Research Article

DEVELOPMENT OF NOVEL NANOTRANSFERSOMAL GEL FOR THE INTRANASAL DELIVERY OF ROPINIROLE HYDROCHLORIDE FOR THE EFFECTIVE MANAGEMENT OF PARKINSONISM

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ABSTRACT

The aim of the study was to prepare Nanotransfersomal gel of Ropinirole hydrochloride for intranasal delivery for the treatment of Parkinsonism. The nanotransfersomes were prepared by thin-film hydration technique. The prepared formulations were optimized for type and concentration of edge activator. Span 60 and Tween 80 were selected as edge activators for the present study. The formulations were evaluated for vesicular shape, size, drug entrapment efficiency, zeta potential, deformability, in-vitro release. The optimized nanotransfersomes formulated with 85:15 soya lecithin: Tween 80 ratio exhibited particle size of 67.5 nm, percentage entrapment efficiency of 62.3%, zeta potential of -32 mV and deformability of 15.89%. The optimized nanotransfersomes of Ropinirole hydrochloride were formulated as Nanotransfersomal gel using Carbopol 934. A 0.4%W/V percentage Carbopol in-situ gel was optimized on the basis of evaluations like drug content, viscosity, pH, gelation study, in-vitro drug release and ex-vivo drug release. The in-vitro release studies of nanotransfersomal gel NG2 showed 90.32% drug release in 24 hours. The ex-vivo release studies performed through nasal mucosa goat showed 98.12% drug release in 24 hours.

Keywords: Ropinirole HCl, Parkinsonism, nanotransfersomal gel, intranasal delivery, in-situ gel, bioavailability

INTRODUCTION

Parkinson's disease is a neurodegenerative disorder of the brain that slowly develops in most people. The symptoms may take years to develop, and most people live for many years with this disease¹. The symptoms caused by Parkinson's include continuous loss of motor control including tremors, stiffness, slow motion, postural instability. Also includes a wide range of non-motor symptoms such as depression, loss of smell, gastric problems, and cognitive changes. The progressive degeneration of pigmented neurons in substantial nigra in Idiopathic Parkinson's disease results in dopamine deficiency. The neurochemical imbalance in the basal ganglia shows the characteristics and symptoms of the disease².

Ropinirole hydrochloride is a dopamine agonist used in the treatment of advanced Parkinson's disease caused by the deficiency of dopamine³. For the treatment of Parkinson's disease, the mechanism of the Ropinirole was considered to be associated with ability to stimulate the dopamine D2 receptors in the brain within the caudate-putamen region. The drug has an oral bioavailability of around 50 percent due to metabolism mainly by cytochrome P450 (CYP1A2) in the hepatic enzyme system. It has a biological half-life of 5 to 6 hours⁴.

Ultra-deformed vesicles known as nanotransfersomes is a new approach for the delivery of drugs consists of phospholipids and edge activators (EAs)⁵. They offer a number of advantages such as effective pharmaceutical carriers, controlled release of drugs, increased drug bioavailability, drug targeting and low toxicity. They have an ultra flexible two-layer membrane that gives high deformability to the vesicles, so they can be squeezed through

narrow pores in the stratum corneum (one-tenth of their own diameter) without occlusive conditions⁶.

Ropinirole, when administered intranasally, can bypass the metabolism occurring via hepatic first pass and therefore can increase the bioavailability⁷. The lipophilicity of the drug is low and therefore has less permeability. However, in the nanotransfersomes preparation, due to its structural specificity, increases the permeability. They also act as a depot, releasing their content slowly and gradually. This reduces the frequency of the dose and improves the patient's compliance. The nasal mucosa is considered as a potential route of administration to achieve a faster and higher level of drug absorption. This is due to the large surface, the porous endothelial membrane, the high total blood flow, the avoidance of metabolism of the first pass and ready access⁸.

The *in situ* gelation is a process of gel formation after application of the formulation on the site. It is achieved by the application of the drug solution to required site and turning it into semi-solid mucoadhesive depot. This preparation can be delivered in the form of a liquid or solution. The mucociliary clearance of the drug from the nasal cavity can be avoided by incorporating the nanotransfersomes in an in-situ forming gel and hence increasing its retention time in the nasal cavity⁹.

MATERIALS AND METHODS

Ropinirole hydrochloride was procured from Yarrow Chem products. Soya lecithin, Tween 80, Span 60 was procured from Sigma Aldrich. Carbopol 934 was purchased from HiMedia Laboratories. All other chemicals and solvents were of analytical grade.

Formulation of Ropinirole Hydrochloride Nanotransfersomes

The Ropinirole Nanotransfersomal vesicles were prepared by the thin film hydration technique. The composition of Ropinirole Nanotransfersomes was shown in table 1. The mixture consisting of phosphatidyl choline and surfactant (edge activators) in varying ratios (total weight 100mg) was dissolved in chloroform: methanol (2: 1) in a round bottom flask. The organic solvents were removed under vacuum in a rotary evaporator at 40 °C for 20 minutes to form a thin film inside the flask and stored in the desiccator under vacuum to make certain the complete removal of solvents¹⁰.

The required quantity of Ropinirole HCl was dissolved in 10ml of pH 4.5 phosphate buffer solution. It was then poured to the round bottom flask for hydration of film. The complete hydration of the dry film was obtained by rotation at 60 rpm for 1 h at room temperature. The resulting vesicles were sonicated for 10 min in a bath sonicator to reduce the size of the vesicles.

Evaluation of Ropinirole Hydrochloride Nanotransfersomes

Entrapment Efficiency

The entrapment efficiency of Ropinirole hydrochloride in Nanotransfersomal suspension was determined using centrifugation method. The 10 ml transfersomal suspension was taken in a centrifugal tube and centrifuged at 11000 rpm for 30 min. The total amount of untrapped drug was determined by removal of supernatant and diluting with phosphate buffer pH 6.4. The absorbance was determined at a wavelength of 249 nm by UV visible spectroscopy. The percentage of drug entrapped was determined using the formula¹¹

Percentage drug entrapment = $\frac{\text{Total amount of drug added} - \text{Untrapped drug}}{\text{Total amount of drug added}} \times 100$

In-vitro drug release study of Nanotransfersomes

The in-vitro drug release studies were performed using modified vertical diffusion tube (surface area: 2cm²). The nanotransfersomal suspension of different formulations equivalent to 3 mg drug was placed in the donor compartment. The receptor compartment was comprised of 50 ml of pH 6.4 Phosphate buffer. The temperature of the receptor compartment was maintained at 37 ±0.5°C under continuous stirring with magnetic bar at 100 rpm. The donor compartment was separated from the receptor compartment by pre hydrated cellophane membrane. At predetermined time intervals, 3ml aliquots were withdrawn from the sampling port and were replaced with an equal volume of fresh medium to maintain constant volume. The samples were filtered using 0.45µm syringe filter and analyzed for drug content by UV visible spectrophotometer at 249 nm after suitable dilutions. The cumulative amount of drug released across the cellophane membrane was determined as a function of time¹².

Fourier Transform Infrared Spectroscopy (FT-IR)

The compatibility and stability of drug in Nanotransfersomal formulation was evaluated using FT-IR peak matching method. The sample was prepared by triturating dried Nanotransfersomal preparation (NT2) with approximately 300 mg of dry finely powdered potassium bromide. The mixture was ground thoroughly and was spread uniformly in a suitable die and compressed under vacuum at a pressure of about 800 Mpa¹³. The prepared disc was then mounted on a suitable holder in the FTIR spectrophotometer. The spectrum was recorded in the wavelength range of 400-4000 cm⁻¹

Scanning Electron Microscopy

The morphologies of the prepared nanotransfersomes were characterized by using Scanning Electron Microscope. Based on the results of entrapment efficiency and drug loading, the optimum nanotransfersomes were subjected to SEM analysis. The solid samples were spread on a carbon tape, dried in vacuum, coated with gold and examined under the microscope to determine the surface morphology. For liquid samples were dried under vacuum and analyzed as that of solid samples¹⁴.

Vesicle Size and Zeta Potential

The average size of the vesicles and zeta potential was measured by light scattering method using a Malvern Zetasizer (Malvern, UK)¹⁵.

Formulation of Nanotransfersomal In-Situ intranasal gel of Ropinirole Hydrochloride

The in-situ intranasal gel of Ropinirole hydrochloride with varying concentrations of carbopol 934 (Table 2) was prepared by dispersing required quantity of carbopol in the optimised Nanotransfersomal dispersion with continuous stirring in magnetic stirrer at 500 rpm and keeping overnight for complete hydration¹⁶.

Evaluation of Nanotransfersomal intranasal In-Situ Gel

Determination of Physical characteristics, pH and Viscosity of In-Situ gel

The Nanotransfersomes based *in situ* gels were inspected visually for colour, feel, presence of clog and consistency. The pH was measured in by using a pH meter, which was calibrated before each use with standard buffer solutions before measurements. The electrodes were completely dipped into the formulations and pH was noted. The viscosity of developed Nanotransfersomal *in situ* gels were determined using Brookfield viscometer DV- II using Spindle no 52¹⁷.

Gelation studies

In-situ gelation is the process by which the liquid phase (sol) undergoes transition into gel. The gelling capacity of intranasal in-situ gel forming nanotransfersomal dispersion was evaluated. The dispersion has to get converted to an in-situ gel upon reaching the nasal pH. For gelation study, 5ml carbopol dispersed nanotransfersomal preparation was mixed with 0.5 ml of 0.5 M NaOH in 10 ml measuring cylinder to form a firm gel. The gelation was assessed by visual examination. The consistency of formed gel was checked and graded, as follows. The grades of gelation are given in table 3¹⁸.

In-Vitro drug release study of Nanotransfersomal intranasal In-Situ Gel

The in vitro drug release studies were performed using modified vertical diffusion tube (surface area: 2cm²). The nanotransfersomal in-situ gel equivalent to 3 mg drug was placed in the donor compartment. The receptor compartment was comprised of 50 ml of pH 6.4 Phosphate buffer. The temperature of the receptor compartment was maintained at 37 ±0.5°C under magnetic stirrer at 100 rpm. The donor compartment was separated from the receptor compartment by pre hydrated cellophane membrane. At predetermined time intervals, 2ml aliquots were withdrawn from the sampling port and were replaced with an equal volume of fresh medium to maintain constant volume. The samples were filtered using 0.45µm syringe filter and analyzed for drug content by UV visible spectrophotometer at 249 nm after suitable dilutions. The cumulative amount of drug released across the cellophane membrane was determined as a function of time¹⁹.

Ex-Vivo drug release study

The freshly excised sheep nasal mucosa except the septum part was collected in pH 6.4 phosphate buffer. After complete removal of the adhering mucosa, the intact membrane was kept in phosphate buffer pH 6.4 for 30 min to equilibrate. The excised superior nasal membrane was then mounted on vertical diffusion tube (surface area 2cm²)²⁰. The nanotransfersomal suspension of different formulations equivalent to 3mg drug was placed in the donor compartment. The remaining procedure was carried out similar to in-vitro drug release study. The cumulative amount of drug released across the sheep nasal mucosa was determined as a function of time²¹.

RESULTS AND DISCUSSION

Formulation of Ropinirole Hydrochloride Nanotransfersomes

Ropinirole nanotransfersomal vesicles were prepared according to the thin film hydration technique. Transfersomes consisted of phospholipid constituent along with a surfactant mixture. The ratio between the surfactants controls the flexibility of the vesicle. This type of drug carrier system can accommodate lipophilic, hydrophilic as well as amphiphilic drugs. Soya lecithin was used as the bilayer-forming agent. The edge activators used were span 60 and tween 80. The ratio between the phospholipid and surfactants were varied and different formulations were prepared. Formulations NS1 to NS4 were prepared with Span 60 as surfactant whereas formulations NT1 to NT4 were prepared with tween 80 as surfactant. The vesicles size was reduced after preparation by sonication in a bath sonicator for 10 min.

Evaluation of Ropinirole Hydrochloride Transfersomes

Entrapment Efficiency

The results of entrapment efficiency were given in table 4. The entrapment efficiency was found to be in the range of 30.48% to 71.11%. The entrapment efficiency was found to be higher for preparations using Span 60 as edge activator (EA).

It was observed that the drug entrapment efficiency increased with increase in surfactant concentration from 5% to 15%. This can be attributed to the growth of vesicular size resulting in the entrapment of more amount of drug. The entrapment efficiency was found to be decreased with further increase in edge activator above 15%. These suggest the formation of pores resulting due to dissolution of phospholipid bilayer in edge activator.

The formulation NS2 has shown maximum entrapment efficiency when compared with other formulations. The lipophilic nature of span 60 resulted in higher affinity for lipids, which contributed for higher drug entrapment when compared to the hydrophilic EA tween 80.

In-Vitro drug release study of Ropinirole Hydrochloride Nanotransfersomes

The in-vitro release studies were performed to study the drug release pattern from the prepared Ropinirole hydrochloride Nanotransfersomes. It was carried out using modified vertical diffusion tube. The drug release studies were carried out in pH 6.4 phosphate-buffer for a period of 24 hours.

The in-vitro release profile of Ropinirole HCl from transfersomes prepared from span 60 as edge activator with different phospholipid: edge activator ratios showed rapid drug release in the first few hours, due to the liberation of surface adsorbed drug on the nanotransfersomes, followed by a sustained release pattern up to 24 hours. The results were shown in figure 1.

The drug release from Nanotransfersomal formulations first increased with increase in span 60 concentrations from 5 to 15%, w/w (NS1 and NS2). The highest drug release (80.34%) was observed in the formulation containing 15% of span 60 (NS2), at the end of 24 hours because at this concentration the surfactant molecule gets associated with the phospholipid bilayer resulted in better partitioning of the drug, and resulted in higher drug release from the vesicles. But with further increase in edge activator concentration (NS3 and NS4) showed a decrease in drug release.

The in-vitro drug release of formulations NT1 to NT4 prepared using Tween 80 as edge activator was also carried out. The results were shown in figure 2. The formulation NT2 prepared using 15% edge activator showed a sustained release for 24 hours with a cumulative drug release of 98.33%. Further increase in edge activator concentration (NT3 and NT4) showed a decrease in drug release similar to formulations prepared with Span 60. At high edge activator concentrations, the release of the drug was less due to the formation of rigid mixed micelles and loss of vesicular structure.

The in-vitro drug release of formulations prepared with Tween 80 showed better drug release when compare to Span 60. It can be due to the increased fluidity of the lipid bilayer which resulted in improved drug permeability and release. The hydrophilic nature of Tween 80 enabled the hydrophilic drug moieties to pass through the lipid bilayer and also through the pores of the bilayer resulting in better drug release in comparison with that of Span 60.

Based on in-vitro drug release and entrapment efficiency, formulation NT2 was selected for further evaluations for the preparation of Nanotransfersomal gel.

The FT-IR spectroscopy was performed to analyze any change in the characteristics of Ropinirole hydrochloride in the prepared formulation (NT2) and also to identify any possible drug-polymer interactions (figure 3). All the major peaks present in the spectrum of pure Ropinirole hydrochloride were clearly observed in the spectra of formulation NT2. This indicated that there was no characteristic change of Ropinirole hydrochloride in the formulation (NT2) and excludes any possible drug polymer interaction.

Scanning Electron Microscopy (SEM)

The SEM analysis was performed for visualization of the morphology of transfersomes. It has shown to have a spherical shape and lies in nanometer size range (figure 4).

Vesicle size and Zeta potential

The vesicle size distribution of the optimized nanotransfersomes (NT2) showed a mean vesicle size of 460.3 nm and a polydispersibility index of 0.276 (figure 5). The low value of polydispersibility index indicates the narrow variation in the size range of vesicles. The zeta potential of the prepared transfersomal suspension was observed to be -32 mV (figure 6), suggesting, that the formulation was stable with respect to surface charge.

Formulation of Intranasal In-Situ Gel Containing Ropinirole Hydrochloride Nanotransfersomes

The optimized Nanotransfersomal formulation NT2 was selected for preparation of gel. Carbopol 934 was selected as the gelling agent for the formulation of Ropinirole hydrochloride Nanotransfersomes. The Carbopol 934 was used at three concentrations 0.2%, 0.4%, 0.6% W/V for formulations NG1, NG2, NG3 respectively. The Carbopol 934 was dispersed in to the nano transfersomal solution with continuous stirring in magnetic stirrer at 500 rpm and kept overnight for complete hydration.

Table 1. Composition of Ropinirole Hydrochloride Nanotransfersomes

Formulation code	Ropinirole hydrochloride (mg)	Soya lecithin: span 60	Soya lecithin: tween 80	Chloroform: methanol (2:1) ml
NS1	20	95:5	-	15
NS2	20	85:15	-	15
NS3	20	75:25	-	15
NS4	20	65:35	-	15
NT1	20	-	95:5	15
NT2	20	-	85:15	15
NT3	20	-	75:25	15
NT4	20	-	65:35	15

Table 2. Composition of Nanotransfersomal intranasal In-Situ Gel of Ropinirole HCl

Formulation Code	Ropinirole Hydrochloride Nanotransfersomal preparation (ml)	Carbopol 935 (%w/v)
NG1	10	0.2
NG2	10	0.4
NG3	10	0.6

Table 3. Grading of gelation

Sign	Gradation
-	No gelation occurred
+	Gelation occurred within few minutes and remained for few hrs
++	Gelation occurred immediately and remained for extend period
+++	Gelation occurred immediately and very stiff gel was formed

Table 4. % Entrapment Efficiency of Ropinirole Hydrochloride Nanotransfersomes

Formulation Code	% Entrapment Efficiency
NS1	52.37
NS2	71.11
NS3	64.37
NS4	49.84
NT1	48.3
NT2	62.3
NT3	42.1

Table 5: pH, Viscosity and Gelation of the Nanotransfersomal intranasal In-Situ gel

Formulation Code	Viscosity(cps)	pH	Gelation
NG1	980	4.56±0.05	+
NG2	1020	4.52±0.03	++
NG3	1051	4.58±0.06	+++

Figure 1. In-Vitro drug release profile of formulations NS1-NS4

Figure 2: In-Vitro drug release profile of formulations NT1-NT4

Figure 3: FT-IR spectrum of Pure Ropinirole HCl and formulation NT2

Figure 4: SEM images of Nanotransfersomes of Ropinirole Hydrochloride

	Size (d.nm):	% Intensity:	St Dev (d.nm):
Z-Average (d.nm): 460.3	Peak 1: 671.3	90.6	237.1
Pdl: 0.276	Peak 2: 105.6	9.4	19.93
Intercept: 0.775	Peak 3: 0.000	0.0	0.000
Result quality : Good

Figure 5: Vesicle size and Poly dispersibility index of Ropinirole hydrochloride Nanotransfersomes

Figure 6: Zeta potential of Ropinirole Hydrochloride Nanotransfersomes NT2

Figure 7. In-Vitro and Ex-Vivo drug release of intranasal Nanotransfersomal In-Situ gel formulation NG2

Evaluation of Formulated Nanotransfersomal In-Situ forming intranasal gel

Determination of Physical characteristics, pH and Viscosity of In-Situ gel

The prepared formulations showed acceptable colour, feel and absence of any clogs and possess required consistency. The pH of nanotransfersomal *in situ* gels formulations were found to be in the range of nasal physiological pH between 4.50 ± 0.05 to 4.58 ± 0.06 and the viscosities of the developed formulation were given in table 5. Viscosity is an important parameter of topical gels which impart better rheological property to them. The viscosity of the formulations increased with increase in carbopol concentration

Gelation studies

The gelation studies showed that formulation NG1 containing 0.2% concentration of carbopol 934P could form weak gel, while formulations NG2 (0.4%) showed good gelation (table 5). Formulation NG3 with 0.6% carbopol 934 P concentration formed a very stiff gel at physiological pH. Hence formulation NG2 was selected for further studies.

In-Vitro drug release study of Nanotransfersomal intranasal In-Situ gel

The in-vitro release studies for Ropinirole hydrochloride nanotransfersomal in-situ gel were carried out in phosphate-

buffer pH 6.4 for a period of 24 hours and the results were shown in figure 7. Based on the gelation studies, the formulation NG2 were selected for in-vitro drug release study. The in-vitro release data showed that formulation NG2 showed sustained release pattern with a Cumulative drug release of 90.32% at the end of 24 hours.

Ex-vivo drug release of Nanotransfersomal intranasal In-Situ gel

Based on in-vitro drug release, ex-vivo drug release study was carried out in sheep nasal mucosa for formulation NG2. It showed a higher drug release of 98.12% at the end of 24hrs (figure 7). The ex-vivo permeation studies provide valuable information about the product behaviour *in vivo*, since they indicated the amount of drug available for absorption. Ex-vivo data also suggested the possibility of in-vitro/ in-vivo correlation.

The ex-vivo release mechanism suggests that the vesicles enhances the penetrating ability of the drug, by opening new pores in the paracellular tight junction at the time when it enter into the nasal mucosa and thereby increase its fluidity. Besides this, the phospholipids have a high affinity for biological membranes which contribute to permeability enhancement of transfersomes.

The flexibility of the nanotransfersomes allows them to pass through the nasal mucosa more easily. Since the flexibility of the

membrane is extremely high. The membrane allows the nanotransfersomes to squeeze them even if the pore of membrane is smaller than the diameter of the Nanotransfersomes.

CONCLUSION

From the study, it can be concluded that the Ropinirole hydrochloride loaded intranasal in-situ nanotransfersomal gel NG2 can successfully cross mucous membrane and reach the systemic circulation and provide sustained drug release. It can thereby improve the patient compliance. The intranasal in-situ gel preparation can increase the bioadhesion on the mucous membrane and prevent mucociliary clearance without affecting the structure of nanotransfersomes and can effectively transport the drugs. The formulation can bypass the first pass metabolism and improve the bioavailability. It can be considered as an alternative to oral delivery, hence intranasal delivery of Ropinirole hydrochloride by nanotransfersomal intranasal in-situ gel can be a very promising approach for patients suffering from Parkinson's disease.

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