of paliperidone (PPD) in various oils was determined by adding an excess amount of drug in 2 ml of the oils (Oleic acid, Labrafil M 1944 CS, Capmul MCM) separately in 5-mL-capacity vial, and then mixed using a cyclomixer (CM 101, REMI, India). Then the vials were kept on water bath shaker (R100/TW, England) for stirring at 25ºC for 48 h. After equilibrium, vials were removed from the water bath shaker and centrifuged (R2, REMI) at 15000 rpm for 10 min [13]. The supernatant was taken and filtered through a membrane filter (0.45µm). The concentration of paliperidone was determined in oils using UV spectroscopy. The study was carried in triplicate.

Screening of Surfactants

Different types of surfactants were screened for the formulation, which included Tween 80, Cremophor RH 40 and Tween 20. In water, 2.5 ml of surfactant solution was prepared, and 5% of oil was added with vigorous vertexing. If a one-phase clear solution was obtained, the addition of the oil was repeated until the solution became turbid.

Screening of Cosurfactants

Tween 80 was combined with different types of solubilizers as cosurfactants, Transcutol HP, Polyethylene glycol 200, propylene glycol, at a Smix ratio of 1:1,2:1,3:1,1:2 the pseudoternary phase diagrams were made. Different weight ratios of oil and Smix, 9:1 ,8:2,7:3,6:4,5:5,4:6,3:7,2:8 ,1:9, were taken so that maximum ratios were Perform to define the boundaries of phases precisely formed in the phase diagrams. [14,15]

The pseudo ternary graphs are plotted by using CHEMIX software.

Preparation of microemulsion containing Paliperidone

PPDME formulations were prepared by water titration method [16] by different the ratios of oil, Surfactant, co-surfactant, and water; keeping the paliperidone drug concentration of constant.

50 mg drug was mixed with oil (Oleic acid), and to that surfactant mixture was added and mixed thoroughly for 5 minutes at room temperature. The mixture was titrated with water drop wise until a transparent and stable PPDME was formed. PPDMMEs were prepared by adding 0.5% w/w chitosan solution in 1% acetic acid to microemulsion formulation, were represented in Table 1.

Characterization of Formulation

Zeta potential, Globule size and Polydisperse index

Zeta potential, Globule size, PDI and measurements were performed by photon correlation Spectroscopy using Zetasizer (Nano-ZS90, Malvern, Worcestershire, UK) by taking 1ml of formulation into polystyrene cuvettes for globule size and PDI and disposable folded capillary Cell for zeta potential at 25ºC respectively.

Transmittance (%T)

Transparency of microemulsion was determined by measuring percentage transmittance through UV Spectrophotometer (UV 3000-LABINDIA). Percentage transmittance of samples was measured at 650nm with purified water taken as blank and triplicate were performed for each formulation [17]

Drug content

Drug content of PPDME and PPDMME was determined by taking equivalent to 50mg of paliperidone and diluted using methanol. Samples were prepared in triplicate and the absorbance was measured at 278 nm using UV-Vis Spectrophotometer.

Viscosity

The viscosity of formulation was determined using Brookfield viscometer. Viscosity determinations were performed at 40 rpm at 25 ± 0.3ºC.

pH

The pH of Formulation was determined at room temperature using a calibrated digital pH meter by taking 5 ml of formulation individually in a beaker

Stability studies

The optimized PPDME was stored at three different temperature ranges for 3 months i.e., refrigerating condition (2– 8ºC), room temperature and elevated temperature (40 ± 2), shelf life of the stored microemulsion system was evaluated by phase separation, rheological behavior, emulsifying time, electrical conductivity, pH, percentage transmittance, assay and *In vitro* drug diffusion studies [16]

Statistical Analysis

Experimental data from more than triplicate are shown as means ± standard deviations (SD).

RESULTS AND DISCUSSION:

Screening Criteria for Oil Selection

In the development of microemulsion systems for poorly soluble drugs, drug loading in the formulation is very critical factor, which is dependent on the drug solubility in various components used in the formulation. Hydrophilic drugs are preferably solubilized in w/o microemulsions, whereas o/w systems seem to be a better choice for lipophilic drugs. The amount of the formulation should be minimized to deliver the therapeutic dose of the drug. Solubility of the drug in the oil phase is an important measure for the selection of the oil, it influences to maintain the drug in solubilized form in the microemulsion formulation. If the surfactant or cosurfactant is influence to drug solubilization, there could be a risk of precipitation. Thus, an understanding of factors that influencing drug loading ability while maintaining the capability of the system to undergo monophasic dilution with water and minimizing the propensity for drug precipitation or crystallization in diluted systems is essential to the development of stable and appropriately less-volume microemulsion systems for drug delivery applications.

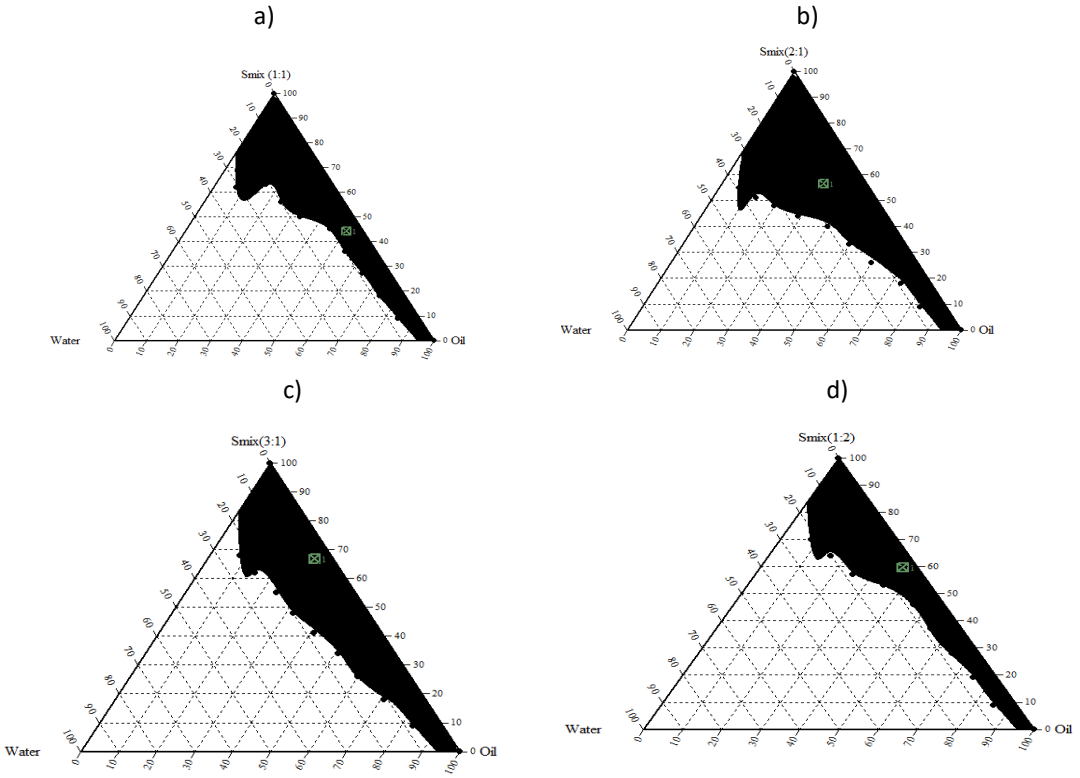

Fig. 1. Pseudo ternary phase diagram using oleic acid as oil, Tween 80 as surfactant, Transcutol HP as cosurfactant and water,ratio of S mix (Tween 80: Transcutol HP) a) 1:1, b)2:1 c)3:1 and d)1:2.

Oleic acid was selected as Oil Phase, Smix was Tween 80: Transcutol HP (2:1), water from the Pseudo ternary phase diagrams (Fig 1).

The solubility of paliperidone in different oils was determined (Table I). The solubility of paliperidone was found to be highest in Oleic acid (16.20±0.45 mg/ml) as compared to other oils.

Table I. Solubility of paliperidone in different Oils at 25°C (mean ±SD, n=3)

S. No	Solubility	Solubility (mg/ml)
1	Oleic acid	16.20±0.45
2.	Labrafil M 1944CS	4.21±0.29
3.	Capmul MCM	2.03±0.41

Table II. Solubility of Paliperidone in different surfactants and cosurfactants at 25°C (mean ±SD, n=3)

S. No	Solubility	Solubility (mg/ml)
1	Tween 20	1.6±0.14
2	Tween 80	14.56±0.10
3	Cremophor RH 40	5.63±0.23
4	Transcutol HP	10.72±0.42
5	PEG200	2.9±0.54
6	Propylene glycol	4.53±0.46

The microemulsion were selected so that all the formulations contain increasing concentrations of oil and Smix Table III.

Table III: composition of microemulsion containing Paliperidone

Formulation	Drug (mg)	Oil (%)	Smix (%)	Water (%)	Chitosan (%)
PPD1	50	5	30	65	-
PPD 2	50	5	35	60	-
PPD 3	50	5	40	55	-
PPD 4	50	5	45	50	-
PPD 5	50	5	50	45	-
PPD 6	50	5	55	40	-
PPD 7	50	5	60	35	-
PPD 8	50	10	30	65	-
PPD 9	50	10	35	60	-
PPD 10	50	10	40	55	-
PPD 11	50	10	45	50	-
PPD 12	50	10	50	45	-
PPD 13	50	10	55	40	-
PPD 14	50	10	60	35	-
PPDMME	50	5	40	55	0.5

Characterization of formulation

Characterization of the PPDME and PPDMME are shown in Table IV. The globule size was of 50.5 ± 0.26nm and 94.8±0.34 nm, Zeta potential measurements of –30.8±1.2 and 14.5±0.4 mV on the globules of PPDME and PPDMME indicated that the system is physically stable and PDI of 0.12 ± 0.14 and 0.25±0.22 for PPDME and PPDMME, respectively, indicate that the ME approached a monophasic stable system. This microemulsion system can more efficiently deliver a drug due to the presence of a larger surface area. pH was of 6.45 and 6.42 for the PPDME and PPDMME. A formulation whose pH is in this range may help in reduce the irritation give upon administration.

Formulation was stable for 3 months.

Table IV: characterization of Formulations. Data shown as mean ± SD (n=3)

Formulation	Globule Size (nm)	Zeta size (mV)	PDI	pH	Viscosity (mPa-s)
PPD1	89.3±0.12	-23.5±0.3	0.21±0.12	6.29	191
PPD 2	77.3±1.10	-24.9±0.7	0.19±0.31	6.53	189
PPD 3	50.5±0.26	-30.8±1.2	0.12±0.14	6.45	205
PPD 4	45.8±0.41	-22.7±0.2	0.13±0.23	6.51	164
PPD 5	43.2±0.38	-27.4±0.5	0.22±0.26	6.56	191
PPD 6	41.7±0.35	-26.2±1.4	0.18±0.31	6.37	190
PPD 7	40.4±0.72	-24.6±1.8	0.19±0.46	6.23	184
PPD 8	135.3±0.47	-28.7±1.2	0.22±0.27	6.29	205
PPD 9	134.4±0.62	-24.8±1.4	0.13±0.34	6.26	276
PPD 10	122.3±0.58	-27.8±1.3	0.14±0.25	6.14	248
PPD 11	109.4±0.55	-23.6±0.2	0.15±0.44	6.57	262
PPD 12	95.3±0.30	-24.5±0.9	0.16±0.72	6.79	227
PPD 13	92.6±0.44	-25.3±0.7	0.17±0.36	6.48	225
PPD 14	89.7±0.18	-27.7±0.3	0.18±0.64	6.62	231
PPDMME	94.8±0.34	14.5±0.4	0.25±0.22	6.42	230

CONCLUSION:

The formulation contained 0.5% w/w chitosan exhibited a small globule size, poly disperse index and optimum Smix concentrations, which ensured in that formulation having highest mucoadhesive potential and the formulation was found to be stable for 3 months. According to this study, PPDMME formulation is potentially useful for increase permeation of formulation delivered intranasally. Intranasal admintration of may be considered as replacement to oral administration to overcome drawbacks of these delivery route.

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