Research Article

Formulation and Characterization of Fast Dissolving Sublingual Films of Ropinirole Hydrochloride for Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative condition affecting the central nervous system. It occurs due to the death of dopamine-generating cells in the substantia nigra. The treatment options of Parkinsonism include pharmacological, non-pharmacological and surgical treatments like deep brain stimulation but it may cause several bioavailability problems. The sublingual route is more acceptable for the treatment of CNS disorders due to their structural properties and the main advantage is improving bioavailability of poorly bioavailable drugs. The present study was focused on preparing fast dissolving sublingual films of Ropinirole hydrochloride for the treatment of parkinsonism. The Ropinirole have low oral bioavailability due to extensive first pass metabolism. The fast-dissolving sublingual films was prepared by Solvent casting method by using HPMC E5 LV as mucoadhesive polymer. Formulations were evaluated for various parameters such as Thickness, Weight variation, surface pH, folding endurance, disintegration and in vitro release studies. A five-fold increase in bioavailability was observed on sublingual administration as compared to IV route.

Keywords: Fast dissolving Sublingual films, Parkinson's disease (PD), Ropinirole hydrochloride, HPMC E 5 LV.

INTRODUCTION

Parkinson's Disease (PD) is a neurodegenerative disorder of the central nervous system, characterized by the loss of dopamine-producing neurons in the substantia nigra, a region of the midbrain. The etiology of this neuronal degeneration remains unclear.[1]

The primary objective of this study is to enhance the bioavailability of Ropinirole while minimizing patient discomfort by formulating it as fast dissolving sublingual films utilizing mucoadhesive gelling agents.

Sublingual films represent a specialized drug delivery system that is placed under the tongue, allowing for rapid dissolution and direct absorption into the bloodstream through the rich vascular network in the sublingual region. Orally dissolving films offer a novel pharmaceutical approach, providing a convenient and efficient means of drug administration. However, this technology has been underutilized, and its potential to address biopharmaceutical challenges of certain drug molecules has not been fully realized.[2]

Drugs administered via buccal or sublingual routes bypass first-pass metabolism, leading to improved bioavailability and rapid systemic circulation. Consequently, the combination of oral films with buccal or sublingual delivery presents an attractive strategy for delivering Ropinirole to PD patients. This method offers a straightforward means of drug administration without the need for water, providing swift drug action due to rapid disintegration and release. This is particularly beneficial for PD patients seeking to regain mobility and motor function.

Advantages of fast dissolving sublingual films[3]:

- Ease of administration for patients who have difficulty swallowing tablets, such as pediatric, geriatric, and psychiatric populations.
- Greater convenience and precision in dosing compared to liquid formulations.
- Elimination of the need for water during administration, ideal for patients on the move.
- Improved palatability, helping to shift the perception of medication away from the notion of "bitter pills," especially among children.
- Quick dissolution and absorption, resulting in a fast onset of action.
- Enhanced drug absorption via the oral mucosa, pharynx, and esophagus as saliva passes into the stomach, further increasing bioavailability.
- The solid dosage form combines the benefits of liquid formulations, while pre-gastric absorption can enhance clinical efficacy and reduce adverse effects through lower dosages.[3]

Disadvantages of fast dissolving sublingual films[3]:

- Sublingual administration may interfere with eating, drinking, and speaking, making it unsuitable for extended use.

- The sublingual site is not well-suited for sustained-release systems.
- Smoking can cause vasoconstriction of blood vessels, potentially diminishing the effectiveness of sublingual medications.[3]

MATERIALS AND METHODS

Analysis of drug:

Physical appearance

The physical characteristics of the drug are evaluated based on various organoleptic properties.

Identification by FT-IR Spectroscopy

The IR spectrum of Ropinirole hydrochloride is obtained and compared to a reference spectrum. A sample is prepared by triturating 10 mg of the drug with approximately 300 mg of dry, finely powdered potassium bromide. The mixture is ground thoroughly, compressed under vacuum, and scanned in the range of 400-4000 cm^{-1} using an IR spectrophotometer.[4]

Determination of melting point

A fine powder of the drug is packed into a glass capillary tube, with a thermometer attached. The system is immersed in liquid paraffin, and the temperature is recorded when the sample becomes completely liquid, indicated by a clear meniscus.[5]

Loss on drying

A glass stoppered weighing bottle is weighed, and 1 g of Ropinirole hydrochloride is added. After recording the initial weight, the sample is dried in an oven at 105^{0}C for 3 hours. The final weight is measured to determine the loss on drying.[8]

Determination of λmax of Ropinirole hydrochloride

A stock solution of 100 µg/ml of Ropinirole is prepared in pH 7.2 phosphate buffer. The absorption spectrum is recorded using a UV-visible spectrophotometer from 200-400 nm.[6]

Preparation of standard calibration curve of Ropinirole hydrochloride in phosphate-buffer pH 7.2

To prepare the standard calibration curve for Ropinirole hydrochloride in a pH 7.2 phosphate buffer, dissolve 6.8 g of potassium dihydrogen phosphate and 0.464 g of sodium hydroxide in water to make a final volume of 1000 ml.

Standard Calibration curve of Ropinirole hydrochloride in pH 7.2, phosphate buffer

A known quantity (100 mg) of pure Ropinirole is accurately weighed and transferred into a 100 ml volumetric flask, dissolved, and diluted with phosphate buffer to yield a stock solution of 1000 µg/ml. Aliquots of 0.4, 0.8, 1.2, 1.6, 2.0, 2.4, 2.8, and 3.2 ml are transferred into separate 100 ml volumetric flasks, with the volume made up to 100 ml using phosphate buffer pH 7.2. The absorbance of these solutions is measured spectrophotometrically at 249 nm.[7]

Preparation of fast dissolving sublingual films

Solvent casting method:

The drug and various excipients are dissolved in a suitable solvent, while water-soluble polymers are also dissolved separately. The two solutions are then combined and agitated, followed by degassing to remove air bubbles. The final bubble-free solution is cast into a Petri dish and allowed to dry. The resulting films dissolve easily in saliva, avoiding the formation of insoluble materials.[7]

Table 1: Composition of Ropinirole Hydrochloride Fast Dissolving Sublingual Films

Formulation code	Drug Loaded (mg)	HPMC E 5 LV (%)	Propylene Glycol (ml)	Saccharine Sodium (mg)	Water (ml)
F1	20	0.6	0.1	40	10
F2	20	0.8	0.1	40	10
F3	20	1.0	0.1	40	10
F4	20	1.2	0.1	40	10
F5	20	1.4	0.1	40	10

Evaluation parameter of fast dissolving sublingual film:

Thickness:

The film thickness was assessed using a digital Vernier calliper with a least count of 0.01 mm. Measurements were taken at three different locations on the film, and the average was calculated along with the standard deviation. [8]

Weight variation:

Samples of 4 cm^2 (2 x 2 cm) were cut from three distinct areas of the cast film, and the weight of each sample was measured to determine weight variation. [9]

Folding endurance:

Folding endurance was evaluated by repeatedly folding the film at the same location until it broke. The number of folds completed before breaking was recorded as the folding endurance value.[10]

Tensile strength:

Tensile testing involved cutting the film into strips measuring 30 x 20 mm. Each strip was adhered to a glass slide using Feviquick, with an initial grip separation of 20 mm. The test concluded when the film broke. Tensile

strength was calculated using the load required to break the film divided by its cross-sectional area.[11]

Tensile Strength=Force at break (N)/ Cross sectional area(mm^2)

Tensile strength (TS):

Tensile strength refers to the maximum stress applied until the film specimen breaks, calculated by dividing the maximum load by the original cross-sectional area and expressed in MPa.

Surface pH:

The surface pH of the fast-dissolving film was measured to assess the potential for oral mucosal irritation. A combined pH electrode was used after slightly wetting the film. Measurements were conducted in triplicate, and the average with standard deviation was reported.[12]

Disintegration Time:

The disintegration time of the film was visually evaluated in a petri dish containing 25 ml of phosphate buffer at pH 7.2, with stirring occurring every 10 seconds. This time is defined as the moment when the film begins to break apart.[13]

% Drug Content:

For the assessment of drug content, a 4 cm^2 film was dissolved in 100 ml of the same a pH 7.2 phosphate buffer using a magnetic stirrer for one hour. The concentration of the drug was then measured spectrophotometrically at 249 nm, and the procedure was repeated three times to calculate the average and standard deviation.[14]

***In vitro* dissolution**

Dissolution studies were conducted using a USP Type I (Basket type) apparatus, with the process performed in 900 ml of pH 7.2 phosphate buffer maintained at 37°C at 50 rpm. Samples were taken at various time intervals and analysed spectrophotometrically at 249 nm, with results expressed as the mean of three determinations.[15]

RESULTS AND DISCUSSION

Preformulation study

Analysis of drug

Analysis of drug Appearance

Ropinirole hydrochloride appeared as a crystalline white to off-white powder, in accordance with IP standards.

Melting point determination:

The melting point was determined using the capillary melt method, and observed melting point was found to be 241.6±0.40°C. The determined melting point was found to be within the range of the reported melting point.

Loss on drying

The loss on drying was recorded at less than 0.5%.

Determination of λ max

The UV spectrum analysis indicated that the maximum absorbance (λmax) of Ropinirole hydrochloride was at 249 nm in pH 7.2 phosphate buffer.

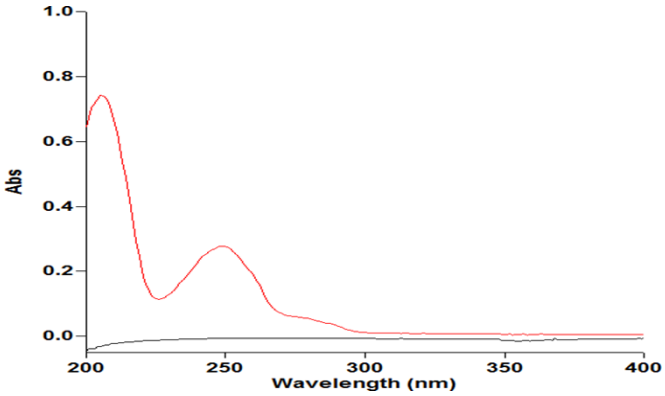

Figure 1: Determination of λmax of Ropinirole hydrochloride

Preparation of standard calibration curve

A standard calibration curve for Ropinirole hydrochloride in phosphate buffer pH 7.2 was prepared, showing a linear relationship with absorbance measured at 249 nm:

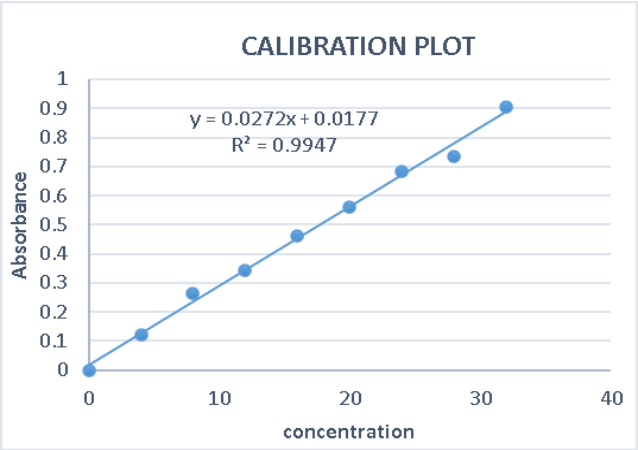

Figure 2: Standard calibration curve of Ropinirole hydrochloride in saline pH 7.2 Phosphate buffer

The plot of concentration versus absorbance graph showed a linear relationship with R^2 value of 0.9947(Fig: 2). Hence Beer-Lambert's law was obeyed.

Formulation of fast dissolving sublingual films:

Figure 3: Fast dissolving sublingual films

Evaluation of fast dissolving sublingual films

Table 2: Thickness, Weight variation, Folding endurance and Surface pH of prepared Fast Dissolving Sublingual Films

Formulation Code	Thickness (mm)	Weights (mg)/4cm^2	Folding Endurance (no. of times to break)	Surface pH
F1	0.98±0.0055	49.22±0.371	203 ± 3.69	6.84 pH
F2	0.110±0.0055	51.34 ±0.489	215 ± 2.12	7.28 pH
F3	0.076±0.0008	63.48±0.569	243 ± 9.15	7.04 pH
F4	0.090±0.0055	66.68±0.421	231 ± 7.60	7.35 pH
F5	0.123±0.0008	60.89±0.451	225 ± 5.10	7.38 pH

Table 3: Disintegration time and drug content of prepared Fast Dissolving Sublingual Films

Formulation code	Disintegration time in seconds	Drug content (%)
F1	27.13±0.53	99.16 ± 0.23
F2	22.07±0.53	99.23 ± 0.36
F3	20.05±0.53	100.33 ± 0.24
F4	30.20±1.02	99.01 ± 0.12
F5	32.63±0.53	99.47 ± 0 .27

***In vitro* dissolution:**

Table 4: *In vitro* releases of sublingual films

Time In Mins	%CDR F1	%CDR F2	%CDR F3	%CDR F4	%CDR F5
0	0	0	0	0	0
2	39.37	52.7	53.4	14.8	56.3
4	66.3	68.9	73.8	28.9	68.7
8	73.9	80.8	89.3	30.91	80.69
10	86.76	89.89	91.48	42.76	89.67

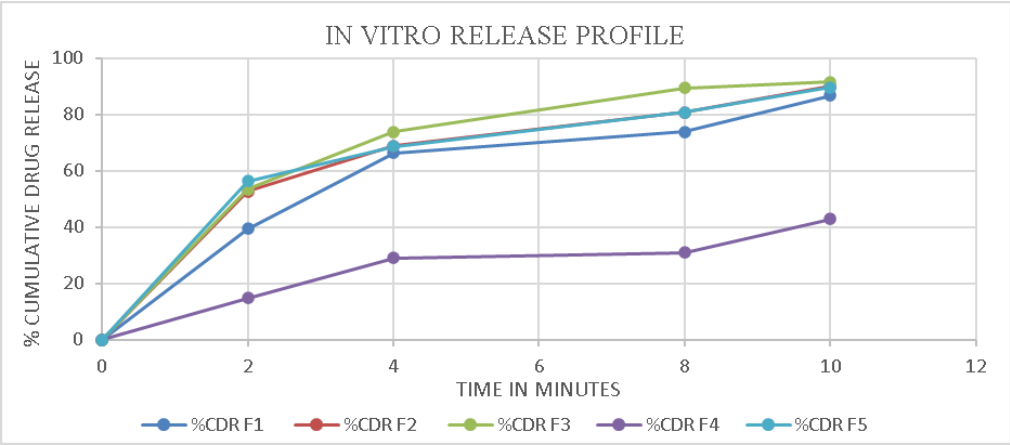

Figure 4: Fast dissolving sublingual film In vitro release profile at pH 7.2 Buffer

CONCLUSION

This study highlighted the considerable potential of Ropinirole hydrochloride fast-dissolving sublingual films in overcoming bioavailability challenges and first-pass metabolism.

Ropinirole hydrochloride was analysed using FT-IR spectroscopy, confirming its compatibility with the formulation. The sublingual films were successfully prepared using the solvent casting method with HPMC E 5 LV as the polymer. Different concentrations of HPMC E 5 LV (0.6%, 0.8%, 1%, 1.2%, and 1.4%) were evaluated to

optimize drug permeability. Among the formulations, F3, which contained 1% HPMC E 5 LV, exhibited a thickness of 0.076 ± 0.0008 mm, a neutral pH of 7.04, and impressive folding endurance of 243 ± 9.15 folds. Additionally, formulation F3 demonstrated a rapid disintegration time of 20.05 ± 0.53 seconds in pH 7.2 phosphate buffer, achieving a maximum drug content of 100.33 ± 0.24%. *In vitro* release studies for formulation F3 showed a cumulative drug release of 91.48% in pH 7.2 phosphate buffer within 10 minutes.

In conclusion, the development of Ropinirole hydrochloride fast-dissolving sublingual films utilizing HPMC E5 EV as a polymer demonstrated significant promise in improving drug delivery and patient adherence. The formulation effectively addressed bioavailability issues associated with traditional oral dosage forms by facilitating rapid dissolution and absorption, thereby bypassing first-pass metabolism. The use of HPMC E5 EV contributed to optimal film properties, ensuring a pleasant taste and suitable mechanical strength, which are crucial for patient acceptance. Overall, this innovative delivery system not only enhances the therapeutic effectiveness of Ropinirole hydrochloride but also represents a practical solution for patients requiring frequent dosing, ultimately improving their quality of life.

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