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Development and In Vitro Evaluation of Buccal Effervescent Tablet Containing Ropinirole Hydrochloride

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Abstract

The buccal delivery is an attractive route to improve the clinical efficacy of ropinirole hydrochloride (RH) for the treatment of Parkinson and restless syndrome since this drug undergoes extensive first-pass effect, which has only 50% bioavailability after oral administration. The purpose of this study was to develop and optimize the formulation of fast disintegrating buccal effervescent tablets of RH using four types of superdisintegrants. The direct compression method was used to develop four different formulas containing RH using Kyron T-314, crospovidone, croscarmellose sodium, and sodium starch glycolate separately as a superdisintegrant. Sodium bicarbonate and citric acid were added to the formulations to produce effervescence, while sodium carbonate was used as a pH adjusting agent. All the prepared formulas were evaluated, in terms of weight variation, friability, content dose uniformity, hardness, disintegration, and dissolution test. The best formulation was selected for the subsequent study. The obtained results from pre-compression studies were in acceptable range according to British Pharmacopoeia. All formulas passed through the quality control test and significant difference ($P < 0.05$) was observed for the formula four compared to other formulas, due to the presence of Kyron T-314 as a superdisintegrant in formulation number 4. RH could be prepared as a buccal effervescent tablet and superdisintegrant provide fast disintegration of the tablet to exert rapid action.

Keywords

Buccal delivery, Kyron T-314, Ropinirole hydrochloride, Superdisintegrants

RESEARCH ARTICLE

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ABSTRACT

The buccal delivery is an attractive route to improve the clinical efficacy of ropinirole hydrochloride (RH) for the treatment of Parkinson and restless syndrome since this drug undergoes extensive first-pass effect, which has only 50% bioavailability after oral administration. The purpose of this study was to develop and optimize the formulation of fast disintegrating buccal effervescent tablets of RH using four types of superdisintegrants. The direct compression method was used to develop four different formulas containing RH using Kyrone T-314, croscopolidone, croscarmellose sodium, and sodium starch glycolate separately as a superdisintegrant. Sodium bicarbonate and citric acid were added to the formulations to produce effervescence, while sodium carbonate was used as a pH adjusting agent. All the prepared formulas were evaluated, in terms of weight variation, friability, content dose uniformity, hardness, disintegration, and dissolution test. The best formulation was selected for the subsequent study. The obtained results from pre-compression studies were in acceptable range according to British Pharmacopoeia. All formulas passed through the quality control test and significant difference ($P < 0.05$) was observed for the formula four compared to other formulas, due to the presence of Kyrone T-314 as a superdisintegrant in formulation number 4. RH could be prepared as a buccal effervescent tablet and superdisintegrant provide fast disintegration of the tablet to exert rapid action.

Keywords: Buccal delivery; Kyrone T-314; Ropinirole hydrochloride; Superdisintegrants

INTRODUCTION

Despite the oral route for drug delivery being convenient due to ease administration with low cost, while the oral route is not efficient for delivery of drugs which are unstable in gastrointestinal tract or undergo massive hepatic effect. Per-oral drug administration also needs time to reach the systemic circulations to exert its action. Drug delivery through oral mucosa is considered to be a promising alternative to the oral route, as buccal mucosa provides drug absorption directly to the systemic circulation without passing through the liver, and fast effect. Therefore, this route is suitable for the administration of the therapeutic agents which are susceptible to the enzymatic degradation in the gastrointestinal tract following oral administration (Bhimani et al., 2014).

Focusing on the development of oral disintegrating tablets has increased as it improves drug absorption and patient compliance. Tablets are designed to be disintegrated rapidly on contact with saliva and enable oral administration without water or chewing. This route is important when swallowing of conventional solid oral dosage forms presents difficulties and the drugs less bioavailable (Durfie et al., 2006).

Strategies to develop a novel delivery system such as OraVescent to enhance drug absorption through the oral mucosa this may enable more rapid absorption of drugs and improving patient compliance (Jany et al., 2012).

OraVescent tablet is an oral transmucosal delivery system. It contains effervescent materials besides other tablet components. It is intended to be placed in the oral cavity where it is allowed to disintegrate and provides drug release over a short time. OraVescent technology has been reported potentially enhanced transmucosal permeability of some drugs caused by the liberation of carbon dioxide; as a result chemical reaction between acidic and basic components of tablet during disintegration and dissolution process after contact with saliva, then produces a transient pH changes of the oral cavity (Velmurugan et al., 2010).

The liberation of carbon dioxide produces a modest decrease in the pH of the tablet environment. For weakly basic drugs, a lower pH (below its pKa) accelerates drug dissolution and favors the drug molecules in ionized form. The pH in the tablet environment increases when pH-modifying materials present in the tablet (e.g., sodium carbonate) dissolves; the ionized drug molecules convert predominantly to the un-ionized form, which can be more

permeable to the biological membrane and can result in higher drug absorption (Wolfgang and Angersbach, 2005).

Ropinirole hydrochloride (RH) is a non-ergoline dopamine agonist which has been proven to be effective in idiopathic Parkinson's disease and restless legs syndrome. In addition to reducing bradykinesia, tremor, and rigor, ropinirole improves the daily life and depressive moods of patients with Parkinson's disease (Wolfgang and Angersbach, 2005).

The main problem of RH after oral administration is low bioavailability (50–55%). It has been reported RH undergoes massive hepatic metabolism (Rao, 2013).

Polacrillin potassium (Kyron T-314) is 2-methyl-2-propenoic acid polymer with divinylbenzene, potassium salt. It is used as a fast disintegrating agent in oral pharmaceutical formulations to facilitate the disintegration of tablets and the dissolution of drug molecules (Rowe et al., 2006).

The aim of this study was to prepare fast disintegrating buccal tablets of RH using four different types of superdisintegrants: Kyron T-314, crospovidone (CP), croscarmellose sodium, and sodium starch glycolate (SSG) to improve drug permeation through oral mucosa.

MATERIALS AND METHODS

Materials

Ropinirole HCl was supplied by Apollo healthcare, Singapore. Kyron T-314 was donated by Corel Pharma Chem, India. SSG, croscarmellose sodium, microcrystalline cellulose, and CP were supplied from Sigma-Aldrich Ltd, UK. Sodium bicarbonate, citric acid, sodium carbonate, and magnesium stearate were from Scharlau Chemie Spain.

Methods

Determination of melting point

The melting point of RH was determined by a capillary tube method using electrical melting point apparatus (Stuart, Copley Scientific, UK).

Determination of λ max

To determine λ max of RH, a solution of RH 10 μ g/ml in distilled water was prepared, then scanned using UV spectrophotometer (JENWAY 6305, UK).

Preparation of calibration curve of ropinirole

A stock solution of RH was prepared by dissolving 10 mg of RH powder in 100 ml of distilled water. A series of different concentrations of RH solutions (10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 μ g/ml) were prepared from the stock solution. The prepared solutions were scanned

spectrophotometrically at 249 nm against blank solvent (Kumudhavalli et al., 2011).

Angle of repose

A flowability study was conducted for the powder mixture, which was prepared from mixing of the drug with other excipients using the angle of repose method. It was determined by the funnel method, in which the powder was poured from a funnel until a cone was obtained. The high (h) and diameter (D) of cone were measured then the angle of repose (θ) was calculated by the equation:

$$\theta = \tan^{-1} (h/r) \quad (\text{Eq. 1})$$

Where, h is the height in cm and r is the radius (Bhimani et al., 2014).

Preparation of RH tablets

Four different formulas of RH were prepared [Table 1] using a direct compression method. Four types of superdisintegrant; Kyron T-314, CP, croscarmellose sodium, and SSG were separately added to the formulations. All the ingredients were passed through sieve 100#, and then they mixed geometrically to produce a simple physical mixture. Magnesium stearate was added to the mixture of powder to produce tablets weighing 150 mg. The resultant blend was compressed into tablets using a single punch, Erweka tablet compression machine.

Evaluation of ropinirole tablets

Disintegration studies

A modified method was used to determine the disintegration time of tablets. A single tablet was added to a cylinder containing 8 ml of phosphate buffer (pH 6.8) and complete dispersion of the tablet in phosphate buffer was recorded as the disintegration time (Bhimani et al., 2014). This experiment repeated 3 times.

Weight variation

Weigh of 10 tablets individually and finding the average weight of them. The deviation of the weight of the tablets

Table 1: Composition of ropinirole buccal effervescent tablets

Ingredients (mg)	F1	F2	F3	F4
Ropinirole HCl	1	1	1	1
Sodium bicarbonate	30	30	30	30
Citric acid	19.5	19.5	19.5	19.5
Sodium carbonate	15	15	15	15
SSG	22.5	---	---	---
CP	---	22.5	---	---
CCS	---	---	22.5	---
Kyron T-314	---	---	---	22.5
MCC	59	59	59	59
Magnesium stearate	3	3	3	3
Total weight of tablet (mg)	150	150	150	150

from the average weight was determined (Kumudhavalli et al., 2011).

Friability

The friability of 10 tablets was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed. The percentage of friability was calculated. The standard weight loss should not be more than 1% (Tangri and Madhav, 2012).

Hardness

Pharmatest hardness tester was used to determine the hardness of the formulated tablet. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of 6 tablets, from each formula, was measured and mean hardness was calculated (Kumar et al., 2014).

Effect of type of superdisintegrant on hardness and disintegration time on RH tablets

Superdisintegrants; SSG, CP, croscarmellose sodium, and Kyron T-314 were included in formulations F1, F2, F3, and F4. The effect of superdisintegrants on the properties of prepared tablets was determined in terms of weight variation, hardness, friability, dose content uniformity, and disintegration rate. The optimum formula was selected based on the tablet disintegration rate, hardness, powder flowability, and friability test. Generated tablets from optimum formulation were selected for subsequent study.

In vitro dissolution studies

A dissolution study was carried out for the tablets prepared from the best formula in 250 ml of phosphate buffer as a dissolution medium (pH 6.8) at 50 RPM and $37 \pm 0.5^\circ\text{C}$ using USP paddle method (Apparatus 2). Samples were periodically taken at suitable time intervals and the drawn volume replaced with equivalent amounts of drug-free dissolution medium. The samples were quantified spectrophotometrically at 249 nm (Gayke et al., 2017).

Content uniformity

This test was carried out only for tablets prepared from the best formula containing RH. Five tablets were weighed and crushed to a fine powder using motor and pestle. The equivalent quantity to 5 mg of RH was transferred to 100 mL volumetric flask. Then, 50 mL of phosphate buffer (pH 6.8) was added to the volumetric flask and shake for 1 h. The solution was filtered and the residue was washed with 25 mL of fresh phosphate buffer. The filtrate solution obtained from the second washing was added to the initial filtrate and the volume was made up to 100 mL with phosphate buffer. Then, 1 ml of the final solution was placed in 10 ml volumetric flask and diluted

to 10 mL with a phosphate buffer solution. The drug content was determined spectrophotometrically at 249 nm (Sharma et al., 2010).

Statistical Analysis

All experiments were carried out in triplicate. Effect of types of superdisintegrants on different properties of the prepared tablets was tested for significance using paired samples *t*-test with the aid of SPSS Statistics 18 program. The difference was considered statistically significant when $P < 0.05$.

RESULTS

Characterization of RH

Determination of melting point

The melting point of RH powder was 245°C , which is within the normal range for RH ($243\text{--}250^\circ\text{C}$) (Mohan et al., 2012), indicating the purity of the drug powder.

Determination of λ_{max}

Figure 1 demonstrates the maximum wavelength of RH when it was obtained from scanning of the drug solution between 200 and 400 nm (Rowe et al., 2006).

Preparation of calibration curve of ropinirole

Figure 2 shows the calibration curve of RH. It was drawn when the series drug concentrations plotted on X-axis against their wavelengths on the Y-axis.

Angle of repose

The angle of repose values for all formulations was determined and found to be in the range of $27^\circ.12$ to $29^\circ.38$, as shown in Table 2.

Evaluation of tablets

All formulas (F1-F4) were evaluated for hardness, disintegration time, weight variation, and hardness test, as illustrated in Table 2. All formulas passed the quality-control tests and were within normal range values.

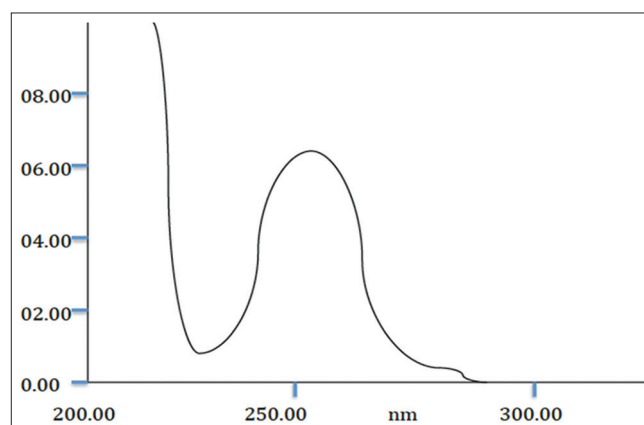
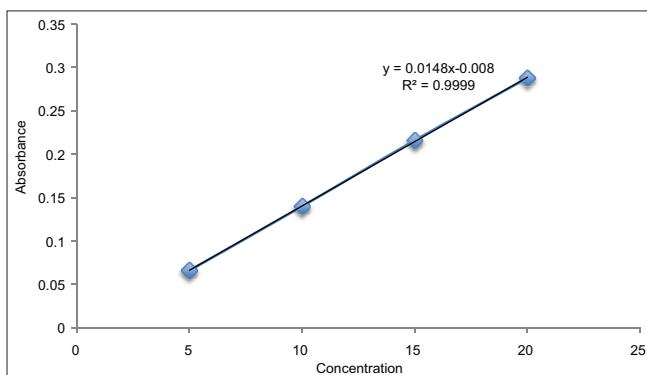
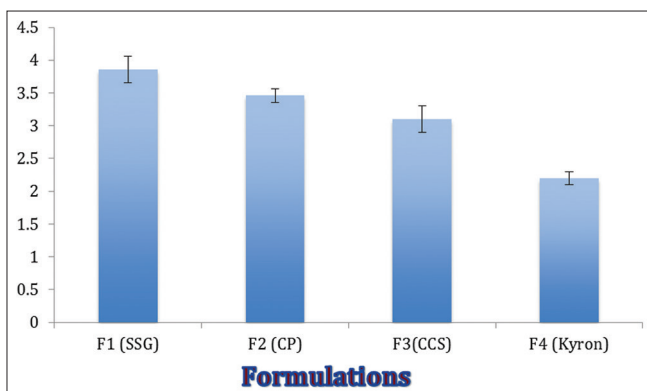


Figure 1: UV scan of ropinirole hydrochloride in distilled water

Table 2: Hardness, disintegration time, weight variation, hardness, and flowability of formulas (F1-F4) (expressed as mean±SD)

Quality control	F1	F2	F3	F4
Hardness (kg)	3.86±0.02	3.46±0.01	3.1±0.02	2.2±0.01
Disintegration time (s)	00:36±0.02	00:30±0.04	00:38±0.02	00:16±0.02
Weight variation (mg)	151.70±1.20	149.61±1.40	150.12±1.60	150.05±1.30
Friability (%)	0.61±0.02	0.43±0.04	0.54±0.02	0.41±0.01
Angle of repose (°)	27°.12±0.18	28°.63±0.32	29°.38±0.42	28°.01±0.11

**Figure 2: Calibration curve of ropinirole in distilled water using UV spectrophotometer****Figure 3: Effect of type of superdisintegrant on the hardness of prepared tablets**

Effect of type of superdisintegrant on hardness and disintegration time of tablets

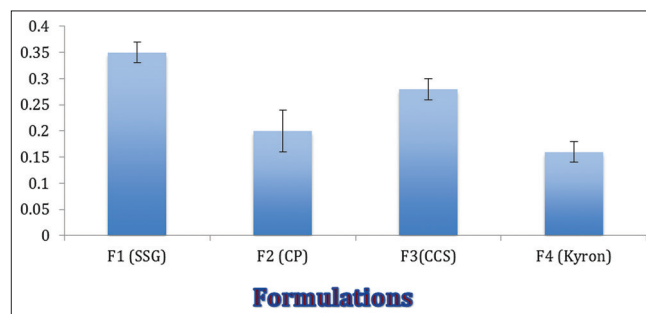
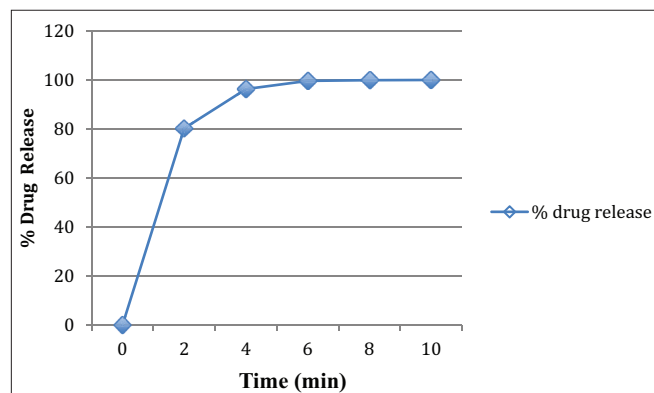
The effect of superdisintegrant on properties of prepared tablets was studied, as shown in Figures 3 and 4. The best formula was F4, which was selected based on the results, as demonstrated in Table 2. Superdisintegrants Kyron T-314 was used in F4.

In vitro dissolution studies

The dissolution test showed that the release of RH was 99.54% within 6 min. Figure 5 shows the release profile of RH tablets.

Content uniformity

The percentage of drug content in the best formula of RH tablets was found to be 98.6% which complies with BP criteria.

**Figure 4: Effect of type of superdisintegrant on disintegration time of prepared tablets****Figure 5: The release profile of ropinirole HCl best formula (F4)**

DISCUSSION

The angle of repose of the formulations (F1, F2, F3, and F4) containing various superdisintegrants was in the range of 27°–29°, indicates a good flow characteristic of the formulas. Powder flowability is an important property of powder for the successful development of tablet preparation (Taylor et al., 2000). It has been reported an optimum powder flowability provides a uniform distribution of the active ingredient among the tablets (Mallikarjuna, 2008).

The range of hardness for all formulations was between 2.2 kg and 3.86 kg, which gives a good mechanical stability to the prepared buccal effervescent tablets since superdisintegrants used in all formulations, a very fast disintegration of tablets was achieved.

Hence, time needed for breaking the tablets was ranging from 16 to 38 s. Weight variation test is an indicator to

give us dose variation among tablets, and it showed that all tablets were in the permissible range (not more than two tablets differ from the average weight by more than 7.5%) (Sandri et al., 2006).

Results obtained from the friability test show that the percent of friability is <1%, indicating all tablets have acceptable friability, and there are no fears of breakage during manufacture, storage, and transportation.

From the prepared formulas, F4 was selected as the best formula, because it has the best properties regarding disintegration time and hardness (fast disintegration with lower hardness) compared to other formulas. According to the results of the hardness test, also there is a significant difference between hardness of F4 compared to other formulas since it is a buccal effervescent tablet, so lowest hardness is needed to give faster disintegration.

Lower disintegration time is preferred for the preparation of fast disintegrating tablets because it offers increased patient compliance and convenience. The disintegration time for F4 was 16 seconds and is significantly lower than the disintegration time of other formulas ($P < 0.05$).

In F4, Kyron T-314 was used as a superdisintegrant which gives a faster disintegration rate than other disintegrants: SSG, CP, and croscarmellose sodium.

Kyron T-314 has a porous structure, which provides faster water uptake; hence, it facilitates wicking action and bringing about faster disintegration (Mundada, 2010). Kyron T-314 swells well and it enables to absorb water quickly. This may indicate that aqueous medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bonds and breaks the tablet into fine particles (Jyothi and Lakshmi, 2011).

The results were in agreement with the results obtained by Jyothi and Lakshmi. They compared the effect of natural and synthetic superdisintegrants in the formulation of fast dissolving tablets. They observed that the disintegration time of tablets decreased when Kyron T-314 was used in the formulation; this may be due to swelling at a faster rate on contact with water and elimination of lump formation after disintegration (Jyothi and Lakshmi, 2011).

CONCLUSIONS

Fast disintegrating buccal tablets of RH were successfully prepared using four various superdisintegrants. Kyron T-314 provided fast disintegration rate of the tablet

compared to other superdisintegrants. The prepared tablet could be used for delivery of RH sublingually to exert fast onset of action and avoiding first-pass metabolism.

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