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RESEARCH ARTICLE

NANOEMULSION BASED INTRANASAL DELIVERY OF RISPERIDONE FOR NOSE TO BRAIN TARGETING

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Risperidone nanoemulsion using different mucoadhesive agent as nasal drug delivery system was prepared to produce quick effect as compared to that of oral route. Solubility of drug was determined in different vehicles. Pseudo ternary phase diagram were generated using Acrysol K 150 as oil, tween 80 as a co-surfactant, and caproyl PGMC as a surfactant. The four formulations were prepared by the spontaneous emulsification method and were further characterized for their percentage transmittance, droplet size and zeta potential. *Ex vivo* diffusion study of the optimized batch was carried out using goat nasal mucosa. Histopathological study of the optimized batch was studied. Optimized formulation was found to possess the mean globule size 149 nm and zeta potential -17.3 mV. *Ex vivo* study revealed that at the end of 4 h, 93.76% of the dose was diffused successfully. In histpathological study, formulation treated mucosa did not show any damage to the epithelium layer.

Key words: Risperidone, Nanoemulsion, Spontaneous emulsification, Nasal ciliotoxicity.

INTRODUCTION

One of the major psychotic disorders is a schizophrenia that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life threatening behaviors. The primary goal in management of schizophrenia is to achieve optimal control of symptoms (Nasrallah *et al* 2005). Antipsychotics are a group of powerful psychoactive drugs thought to block specific receptors in the brain that affect the central nervous system. A number of strategies are followed to target various body tissue/organs. The brain is a delicate organ with many vital functions, and formidable mechanisms isolate and protect it from the outside world. Unfortunately, the same mechanisms that prevent intrusive environmental chemicals accessing the brain also prevent the access of therapeutic chemicals (Soni *et al* 2004). The need for treatment options has been emphasized by the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, in which 74% of 1493 patients with schizophrenia discontinued study medication within 18 months. The reasons for discontinuation included lack of efficacy, intolerability, and patient decision. The CATIE study has increased awareness of the need for new treatment options tailored to the choice of the individual patient and clinician (Canuso *et al* 2008).

There is a need of a therapeutic prompt action to rapidly control agitation and disturbed behaviors in patients with schizophrenia, make Risperidone (RPD), a possible candidate for the development of an intranasal formulation. RPD, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl] - 6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, is an approved antipsychotic drug belonging to the chemical class of benzisoxazole derivative and is available as tablet, oral liquid (Risperidal®) and orally disintegrating tablet (Risperidal® M-TAB) (DrugBank, DB00734).

Orally disintegrating tablet of RPD exhibit low bioavailability due to extensive first-pass metabolism. The nontargeted delivery results in numerous side effects. Intramuscular route can be painful and cause a patient already in psychotic, fragile state of mind to feel even more insecured and increase their sense of being attacked (Wermeling and Miller, 2006). Target site of the RPD is brain, and direct transport of drugs to brain across the brain barriers following intranasal (*i.n.*) administration that provides a unique feature and better option for targeting drugs to brain (Behl *et al* 1998).

The olfactory region of nasal mucosa provides a direct connection between nose and brain and that can be exploited for targeting central nervous system (Kumar *et al* 2008). Mucoadhesive product provides a rapid transport of drug across nasal mucosa and a longer residence time in nasal cavity to overcome the nasal mucociliary clearance (Talegaonkar and Mishra, 2004; Kumar *et al* 2008). Nanoemulsion has already been utilized for intranasal as well as transdermal drug delivery (Talegaonkar *et al* 2011; Chouksey *et al* 2011; Mishra *et al* 2013). Keeping in view the potential of nanoemulsions (NEs) and target site of RPD in brain, present work was undertaken to investigate the feasibility of nose to brain delivery of RPD by developing its nanoemulsions formulation.

MATERIALS AND METHODS

Risperidone was obtained from the IPCA pharmaceutical, Mumbai as gift sample. Acrysol EL 135 and Acrysol K 150 gifted from the corel chemical, Ahmedabad. Caproyl PGMC and Labrafac PG obtained from Gattefosse France as gift sample. Acconon C-30, Captex 200 and Captex 1000 obtained from Abitech US. Tween 80 and Tween 60 purchased from Finar Chemical Ahmedabad.

Solubility study

Solubility of RPD was determined in various oils, surfactant and co-surfactants. One ml of each component was taken in screw cap vials with known quantity (130 mg) of excess drug. After sealing, vials were kept on water bath incubator shaker (Hicon Instrument, India) at 40±2°C for 48 h. After equilibrium each test tube was centrifuged (Remi, India) at 2500 rpm for 15 min. Solution was appropriately diluted with methanol and UV absorbance was measured at 279 nm against blank (methanol and same amount of oil present in test sample). Concentration of dissolved drug was determined using standard equation.

Construction of pseudo-ternary phase diagram

Pseudo ternary phase diagrams were developed using the aqueous titration method. Slow titration with the aqueous phase was performed for each combination of oil and Smix separately. The amount of aqueous phase added was varied to produce a water concentration in the range of 5% to 95% of total volume at around 5% intervals. Surfactant (Caproyl PGMC) and co-surfactant (Tween 80) were mixed (Smix) in different volume ratios (1:1, 1:2, 1:3, 2:1, 3:1). For each phase diagram, oil (Acrysol K 150) and specific Smix ratio were mixed thoroughly in different volume ratios from 1:9 to 9:1 in different glass vials. After each 5% addition of the aqueous phase to the oil: Smix mixture, visual observation was made. Similar method was used to develop pseudo ternary phase diagram for other ratio, a separate phase diagram was constructed using Chemix (Chemix school version 3.60 evaluation copy) software based on the observations noted (Agrawal *et al* 2012).

Nasal dose calculation of risperidone for human

For the nasal route dose of risperidone for the rat is equivalent to 0.09 mg/kg of body weight (Kumar *et al* 2008) On the bases of body surface area (BSA) human equivalent dose (HED) can be calculated by two way.

a) With the help of K_m factor (Reagan-Shaw et al 2007)

Formula for dose translation based on BSA:

HED (mg/kg) = Animal dose (mg/kg) × Animal K_m / Human K_m

Rat Km = 6, Human adult = 37,
Dose (rat) = 0.09 mg/kg

So, HED = 0.014 mg

b) With the help of body weight

HED = animal dose in mg/kg × (animal weight in kg/human weight in kg)$^{0.33}$

$$\text{HED} = 0.09 \times (0.225/60)^{0.33}$$

$$= 0.09 \times (0.00375)^{0.33}$$

$$= 0.014 \text{ mg}$$

Oral dose of Risperidone = 1-3 mg

Nasal dose of Risperidone = 14 μg

Formulation of nanoemulsion

Formulation of drug solution

The Risperidone solution was prepared by dissolving RSP (35 mg) in 1 ml ethanol (95%, *v/v*) and finally volume was made to 10 ml with distilled water resulting in a solution of 3.5 mg/ml.

Preparation of NE

The NEs for Risperidone were prepared by the spontaneous emulsification method (titration method). The calculated amount of drug was added to the oily phase of NEs and magnetically stirred until dissolved followed by the addition of S_{mix} in a fixed proportion to produce a clear mixture. Then, a definite proportion of water was added and stirred to produce clear NE of Risperidone (**Table 1**).

Table 1. Composition of batch S1 to S6

Formulation Code	Composition (% *v/v*)			
	Acrysol K 150	**Caproyl PGMC**	**Tween 80**	**Water**
S1	14	30	15	41
S2	14	29	14.5	42.5
S3	14	28	14	44
S4	12	30	15	43
S5	12	29	14.5	44.5
S6	12	28	14	46

Primary characterization

Transmittance (%T) (Unit converter) : The percentage transmittance of each of 2 ml NEs was checked against distilled water using UV-VIS spectrophotometer at (Shimadzu-1800, Kyoto, Japan) 650 nm.

Calculation of concentration of drug with the help of dropper

From the prepared NE, 15 drops of formulation were taken in 50 ml of methanol than UV spectrophotometric analysis was carried out. Then, concentration of solution was calculated from the calibration curve and with help of the nasal dose, required concentration of the drug is calculated.

Preparation of nanoemulsion with different formulation with different mucoahdesive agent

The composition of nanoemulsion with different mucoahdesive agents are shown in **Table 2.**

Table 2. Composition of nanoemulsion formulations

	S7 (ml)	**S8 (ml)**	**S9 (ml)**	**S10 (ml)**
Drug solution*	1	1	1	1
Acrysol K 150	12	12	12	12
Caproyl PGMC	30	30	30	30
Tween 80	15	15	15	15
Chitosan	-	0.4%	-	-
Carbopol 940	-	-	0.5%	-
Sodium alginate	-	-	-	0.5%
Water	43	43	43	43

Characterization of nanoemulsion

Qualitative tests

The dilution test was performed by diluting 1 ml of prepared NE(s) to 100 ml and observed for clarity/turbidity. To identify type of NE, methyl orange, a water soluble dye, was sprinkled over the NEs and observed microscopically. Centrifugation test, prepared NE(s) were centrifuged for 15 min and examined for whether the system was monophasic or biphasic.

Drug content

RSP from NE formulation was extracted in methanol. The solutions were filtered using whatman filter paper and the methanolic extract was analyzed for the RPD content by UV-visible spectrophotometer at 279 nm.

Droplet size Analysis and (ζ)-zeta potential measurement

After ensuring the complete dispersion of the formulation, the droplet size and zeta potential of resultant nanoemulsion was determined by Zetasizer Nano Series (Microtrac Zetatrac, Canada).

pH measurement

The pH of the NEs was measured using pH meter (Model EQ 610, Equiptronics, India) using 5 ml sample in a 10 ml beaker.

Conductivity measurement

The conductivity of the NEs was measured with Conductometer (Model CL 220, Chemi line, India) by inserting the probe in 10 ml of prepared NE sample in a beaker.

Viscosity measurement

The viscosity of 20 ml of the sample was determined using a Brookfield viscometer (Model LVDV-II+P, USA) coupled with a Spindle T-B (entry code 92) at 50 rpm at 30°C.

Ex vivo diffusion study of RSP formulation

The freshly excised goat nasal mucosa, except the septum part, was collected from the slaughter house in phosphate buffer saline (PBS), pH 6.4 (Basu and Maity, 2012). The membrane was kept in PBS (pH 6.4) for 15 min to equilibrate. The superior nasal conche was identified and separated from the nasal membrane. The excised superior nasal membrane was then mounted on Franz diffusion cell. The tissue was stabilized using phosphate buffer (pH 6.4) in both the compartments and allowed to stir for 15 min on a magnetic stirrer. After 15 min, solution from both the compartments was removed and fresh phosphate buffer (pH 5) was filled in the acceptor compartment. The mounting of the nasal membrane was done using glue at the brim of the donor compartment to avoid leakage of the test sample and supported with thread crossing over the cell. The temperature of the receiver chamber containing 30 ml of diffusion media (phosphate buffer, pH 5.0) was controlled at 37°C under continuous stirring with Teflon coated magnetic bar at a constant rate, in a way that the nasal membrane surface just flushes the diffusion fluid. A drop of optimized Nanoemulsion formulation was placed in the donor compartment of Franz diffusion cell along with 1.7 ml of phosphate buffer (pH 5) added additionally. Samples from the receptor compartment were withdrawn at predetermined time intervals and analyzed. Each sample removed was replaced by an equal volume of diffusion media. Each study was carried for a period of 4.0 h, during which the drug in receiver chamber (μg/ml) across the goat nasal membrane was calculated at each sampling point. The cumulative values for % drug diffused were plotted against time.

Histopathological study

Freshly excised goat nasal mucosa, except for the septum, was collected from the slaughter house in saline phosphate buffer (pH 6.4). Three goat nasal mucosa pieces (X1, X2, and X3) with uniform thickness were selected and placed in glass petriplate. X1 was treated with 0.5 ml of PBS (pH 6.4, negative control), X2 with 0.5 ml of isopropyl alcohol (positive control), and X3 was treated with NE for 1 h. After 1 h, the mucosa were rinsed with PBS (pH 6.4) and subjected to histological studies to evaluate the toxicities of NEs and photographed by microscope. This test was performed at QUALITECH lab, Ahmedabad.

Short term stability study

The NE formulation was subjected to short term stability study under the following conditions: 40±5°C temperatures and 75±5% relative humidity in stability chamber (Thermolab, Bombay). The stability study was followed for 1 month. The stored sample was evaluated for appearance, color, pH, viscosity, conductivity and RSP content.

RESULTS AND DISCUSSION

Solubility study of risperidone in various excipients

Before selecting suitable excipients for risperidone nanoemulsion, UV spectrophotometric analysis of drug in each individual excipient was done by scanning the methanol drug excipients mixture in the range of 200-400 nm. It is expected that absence of any interference between the drug and the excipients, the absorption maxima of the drug remain intact even in its dissolved state in the said excipients.

In this study, excipients were explored for solubility of Risperidone. For each excipient, λ_{max} of the drug in methanol *i.e.* 279 nm was found to be retained. This information indicates that each of these excipients is well compatible with the drug at room temperature. The important criteria for selection of the excipients are that all the components are pharmaceutically acceptable and fall under GRAS (Generally regarded as safe) category. For solubility studies various oils, surfactant and co-surfactants were selected. The solubility data of risperidone in various oil and surfactant are shown in **Figure 1**.

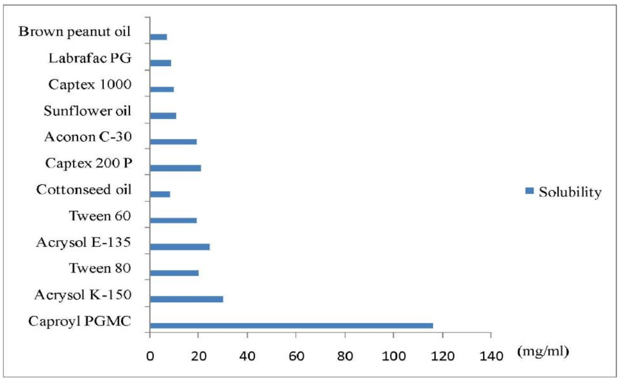

Fig 1. Solubility data of risperidone in various oil and surfactant

Amongst all the tested materials, the maximum solubility of risperidone was found in the Caproyl PGMC (116.30±1.42 mg/ml), Acrysol K 150 (30.30±0.73mg/ml) and Tween 80 (20.44±0.76 mg/ml). Solubility of Risperidone in other oils ranges from 7 to 30 mg/ml. Among oils tested, Risperidone showed maximum solubility in Acrysol K 150, that's why selected as the oil for the NE formulation. Among various surfactants tested, Risperidone showed maximum solubility in Caproyl PGMC (116.30±1.42 mg/ml) and Tween 80 (20.44±0.76 mg/ml). So, Caproyl PGMC selected as a surfactant and Tween 80 as a co-surfactant.

Pseudo ternary phase diagram

A ternary phase diagram was generated to choose the proper concentration of excipients i.e., oil proportion and optimum Smix ratio in the formulation to produce emulsions with good stability (the darken area in **Figure 2**).

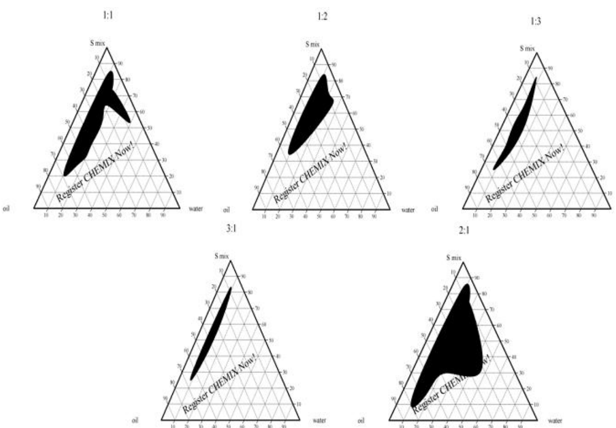

Fig. 2. Pseudo ternary phase diagrams

As per pseudo ternary phase diagrams, it was concluded that the best surfactant mixture ratio is 2:1 this phase diagram contain the maximum region for the nanoemulsion formation compare to other Smix ratio.

Primary characterization

The optically clarity of batches S1 to S4 are shown in **Table 3**.

Table 3. Optical clarity test for batch S1 to S6

Batch	Absorbance	% Transmittance
S1	0.0082	98.13
S2	0.0062	98.58
S3	0.0073	98.33
S4	0.0048	98.90
S5	0.0063	98.56
S6	0.0077	98.23

From the data we can conclude that S4 batch is optically more clear.

Calculation of concentration of drug with the help of dropper

From the NE 15 drops of formulation were taken in 50 ml of methanol than UV analysis was carried out.

Concentration of solution = 10.81 μg/ml (from the calibration curve)

15 drops = 540.5 μg {10.81*50} therefore, 1 drop = 36.03 μg

If the concentration of the NE is 0.35 mg/ml then, 1 drop contain the 36.03 μg of the drug.

Required dose of risperidone for nasal route = 14 μg

So, if we prepare NE with the concentration of 0.136 mg/ml than 1 drop of NE contains the 14 μg of the drug.

Characterization of nanoemulsion

Qualitative test

In general, an emulsion exhibits the characteristics of its external phase. Dilution tests are based on the fact that the emulsion is only miscible with the liquid that forms the continuous phase. Upon dilution, the emulsion retained its clarity indicating to be an *o/w* type of NE.

Staining tests in which a water-soluble dye is sprinkled onto the surface of the emulsion also indicate the nature of continuous phase. With an *o/w* emulsion, there is rapid incorporation of the dye into the system, where as with *w/o* emulsion, the dye forms microscopically visible lumps. Methyl orange, a water soluble dye, could be readily incorporated in the NE system without clumping, hence proving the system to be of *o/w* type. Neither phase separation nor creaming on centrifugation of the NEs indicated stability of the prepared system. Evaluation parameters of batch S7 to S10 are shown in the **Table 4**.

Table 4. Evaluation parameters of batch S7 to S10

Batch	% Drug content*	Average droplet size (nm)	pH*	Conductivity (mS/cm)*	Zeta potential (mV)	Viscosity (cp)*
S7	98.71 ± 0.81	148.7	5.61 ± 0.12	0.139 ± 0.009	-15.3	237.5 ± 4.2
S8	99.32 ± 0.09	6000	5.36 ± 0.16	0.171 ± 0.01	-14.2	248.6 ± 1.6
S9	99.56 ± 0.24	6000	7.4 ± 0.18	0.133 ± 0.012	-15.96	332.5 ± 3.7
S10	99.49 ± 0.41	149.8	6.16 ± 0.13	0.202 ± 0.004	-17.3	635.1 ± 5.4

*Mean ± S.D, n=3

Drug content

Despite of difference in composition, the drug content of formulations S7 to S10 was found in range of 98.71-99.56 %.

Droplet size determination

The droplet size of the emulsion is a crucial factor in the rate and extent of drug release as well as absorption. S7 and S10 formulation passes the limit which is stated for the nanoemulsion particle (20 to 200 nm) while the S8 and S9 fails to pass. The increase in particle size may be related to the solubilization property of mucoadhesive agent incorporated.

Zeta potential (ζ) determination

ζ-potential can be defined as the difference in potential between surface of the tightly bound layer (shear plane) and the electro neutral region of an emulsion. It has got practical application in the stability of emulsion since, ζ-potential governs the degree of repulsion between adjacent, similarly charged, dispersed droplets. If the ζ-potential is reduced below a certain value (which is depends on a particular system being used), the attractive forces exceed the repulsive forces, and the particles come together leading to flocculation. In general, the zeta potential value of ±30 mV is sufficient for the stability of a nanoemulsion. But here as all the excipients used are non-ionic in nature, low zeta potential could be attributed to the drug molecule.

pH measurement

The pH of all the NEs ranged between 5.61 and 7.4. The normal pH range of nasal fluids is 4.5 to 6.5, which is one of the formulation considerations that might help reducing the irritation produced upon instillation. Batch S9 possessed the pH near to the neutral pH because carbopol solubilized at neutral pH. Eventhough many researcher used carbopol 940 in nasal formulation.

Conductivity measurement

Conductivity measurements rely on the poor conductivity of oil compared with water and give low values in water–oil emulsions where oil was the continuous phase. The reverse happened for *o/w* emulsion. The conductivity measurements (0.133–0.202 mS/cm) indicated the NEs to be of *o/w* type.

Viscosity measurement

For the longer residence time in the nasal membrane it is obvious to have moderately high viscosity. Formulations have the viscosity in the range of 237 to 635 cp. Batch S10 showed the highest viscosity among all other batches and hence considered better than other.

Ex vivo diffusion study

Nanoemulsion formulation was subjected to *ex vivo* permeation studies using the goat nasal mucosa. Ex vivo nasal mucosa diffusion profile was shown in **Figure 3**. The drug diffused at faster rate from nanoemulsion. The total percentage diffusion was much higher from the nanoemulsion system. The percent drug permeated after 4 h was found to be 93.76% from nanoemulsion.

Histopathological study

The microscopic observations (**Figure 4**) indicated that the optimized formulation did not significantly affect the microscopic structure of mucosa. As shown in **Figure 4**, neither cell

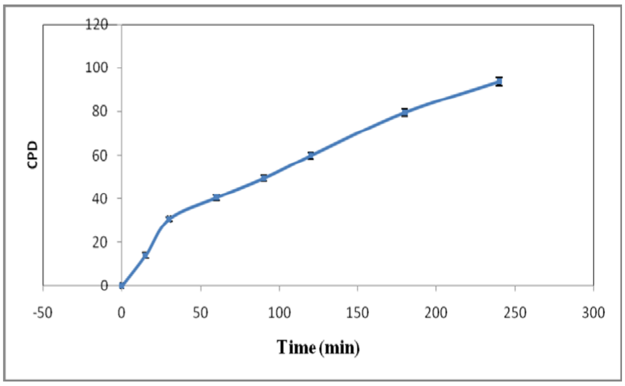

Fig. 3. *Ex-vivo* cumulative percentage drug diffusion

necrosis nor removal of the epithelium from the nasal mucosa was observed after permeation study of S10. Thus, NE formulations seemed to be safe with respect to nasal administration.

Short term stability study

Optimized formulation S10 was kept for the stability study for the one month period. The samples were withdrawn after one month and analysed for all basic evaluation tests and compared with result of initial time.

There was no significant difference in drug content, pH, viscosity and conductivity at zero time and throughout the 1 month stability study period under all storage conditions. This indicated that risperidone is chemically and physically stable in the formulation and proved that the drug did not degrade or precipitate.

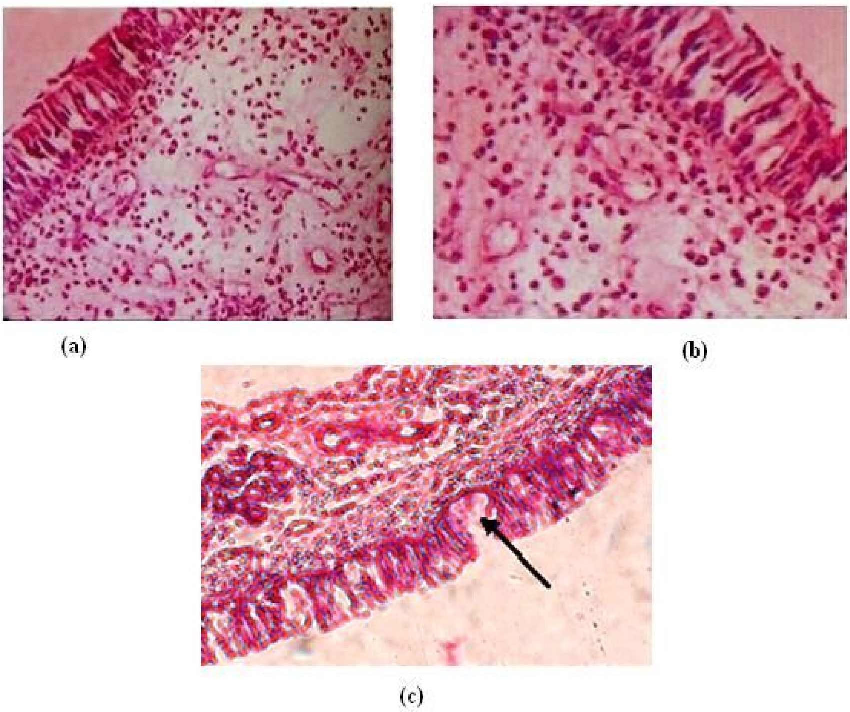

Fig. 4. Goat nasal mucosa treated with
(a) Phosphate buffer 6.4 (b) NE formulation (c) Isopropanolol

CONCLUSION

It was concluded that nasal nanoemulsion of risperidone could be succesfully prepared by the spontaneous emulsification method by using the optimum concentration of 12% (*v/v*) of Acrysol K 150, 30% (*v/v*) of Caproyl PGMC, 15% (*v/v*) Tween 80, 0.5% (*w/v*) Sodium alginate and 43% (*v/v*) of water, which can provide rapid transport of risperidone to brain *via* nasal mucosa by increasing the residence time in the nasal cavity.

The prepared NE was free from nasal ciliotoxicity, narrow particle size distribution, excellent percentage transmittance, moderate Viscosity, suitable conductivity and pH and found stable for one month.

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