ORIGINAL ARTICLE

Selection of Absorption Site of Ropinirole Hydrochloride in the Gastrointestinal Tract Based on its Solubility in Different Physiological Media

Koyel Kar[1], R. N. Pal[2], N. N. Bala[3]

[1]Department of Pharmaceutical Chemistry, BCDA College of Pharmacy and Technology, Barasat, West Bengal, India, [2]Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology and Allied Health Sciences, Uluberia, West Bengal, India, [3]Department of Pharmaceutics, BCDA College of Pharmacy and Technology, Barasat, West Bengal, India

Abstract

Aim: This research work is an attempt to select a suitable absorption site in the gastrointestinal tract for ropinirole hydrochloride for its maximum therapeutic efficacy and stability and for the development of a suitable modified dosage form. **Settings and Design:** Ropinirole hydrochloride is commercially available as conventional tablets for oral administration, but its absorption rate varies from stomach to intestine due to the different surface area, blood flow rate, and pH. It was attempted to select a suitable absorption site in the gastrointestinal tract for ropinirole hydrochloride for its maximum therapeutic efficacy and stability and for the development of a suitable modified dosage form. In these work, three different physiological media such as saliva, gastric fluid, and intestinal fluid were chosen for solubility study. **Materials and Methods:** Ropinirole hydrochloride tablets, sodium hydroxide, potassium dihydrogen phosphate, salivary fluid, gastric fluid, and intestinal fluid were the important materials and Shimadzu ultraviolet (UV)-visible spectrophotometer 1601 and shaker incubator were the equipment used for the determination of absorption site. **Statistical Analysis Used:** UV spectrophotometric method was used for the determination of its solubility in various physiological media. **Results and Discussion:** From solubility studies, it was found that ropinirole hydrochloride showed the highest solubility in intestinal fluid. Solubility studies were performed in triplicate. **Conclusion:** Ropinirole hydrochloride showed the highest solubility in intestine. Hence, the formulation would be modified in such a way so that the drug is absorbed in the intestine.

Key words: Absorption site, gastric fluid, intestinal fluid, modified dosage form, ropinirole hydrochloride, saliva, solubility study, therapeutic efficacy and stability, ultraviolet spectrophotometric method

INTRODUCTION

Ropinirole hydrochloride is an orally administered specific D_2 and D_3 receptor non-ergoline dopamine antagonist. Chemically, it is 4-(2-dipropylaminoethyl)-1,3-dihydroindol-2-one hydrochloride [Figure 1]. It is used in the treatment of early and advanced Parkinson's disease caused by the deficit of dopamine. It has a high relative *in vitro* specificity and acts by binding with higher affinity to D_3 than to D_2 or D_4 receptor subtypes. The drug is listed in Merck Index,[1] Martindale the complete drug reference.[2]

The rate of absorption of a drug largely depends on concentration gradient, effective surface area, pKa (logarithmic acid dissociation constant value) and $K_{m/w}$ of the drug.[3] Neutral pH (negative logarithm of hydrogen ion concentration) of mouth saliva allows the permeability of many compounds due to lack of pancreatic major enzymatic activities. The oral drug delivery is the most desirable route for the drug administration whenever systemic effects are intended, but oral bioavailability of some drugs has promoted the search of more effective route for the systemic delivery.[4-7] The composition of various media used are:

Address of correspondence:
Koyel Kar, Department of Pharmaceutical Chemistry, BCDA College of Pharmacy and Technology, 78, Jessore Road South, Kolkata - 700 127, Hridaypur, India.
E-mail: koyel20@gmail.com

Received: 06-04-2017
Revised: 20-04-2017
Accepted: 26-04-2017

- Salivary fluid: 99.5% water, electrolyte, mucus, antibacterial compound, and various enzyme. pH ranges between 5 and 6.
- Gastric fluid: Majority is hydrochloric acid. Pepsin, renin, mucus, amylase, and water are also present in small quantity. pH ranges between 1 and 3.
- Intestinal fluid: Colipase, bile salts, hormones, digestive enzymes, and mucus. pH ranges between 7.4 and 7.6.

Various analytical procedures have been proved to be a useful tool for the determination of absorption site in the body. These procedures help us to measure the concentration of drug present in a solution. This research involves the use of ultraviolet (UV)-spectrophotometric methods for the determination of drug concentration in the above-mentioned physiological media.[8]

The aim of this study is to select a suitable absorption site in the gastrointestinal tract for ropinirole hydrochloride for its maximum therapeutic efficacy and stability by determining its concentration in saliva, gastric fluid, and intestinal fluid using UV-spectrophotometric method. The objective of this study is to determine the suitable absorption site in the gastrointestinal tract for the development of a suitable modified dosage form.

MATERIALS AND METHODS

Ropinirole hydrochloride is the free sample provided by Central Drug Laboratory, Kolkata. Sodium hydroxide and potassium dihydrogen phosphate were purchased from Roy Scientific Enterprises, Kolkata, India. The pure drug is of standard quality complying with official monographs.

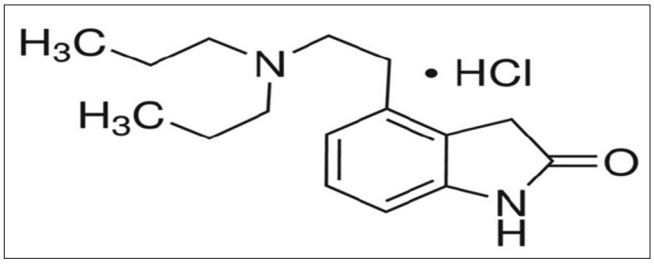

Figure 1: Chemical structure of ropinirole hydrochloride

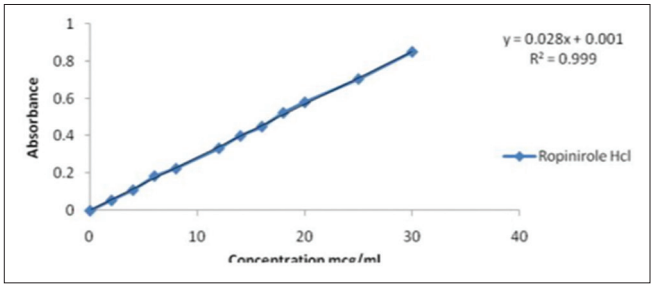

Figure 2: Standard curve of ropinirole hydrochloride in pH 7.4 phosphate buffer at 250 nm

All the chemicals used for the analysis are analytical grade complying with official standards.

Preparation of phosphate buffer[9,10]

About 7 g of potassium dihydrogen orthophosphate was weighed accurately and dissolved in about 500 ml of distilled water and diluted with distilled water up to 1000 ml and the pH was adjusted up to 7.4 with the solution of sodium hydroxide. The final solution was filtered through 0.45 µ Whatman filter paper. This buffer solution was used as diluent.

Preparation of standard curve of ropinirole hydrochloride in phosphate buffer (pH 7.4)[9,10]

About 100 mg of the pure drug was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and diluted to volume with pH 7.4 phosphate buffer to give stock solution containing 1000 mcg/ml. The standard stock solution was then serially diluted with pH 7.4 phosphate buffer to get 2,4,6,8,12,14,16,18,20,25, and 30 mcg/ml (2, 4, 6, and 8) and the absorbance of the solution was measured against pH 7.4 phosphate buffer (Table 1) as the blank at 250 nm using UV-spectrophotometer. The absorbance was plotted against concentration (mcg/ml) to obtain the standard calibration curve (Figure 2 and Table 2).

Table 1: Standard curve of ropinirole hydrochloride in pH 7.4 phosphate buffer at 250 nm

Concentration (mcg/ml)	Absorbance at 250 nm
2	0.055
4	0.110
6	0.185
8	0.225
12	0.334
14	0.400
16	0.450
18	0.524
20	0.580
25	0.705
30	0.850

Table 2: Summary of parameters

Parameters	Measurements
λ_{max}	250 nm
Regression equation	y=0.028x+0.001
Linearity range	2-30 mcg/ml
Slope (m)	0.028
Intercept (c)	0.001
Correlation coefficient (R^2)	0.999

Table 3: Solubility of ropinirole hydrochloride in various physiological medium (at 250 nm)

Solvent used	Measured absorbance	Measured quantity	Mean±SD	LOQ	LOD
Salivary fluid	0.230[a]	7.45	7.47±0.0406	14.50	4.35
	0.232[b]	7.52			
	0.230[c]	7.45			
Gastric fluid	0.132[a]	4.28	4.30±0.0346	12.35	3.70
	0.134[b]	4.34			
	0.132[c]	4.28			
Intestinal fluid	0.338[a]	10.90	10.97±0.0624	22.28	6.68
	0.340[b]	11.02			
	0.339[c]	10.99			

[a]recorded data of absorbance value when salivary fluid was introduced into the UV spectrophotometer for the first time given by UV spectrophotometer, [b]recorded data of absorbance value when salivary fluid was introduced into the UV spectrophotometer for the second time given by UV spectrophotometer, [c]recorded data of absorbance value when salivary fluid was introduced into the UV spectrophotometer for the third time given by UV spectrophotometer. LOQ: Limit of quantification, LOD: Limit of detection, SD: Standard deviation

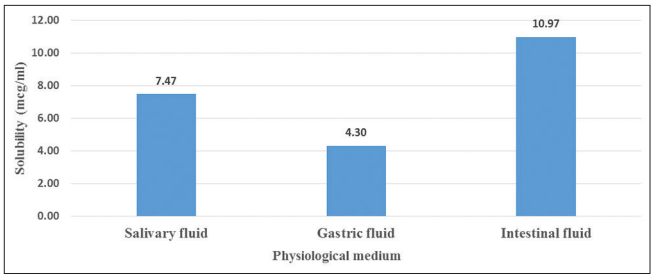

Figure 3: Graphical representation of ropinirole hydrochloride in various physiological medium

Preparation of saturated solution of ropinirole hydrochloride in various physiological media

Excess amount of drug was added to saturated solutions of stimulating fluid (saliva, gastric fluid, and intestinal fluid) each in a 5 ml capacity stoppered vials. They were shaken on the rotary shaker bath for 48 h at 25°C under constant vibration at 100 rpm. Each filtered sample was diluted appropriately with phosphate buffer pH 7.4 and was determined spectrophotometrically from 200 to 400 nm (Table 3). The average value of three trials was taken. The stimulating fluid which could solubilize the highest concentration of drug was selected as the targeted area for the administration of modified dosage forms.

RESULTS AND DISCUSSION

This study was undertaken to select a suitable absorption site for ropinirole hydrochloride in the gastrointestinal tract. This study involves the determination of concentration of drug in the physiological fluids spectrophotometrically. Results and discussion of the above studies are presented below.

Sensitivity

The limit of detection (LOD) and limit of quantification (LOQ) were calculated using the equations LOD = 3 × σ/S and LOQ = 10 × σ/S, where σ is the standard deviation of intercept and S is the slope. The LOD of salivary fluid, gastric fluid, and intestinal fluid was found to be 4.35 µg/ml, 3.70 µg/ml, and 6.68 µg/ml, respectively (Table 3). The LOQ of salivary fluid, gastric fluid, and intestinal fluid was found to be 14.50 µg/ml, 12.35 µg/ml, and 22.28 µg/ml, respectively (Table 3).

Solubility

Solubility of ropinirole hydrochloride in various physiological fluids is shown in Figure 3. From solubility studies, it was found that ropinirole hydrochloride showed the highest solubility in the intestinal fluid and intermediate and lowest solubility in the salivary and gastric fluid, respectively. Solubility studies were performed in triplicate.

CONCLUSION

The main objective of this study is to design a suitable absorption site in the gastrointestinal tract for the development of a suitable modified dosage form. The concentration of drug in each physiological fluid was evaluated spectrophotometrically. The results of UV-spectrophotometric analysis confirmed the presence of more concentration of drug in the intestinal fluid compared to gastric and salivary fluid. Hence, the formulation would be modified in such a way so that the dose will deliver the maximum drug to the intestine.

ACKNOWLEDGMENTS

The authors are highly thankful BCDA College of Pharmacy and Technology, Barasat and Bharat Technology, Uluberia, India, for providing all the facilities to carry out the research work.

REFERENCES

1. Budavani S, editor. In: The Merck Index. 13th ed. White House Station, NJ: Merck Co. Inc.; 2002. p. 454.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 34th ed. London: The Pharmaceutical Press; 2002. p. 1313.
3. Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures. Chem Pharm Bull 1961;9:866-72.
4. Martin A. Solubility and Distribution Phenomena. 6th ed. Baltimore, Philadelphia, PA: Physical Pharmacy and Pharmaceutical Sciences, Lippincott Williams and Wilkins; 2011.
5. Myrdal PB, Yalkowsky SH. Solubilization of drugs in aqueous media. Encyclopedia of Pharmaceutical Technology. New York, NY, USA: Informa Health Care; 2007. p. 3311.
6. Lachman L, Lieberman H, Kanig JL. The Theory and Practise of Industrial Pharmacy. 3rd ed. Philadelphia, PA: Lea & Febiger; 1986.
7. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: *in vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 2008;69:993-1003.
8. International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceutics for Human Use. Validation of Analytical Procedures Methodology. Geneva: ICH-Q2 (R1); 1996. p. 1-8.
9. Kumudhavalli MV, Anandababu K, Jaykar B. Validated spectrophotometric determination of ropinirole hydrochloride in formulation. Asian J Biochem Pharm Res 2011;1:302-6.
10. Susheel JV, Malathi S, Ravi TK. Analysis of ropinirole hydrochloride in tablet. Indian J Pharm Sci 2007;69:589-90.

Source of Support: Nil. **Conflict of Interest:** None declared.