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Nanoparticle: design, characterization and evaluation for oral delivery of ropinirole hydrochloride

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ABSTRACT

The aim of the present study was to develop Ropinirole hydrochloride nanoparticle and to study its release profile. Ropinirole hydrochloride alleviates this deficiency by stimulating striatal dopamine receptors. Ropinirole hydrochloride has got complete but variable oral absorption with less bioavailability approximately 50%. Hence, nanoparticles of Ropinirole hydrochloride was developed to improve drug diffusion profile and hence the oral bioavailability. Ropinirole hydrochloride nanosuspension stabilised by poloxamer F-68 was first prepared by milling technique and was lyophilized to obtain nanoparticle using mannitol (1:1 w/v) as cryoprotectant. Developed nanoparticle was characterized for its particle size and size distribution, drug content and % drug entrapment. In vitro dissolution study using dissolution bag (12000 D) and ex vivo study in rat ileum were carried out using 0.1N hydrochloric acid as dissolution medium. Particle size, Zeta potential, % drug content and % drug entrapment of the nanoparticles of the Ropinirole hydrochloride were found to be 282nm±23, 54.9mV±9.36, 98.9±0.86% and 62±0.87% respectively. In vitro, ex vivo permeation study revealed that cumulative percentage drug permeated was found to be 73.7±1.9% and 65.26±1.1% in 24 hrs. From the results it could be considered that the developed ropinirole hydrochloride nanoparticles may be an alternative for the treatment of Parkinsonism.

Introduction

Nanotechnology is the application of science and technology to control matter at the molecular level. At the nanoscale level, the properties of matter are significantly different from their macroscopic bulk properties. Nanotechnology is also referred to the ability for designing, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale [1]. Nanoparticles are viewed as the fundamental building blocks of nanotechnology. They are the starting points for preparing many nanostructured materials and devices. Their synthesis is an important component of the rapidly growing research efforts in nanoscience and nanoengineering. The nanoparticles of a wide range of materials can be prepared by a number of methods. In synthesis and assembly strategies of nanoparticles or nanomaterials, precursors from liquids, solid or gas phase are used. The submicron size of nanoparticles offers numerous advantages over microparticles. Nanoparticles have relatively higher intracellular uptake compared to microparticles. In the last decade, significant effort has been made to develop nanoparticles for drug delivery [2]. Poloxamers are used in a variety of oral, parenteral, and topical pharmaceutical formulations, and are generally regarded as nontoxic and nonirritant materials. Poloxamers are not metabolized in the body .So it has been the choice of polymer for the preparation of the Nanoparticles [3].

Oral absorption of ropinirole hydrochloride is rapid and essentially complete. Bioavailability of Ropinirole hydrochloride is approximately 50% (36% to 57%) and average peak concentrations of the drug are achieved at a median time of 1.5 hours post dose. The bioavailability of Ropinirole hydrochloride was similar in both the fed and fasted state. As adjunctive treatment of *L*-dopa, Ropinirole hydrochloride enhances the efficacy of *L*-dopa, including control of "on-off" fluctuations and "end of dose" effects associated with chronic *L*-dopa therapy and permits reduction in daily *L*-dopa dose [4]. High aqueous solubility and low bioavailability lead ropinirole hydrochloride to comparatively less brain access.

So the investigation of the study was to develop a novel dosage form for the accomplishment of Ropinirole hydrochloride into brain for the treatment of Parkinsonism.

Materials & methods

Materials

Ropinirole Hydrochloride was obtained as gift sample from Alembic Pvt. Ltd. Baroda, Glycerine from Metro Golden Laboratories, SLS from QFC Fine Chem Industries, Poloxamer 188 (Grade F-68) from Ozone International, Mumbai. All the reagents used were of analytical reagent grade.

Methods

Preparation of nanoparticles

Ropinirole hydrochoride based nanoparticle was prepared by milling technique [5]. 2.1mg of Ropinirole hydrochloride was dissolved in 20ml of mixture of distilled water, glycerin (1%, v/v) and SLS (0.1%, w/v). Poloxamer F-68 (5%, w/v) was added to the above mixture at constant speed of 3500 rpm for 10 minutes in order to get the nanosuspension of Ropinirole hydrochloride. Different concentration of poloxamer F-68 were tried as 2%, 3%, 5% and 7% to develop a stable nanosuspension. The developed nanosuspension was then lyophilized using

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mannitol as cryoprotectant (1:1 w/v) to obtain nanoparticle [6] [7].

Characterization of nanoparticles

Particle size and zeta potential analysis

Droplet size and zeta potential measurement of developed Ropinirole hydrochloride nanoparticles were carried out by dynamic light scattering technique through Zetasizer HAS 3000 (Malvern Instruments Ltd., Malvern, UK) [8].

Percent Yield

Yield of the product was calculated by the following equation

$$\text{Product Yield} = \frac{\text{Weight of product}}{\text{Weight of drug and polymer}} * 100$$

Drug Content Analysis

Developed nanoparticles were analyzed for drug content by Shimadzu UV-Visible Spectrophotometer1800 at 250 nm after reconstituting the nanoparticles using the vehicle (distilled water), using which the nanoparticles are to be administered [9].

Drug Loading Capacity

Free Drug content was analyzed by adding 100ml of propylene glycol with 30 mg of nanoparticles (≈2.5 mg Ropinirole hydrochloride) and kept at room temperature for 24 hours. Filter the above solution through the Whatmann filter paper (0.45µm) and the filtrate was analyzed using Shimadzu UV-Visible spectrophotometer 1800 at 250 nm. Collect the residue on filter paper and dissolve it in 100ml of distilled water and analyze to find out drug loading capacity by UV-Visible spectrophotometer at 250 nm. After that the nanoparticles were centrifuged at 16,000 rpm and the drug loading capacity was analyzed in supernatant liquid by UV-Visible spectrophotometer at 250 nm.

$$\text{Drug loading capacity} = \frac{\text{[Total Drug Content-Free Drug Content]}}{\text{Amount of Drug Taken}} * 100$$

In-vitro drug release study:

In-vitro drug release study was carried out using dialysis bag (12,000 D) in a Modified Dissolution Apparatus equilibrated at 37±2ºC. The dialysis bag was soaked overnight in the dissolution medium i.e. distilled water. One end of the dialysis bag was tied and 30 mg of nanoparticles (≈2.5 mg Ropinirole hydrochloride) was put into it followed by tying up of another end. The dissolution bag was immersed in 250ml of dissolution medium and the process was carried out at 37±2ºC and at 50 rpm. 5ml of sample was withdrawn at 0, 0.5,1,2,3,4,5,19 and 24 hours, replaced with same volume of dissolution medium and was analyzed in triplicate by UV-Visible Spectrophotometer (1800) at 250 nm after required dilutions [10].

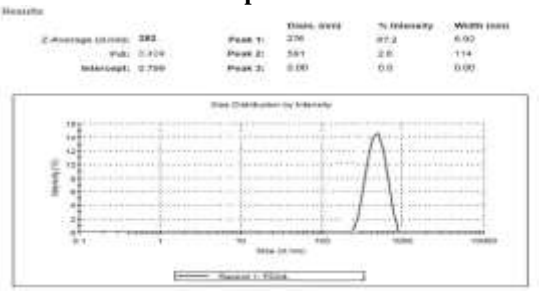
Ex-Vivo Drug Release Study

Ex-vivo drug release study was carried out using rat ileum in a Modified Dissolution Apparatus equilibrated at 37±2ºC. One end of the rat ileum was tied and 30 mg of nanoparticles (≈2.5 mg ropinirole hydrochloride) was put into it followed by tying up of another end. The rat ileum was immersed in 250ml of dissolution medium i.e., simulated intestinal fluid and the process was carried out at 37±2ºC and at 50 rpm with constant aeration. 5ml of sample was withdrawn at 0, 0.5,1,2,3,4,5,19 and 24 hours, replaced with same volume of dissolution medium and was analyzed in triplicate by Shimadzu UV-Visible Spectrophotometer 1800 at 250 nm after required dilutions.

Results and Discussion

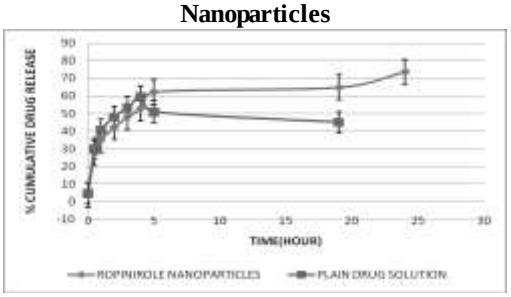
The average particle size was found to be 282nm± 50nm with PdI =0.424 as shown in Figure 1, suggests that the particle size data is significant. Zeta potential was found to be 29.4mV±1.24mV indicating the better stability of the developed formulation.

Figure 1: Average Particle Size of Ropinirole hydrochloride Nanoparticles



Drug content and drug loading capacity were found to be 98.9±0.86% and 62±0.87% respectively. In-vitro release results were found to be 73.7±1.9% in 24 hrs as shown in Figure 2.

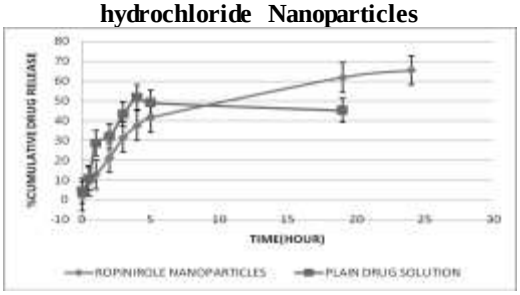
Figure 2: In-Vitro release study of Ropinirole hydrochloride Nanoparticles



Mean ± SEM values of 3 different estimations]

Ex-vivo diffusion results were found to be 65.26±1.1% in 24 hrs respectively and these results revealed that the release of Ropinirole hydrochloride from the formulation is more and sustained as compare to the Plain Drug Solution which release 60% of drug in 6 hrs as shown in Figure 3. The decrease in the percentage cumulative release in the ex-vivo study compared to in vitro may be due to the deposition of ropinirole hydrochloride in the intestinal wall of the rat ileum.

Figure 3: Ex-vivo diffusion study of Ropinirole hydrochloride Nanoparticles



[Mean ± SEM values of 3 different estimations]

Conclusion

The developed nanoparticles through milling technique were prepared with a view to get the sustain release of the Ropinirole hydrochloride following oral administration which may help to improve the patient compliance. The developed nanosuspension found to be physically stable with particles in nano range. Results from the investigation suggested that the Ropinirole hydrochloride nanoparticles represent a promising dosage form for oral drug delivery in dopamine insufficiency as compare to the conventional dosage form which might also reduce the side effects associated with the conventional dosage form. However, the findings of this investigation can only be settled after animal models experimentation followed by an extensive clinical evaluation.

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