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Original Article

TASTE MASKED CLOPERASTINE HYDROCHLORIDE AND RUPATADINE ORAL DISPERSIBLE TABLETS: FORMULATION DESIGN, DEVELOPMENT, CHARACTERIZATION AND PHARMACOKINETICS STUDY ON WISTAR RATS

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ABSTRACT

Objective: The main objective of our study was formulating oral dispersible tablets (ODTs) of taste masked cloperastine HCl and rupatadine fumarate by using the lyophilization technique that also enhanced the dissolution of poor solubility of these active substances.

Methods: Taking 3 super disintegrants as variables using the Minitab® 18 factorial design method, 27 formulae of ODTs were obtained. The powdered mixtures before direct compression were characterized using Carr's index, Hausner's ratio, and angle of repose. The best-powdered formulae were elected to be prepared as ODTs by direct compression to undergo characterization tests such as wetting time, *in vitro* disintegration test, and *in vivo* taste masking. According to the Quality by Design QbD approach; the best formula of ODTs prepared by direct compression was elected to be optimized by the lyophilization technique. Incorporating Eudragit E PO®has a major role in the taste masking of lyophilized ODTs. A comparative *in vivo* pharmacokinetic study of market products of two active substances was carried out for the conventional ODTs, lyophilized tablets, and market products using wistar rats by oral administration of (0.75 mg/ml) for each active substance.

Results: The bitter taste was apparently masked in the lyophilized ODTs assessed by *in vivo* taste masking. The highest Cmax of cloperastine HCl was found at 17.25 mcg/ml in the group of Lyophilized ODTs. Furthermore; the highest Cmax of rupatadine was found at 78.88 mcg/ml in the same group.

Conclusion: Lyophilized tablets owned the best bioavailability for both active substances with the highest Cmax compared to market products and ODTs prepared by direct compression.

Keywords: Orodispersible tablets (ODTs), Cloperastine HCl, Rupatadine, Lyophilized tablets, Taste masking, Eudragit EPO®

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INTRODUCTION

Many active pharmaceutical ingredients as cloperastine HCl and rupatadine have a bitter taste and thus are aversive to children, as well as many adults. Taste masking is a challenge to develop palatable dosage form [1]. Accordingly; the aim of this study is mainly the development of a palatable taste-masked cloperastine HCl and rupatadine ODTs.

Cloperastine is a medication that has a central antitussive action as well as papaverine-like activity, similar to codeine but without its narcotic effects, and an antihistaminic (sharing an ethylamine moiety with H1 receptor antagonists). Pharmacological tests have demonstrated that the molecule has no detrimental effects on the cardiocirculatory system and only affects the cough center without affecting the respiratory center and is suitable for children. Cloperastine, modulates the Sigma-1 receptor, a potential drug target [2].

Acute cough and allergies brought on by an upper respiratory tract infection (URTI) are the most prevalent symptoms in both children and adults around the world. These symptoms have serious economic and social repercussions for the patient, the patient's family, and the healthcare system. Recently, new pathogenic mechanisms for acute cough, including mechanisms for the urge to cough (UTC), have been discovered [3].

Many medications used to treat cough and allergies have a bitter taste like rupatadine. Rupatadine, one of the newest antihistamines with an anti-allergic and anti-inflammatory effect, was employed as a prototype bitter-tasting medication. RUP differs uniquely from other antihistamines and explains the novel mechanism of its anti-inflammatory action since it is a powerful, selective antagonist of platelet-activating factor (PAF) and histamine receptor H1 receptors [4]. The rupatadine dose is estimated as 10 to 40 mg. It has low oral bioavailability (50%) due to low solubility and extensive hepatic first-pass metabolism [5].

On the other hand, orally disintegrating tablets (ODTs) are solid single-unit dosage forms that are designed to be placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed without the aid of additional water. Despite a surge of orally disintegrating tablets in the market in recent years, they potentially can be confused with other solid oral dosage forms that are consumed without additional water intake [6].

MATERIALS AND METHODS

Materials

Rupatadine Fumarate was provided from Parchem (USA), Cloperastine HCl was provided from Sigma Aldrich (Germany), Mannitol was provided from Chemizo Enterprise (India), Croscarmellose was provided from IMCD (USA), Crospovidone was provided from IMCD (USA), Sodium Starch Glycolate was provided from JRS Pharma (Germany), Aspartame was provided from Chempoint (USA), Talc was provided from Sigma Aldrich (Germany), Magnesium Stearate was provided from Mallinckrodt (USA), Aerosil was provided from Evonik (Germany), Eudragit E PO was provided from Evonik (Germany), Microcrystalline cellulose (Avecil PH 102) was provided from Evonik (Germany), Glycine was provided from Sigma Aldrich (Germany, Gelatin was provided from El-Nasr company for Pharmaceuticals (Egypt).

Method

Compatibility studies of cloperastine HCl and rupatadine fumarate with the formulated excipients

Differential scanning calorimetry (DSC)

Melting points of Cloperastine HCl and Rupatadine fumarate are 148 °C and 215 °C consecutively; samples of 3-5 mg were heated in aluminum pans to be tested by Differential scanning calorimetry (DSC) model: Shimadzu, Detector DSC60 (Japan), Atmosphere: Nitrogen, flow Rate: 10 ml/min over a temperature range of 0-300 °C. DSC thermograms were recorded for pure Cloperastine HCl, and pure Rupatadine Fumarate, both 2 active constituents in a mixture (1:1) and a mixture of them with proposed excipients [7].

Fourier transform infra-red spectroscopy (FTIR)

Physical mixtures of active constituents Cloperastine HCl and rupatadine fumarate with the proposed excipients were subjected to FTIR analysis. FTIR Model: Bruker Alpha-P Diamond (Manchester, United Kingdom). The samples were prepared as potassium bromide disks compressed under a pressure of 6 tones/cm^2. The wave number selected ranged between 400 and 4000 cm^{-1}[8].

Physiochemical characterization of cloperastine HCl and rupatadine ODTs

Pre-compression evaluations

Prior to compression, the prepared powdered mixtures were evaluated for their micrometers. Various parameters like bulk density, tapped density, angle of repose, Hausner ratio, and Carr's index were determined according to the official methods of United States Pharmacopeia.

Bulk density and tapped density

The bulk density of a powder is the ratio of the mass of an untapped powder and its volume including the inter particulate void volume. It is measured in grams per ml (g/ml) using the method I as per USP The defined weight of powder in grams of the formula is to be assessed by dividing weight by volume [9].

While the tapped density is the density attained by tapping a graduated measuring cylinder containing a powder. Volume or weight readings are taken until a little further volume or weight changes [10].

Angle of repose

The test was carried out by fixed cone height method by using a glass funnel with an internal stem diameter of 5 mm is positioned 1 cm above a glass slide. The powder flowed through the funnel until a cone reaches the funnel orifice. The test was performed in triplicate.

The angle of repose was calculated using the equation: $\text{Tan } Ø = h/r$ where h is the height of the powder cone and r is the radius of the powder cone [11].

Carr's index and Hausner ratio

They are measures of the propensity of a powder to be compressed. Accordingly, they evaluate the powders to settle and they considered an assessment of inter-particulate interactions. They are calculated as follows:

Carr's Index = $[100\ (Vo - Vf)]/Vo$

Hausner Ratio = Vo/Vf

Where Vo is the apparent volume and Vf is the tapped volume [12].

Table 1: Factorial design of ODTs formulae

Factors	Levels		
A: croscarmellose	0 mg	10 mg	20 mg
B: crospovidone	0 mg	10 mg	20 mg
C: sodium starch glycolate	0 mg	10 mg	20 mg

Table 2: Composition of cloperastine HCl and rupatadine fumarate (ODTs) by direct compression

Ingredients*										
Formula no.	**Clo.**	**Rup.**	**Cros. ca.**	**Cros. po.**	**Sod. gl.**	**Mann.**	**Mic. ce.**	**Aspar.**	**Talc**	**Mg. St.**	**Aer.**
F1	10	10	0	0	0	79	40	10	4	2	0.8
F 2	10	10	10	0	0	69	40	10	4	2	0.8
F 3	10	10	20	0	0	59	40	10	4	2	0.8
F 4	10	10	0	10	10	59	40	10	4	2	0.8
F 5	10	10	10	10	10	49	40	10	4	2	0.8
F 6	10	10	20	10	10	39	40	10	4	2	0.8
F 7	10	10	0	20	20	39	40	10	4	2	0.8
F 8	10	10	10	20	20	29	40	10	4	2	0.8
F 9	10	10	20	20	20	19	40	10	4	2	0.8
F 10	10	10	0	10	20	49	40	10	4	2	0.8
F 11	10	10	10	10	20	39	40	10	4	2	0.8
F 12	10	10	20	10	20	29	40	10	4	2	0.8
F 13	10	10	0	20	10	49	40	10	4	2	0.8
F 14	10	10	10	20	10	39	40	10	4	2	0.8
F 15	10	10	20	20	10	29	40	10	4	2	0.8
F 16	10	10	0	0	10	69	40	10	4	2	0.8
F 17	10	10	10	0	10	59	40	10	4	2	0.8
F 18	10	10	20	0	10	49	40	10	4	2	0.8
F 19	10	10	0	10	0	69	40	10	4	2	0.8
F 20	10	10	10	10	0	59	40	10	4	2	0.8
F 21	10	10	20	10	0	49	40	10	4	2	0.8
F 22	10	10	0	0	20	59	40	10	4	2	0.8
F 23	10	10	10	0	20	49	40	10	4	2	0.8
F 24	10	10	20	0	20	39	40	10	4	2	0.8
F 25	10	10	0	20	0	59	40	10	4	2	0.8
F 26	10	10	10	20	0	49	40	10	4	2	0.8
F 27	10	10	20	20	0	39	40	10	4	2	0.8

*Abbreviations**:** Clo.: Cloperastine HCl, Rup.: Rupatadine, Cross. ca.: Croscarmellose, Cros. po.: Crospovidone, Sod. gl.: Sodium Starch Glycolate, Mann.: Mannitol, Mic. ce: Microcrystalline cellulose (Avecil PH 102), Aspar.: Aspartam, Mg. St.: Magnesium Stearate, Aer.: Aerosil

Preparation of ODTs by direct compression

Experimental design

To define the optimally selected factors that produce ODTs was employed to statistically investigate the effect of different super disintegrants variables on the properties of the prepared formulae by Minitab® 18 Software; a multilevel full factorial design composed of super disintegrant type as independent categorical factors, each factor has concentrations (0, 10, 20) mg were employed as 3 levels for each super disintegrant table 1, resulted in 27 probable different compositions as shown in table 2, the mixture of each formula was compressed by single punch machine (Erweka, EKO, Germany) of compression force 400 kg using a 7 mm flat punch and die set.

Quality by design approach

The development of a dispersible tablet was proposed in the current study through the Quality by Design QbD paradigm for the achievement of patient compliance through product quality targeting. Target product profile (TPP) and quality target product profile (QTPP) imply the objective and efficacy of a drug development program. The primary components of TPP are mainly therapeutic aspects as indications and routes of administration. TPP and QTPP for dispersible tablet dosage formulation are listed in table 3. The quality properties of the drug formula should be available in order to meet requirements set in TPP and are enlisted in the target product quality profile (TPQP) as quantitative analysis [13, 14].

Table 3: TPP and QTPP for ODTs

	QTPP		Criticality
	TPP	TPQP	
Dosage form	ODTs	DT<30 min, Assay±5%,	Ensures complete dispersion, the release of, drug and ease of administration
Appearance	Uncoated tablets 155.8 mg	Round tablets	Patient acceptability
Route of administration	Oral	palatable	Patient compliance
Proposed indication	Treatment of cough	Dissolution and pharmacokinetics study	Therapeutic effect

Characterization of ODTs by direct compression by physicochemical and mechanical tests

Weight variation

Twenty tablets were selected randomly from each batch and their average weight was determined. Then each tablet was weighed individually, and its weight was recorded. The individual weight of each tablet was compared with the average weight. The findings were expressed as a mean value±SD [15].

Friability test

This test is carried out to indicate the physical strength of ODTs by the friability tester model: Pharmatest PTF 100 (Hainburg, Germany). The friability of conventional uncoated tablets is required to be less than 1% [16].

Hardness test

This test is carried out to indicate good mechanical characteristics for the tablets by using the Hardness tester model: PTB 111EP (Hainburg, Germany), But ODTs may have different specifications as far as friability is concerned. The freeze-dried ODTs are more fragile than the directly compressed ODTs, and thus, it is more difficult to maintain in tablet form [17].

Determination of the wetting time

The wetting time experiment mimics the action of saliva in contact with a tablet [18].

This experiment is the indication of the inner structure of the tablets the and hydrophilicity of the excipients. Accordingly, the less value of wetting time, the less value of disintegration. The wetting time can be measured by using five circular tissue papers of 10 cm in diameter, which are placed in a Petri dish of 10 cm in diameter. 10 mls of water-soluble dye eosin solution are added to the Petri dish. A tablet is carefully placed on the tissue surface. The time duration for water to reach the upper surface of the tablet is considered the wetting time [19].

***In vitro* disintegration time**

ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an *in vitro* disintegration time of approximately 30 seconds or less when based on the United States Pharmacopeia (USP) disintegration test method or alternative. ODTs were placed in the baskets of the USP disintegration tester model: Pharmatest PTZ 300 Hainburg, Germany). At 37±0.5 °C, the ODTs used phosphate buffer solution with pH 6.8 as immersion fluid. The time required for the complete dispersion of a tablet was recorded as the disintegration time (DT) [20].

***In vivo* taste masking evaluation**

In vivo taste masking evaluations for the tested formulae are carried out in compliance with the World Medical Association's Code of Ethics (Declaration of Helsinki). In addition, also an ethical committee approved this study, Faculty of Pharmacy, Cairo University, approval no. PI 1607. First, volunteers have informed of the aim of the experiment and probable risks. Twelve adult healthy volunteers aged from 25 to 35 y old of either gender were chosen (male = 6, female = 6). One tablet (about 150 mg) is kept in the mouth for 60 seconds before being spat out. Water was used to wash each volunteer's mouth in between each sample's trial to prevent carryover The bitterness intensity scale was used to measure the bitterness instantly, with 1, 2, 3, 4, and 5 indicating least unpleasant, less unpleasant, neutral, more unpleasant, and most unpleasant consecutively [21].

Optimization of the selected formula by lyophilization technique

This technique was applied to various technologies developed to achieve fast dissolution and dispersion of tablets in the oral cavity. In addition, taste-masking technologies and measurements of disintegration times [22].

Improving of taste masking by using Eudragit EPO as it is pH dependent excipient that is a cationic copolymer based on dimethylamino ethyl methacrylate, butyl methacrylate, and methyl methacrylate, which is soluble in gastric fluid up to pH 5.0 [23].

This characteristic behavior of Eudragit EPO helps inhibit the bitter taste of active constituent's cloperastine HCl and rupatadine fumarate from release in saliva (pH 6.2). The preparation lyophilized tablets is developed by using glycine as a matrix former that prevents the shrinkage of tablets during manufacture [24].

In addition to incorporating gelatin as a binder instead of Mannitol, it is responsible for forming the highly porous matrix structure of the dosage form. Gelatin, a protein, which acts as a glassy amorphous compound, provides structural strength [25]. Water is used as a manufacturing process media, which helps in the induction of the porous structure formation upon sublimation during the freeze-drying stage [26].

The preparation of Lyophilized tablets was performed by dissolving 0.5g of Gelatin into 25 ml of distilled water, the solution was heated over a water bath till complete dissolution. After cooling, 0.25g of Glycine was

added to the Gelatin solution. 10 ml from the previous solution was added to a powdered mixture equivalent to 10 tablets weight of F9 composed of 10 mg of Cloperastine HCl, 10 mg of Rupatadine, 20 mg of Croscarmellose, 20 mg of Sodium Starch Glycolate, 20 mg of Crospovidone, 19 mg of Eudragit E PO, 40 mg of Avicel, 10 mg of Aspartam, 4 mg of Talc. Continuous stirring of dispersion was kept till poured into molds for 10 tablets. The lyophilization process for molded tablets is carried out by using A Novalyphe-NL 500 Freeze Dryer (Savant instruments, Haldbrook, NY, USA).

Assay of cloperastine HCl and rupatadine fumarate

Assay of cloperastine HCl

Chromatographic conditions: HPLC instrument with UV detector Model: Agilent infinity1260 autosampler, column: Symmetry C18 (150*4.6)mm, particle size; 5µ Wavelength: 254 nm, Flow rate: 1 ml/minute, Mobile phase: methanol: 0.02 M potassium dihydrogen phosphate in the ratio (70:30) 1 ml of triethylamine was added to 1 liter then pH was adjusted to 6 with phosphoric acid, Injection volume: 20 µl. Standard was prepared as 50 mg of Cloperastine HCl was weighed and transferred into 100 ml volumetric flask, 80 of methanol was added to dissolve with aid of sonication for 10 min, the volumetric flask was cooled and completed to volume by methanol, 5 ml was diluted into 50 ml volumetric flask and volume were completed by mobile phase to obtain (50 µg/ml of Cloperastine HCl). The test was prepared by grinding 10 tablets of each formula, the weight for one tablet was dissolved by 80 ml of methanol into a 100 ml volumetric flask with aid of sonication for 15 min, the volumetric flask was cooled and completed to volume by methanol, 25 ml was diluted into 50 ml volumetric flask, then the volume was completed by mobile phase to obtain (50 µg/ml of Cloperastine HCl). Standard and test were injected into HPLC.

Assay of rupatadine

Chromatographic conditions: HPLC with UV detector Model: Agilent 1260 autosampler, HPLC column: Hypersil BDS C18 (150*4.6)mm, particle size; 5µ, Wavelength: 264 nm, Flow rate: 1 ml/minute, Column temperature: 50 °C, Mobile phase: methanol: Acetate Buffer (6 g of Sodium Acetate per Litre pH=6 in the ratio (80:20), Injection volume: 20 µl. Standard was weighed as 63.94 mg of rupatadine fumarate equivalent to 50 mg of rupatadine was weighed and transferred into a 100 ml volumetric flask, and 80 of mobile phase was added to dissolve with aid of sonication for 10 min, the volumetric flask was cooled and completed to volume by mobile phase, 5 ml was diluted into 50 ml volumetric flask. The volume was completed by mobile phase to obtain (50 µg/ml of Rupatadine). The test was prepared by grinding 10 tablets of each formula, the weight for one tablet was dissolved by 80 ml of mobile phase into a 100 ml volumetric flask with aid of sonication for 15 min, the volumetric flask was cooled and completed to volume by mobile phase, 25 ml was diluted into 50 ml volumetric flask and volume was completed by mobile phase to obtain (50 µg/ml of Rupatadine). Standard and test were injected into HPLC.

Validation of the assay

Each method of analysis was carried out after validation according to ICH guidelines in order to assure its efficiency and sensitivity to determine the active constituent concentration ICH guideline on Q2(R2) Validation of analytical procedures (EMA/CHMP/ICH/82072/2006)

Linearity: A linear relationship was evaluated across the range of the used HPLC analytical procedure by plotting concentrations in the X-axis and resulting areas in Y axis. It was demonstrated directly on either Cloperastine HCl or Rupatadine by dilution of a standard stock solution using the proposed procedure in order to study the investigation of the range.

Accuracy: it is used to express the closeness of agreement between the expected value and the conventional true value of each active substance.

Precision: The precision of an analytical procedure expresses the degree of scatter between a series of measurements obtained from multiple sampling of the same homogeneous sample of each active under the prescribed conditions.

Precision is considered here at two levels: repeatability and intermediate precision.

Intermediate precision: The extent to which intermediate precision should be established depends on the circumstances of the procedure intended to be used. Such variations as day of testing, operators or HPLC equipment.

Repeatability: Expresses the precision under the same operating analytical conditions over a short interval of time by injecting six individual prepared samples of each active substance.

The limit of detection (LOD): is the lowest amount of active substance in a sample which can be detected but not necessarily quantitated as an exact value.

Method of calculation

LOD = 3.3 σ S (where σ = the standard deviation of the response, S = the slope of which is estimated from the calibration curve of the active substance.

The limit of quantitation (LOQ): is the lowest amount of active substance in a sample that can be quantitatively determined.

LOQ = 10 σ S (where σ = the standard deviation of the response, S = the slope of which is estimated from the calibration curve of the active substance.

Robustness: To measure the capacity of the analytical method to remain unaffected by small variations in method parameters and provides an indication of its reliability during routine application of the method [27].

***In vitro* dissolution**

By using Dissolution tester model: Pharmatest PTWS 120S (Hainburg, Germany) device II (paddle), ODTs were placed into vessels in 900 ml dissolution media 0.1N HCl, 50 rpm/min, temperature 37±0.5 °C [28]. Sampling intervals were taken at 3,5,15,20,30 and 45 min. The measurement of Cloperastine HCl and Rupatadine release was carried out as mentioned above in HPLC assay procedures.

***In vivo* kinetics study**

The experiments were performed on three groups of wistar male rats were caged in pairs and kept in (temperature 22±2 °C) and humidity (55±5 RH %) in controlled environment with 12 h light cycle. Rats (n=2 per each group, average weight 250±10 g) and all rats were allowed free access to food and water. The animal protocol was approved by the ethical committee of (Egypt, Cairo, Cairo University, faculty of Pharmacy) serial number: PI (1321).

Designation of experiment: first group was for commercial products administration for [brand of Cloperastine: Seki®suspension produced by (Zambon, Italy), a brand of Rupatadine: Rupafin® produced by (Uriach, Spain)], the second group was for lyophilized ODTs administration, third group was for ODTs by direct compression. Administration of drug (0.75 mg/ml for each Cloperastine HCl and Rupatadine Fumarate) by dispersing each tablet into water and was applied by a syringe to inject solution into the oral cavity. Plasma withdrawal upon intervals 1/2, 1, 1 1/2, 2 and 4 h. The measured peaks of Cloperastine HCl and Rupatadine Fumarate extracted from plasma were determined by using UPLC MS/MS Waters 3100 (USA)TQ detector, binary solvent manager pump, sample manager auto sampler, Mass lynx V4.1 software. Mobile phase: methanol: 0.1% formic acid (93:7) % flow rate 0.5 ml/min, run time: 5 min., ion mode: ESI, column: Waters X BRIDGE BEH SHIELD RP 18 (2.1*150) mm 2.5 µm. extraction method for standard was performed by adding 225 µl of rat plasma with 25 µl of drug mixture, extracted by 3 ml from a solvent mixture of N Hexane: Methyl tert-butyl ether (50:50) %, then the supernatant was reconstituted with 150 ml Methanol. Calibration *in vivo* concentrations of Cloperastine HCl were (1, 5, 10, 15, 25) ng/m and of Rupatadine (5, 10, 25, 50, 100) ng/ml. The extraction method for tests performed by using 250 µl of rat plasma to be extracted by 3 ml from a solvent mixture of N Hexane: Methyl tert-butyl ether (50:50) %, then the supernatant was reconstituted with 150 ml Methanol.

RESULTS AND DISCUSSION

Compatibility studies of cloperastine HCl and rupatadine fumarate with the formulated excipients

DSC

Both pure substance of Cloperastine HCl and Rupatadine Fumarate exhibited its sharp endothermic peak detected at 148 °C and 215 °C consecutively (fig. 1) as appeared in thermograms A, B. while physical mixture of both of active constituents in ratio (1:1) showed a new sharp peak at 166 °C as appeared in thermogram C. The mixture of active constituents with the excipients of tablets produced DSC thermograms D, E, F, G similar to thermogram C. It is clear to notice that every thermogram shows similarities in the active constituent's mixture and the powdered formula behavior, but the most important thing is that there are no new exothermic peaks and the temperature at which the melting of the API occurs in the formula is pretty close thermogram C. Also, it can be seen that most of the melting or endothermic peaks of the excipients are missing.

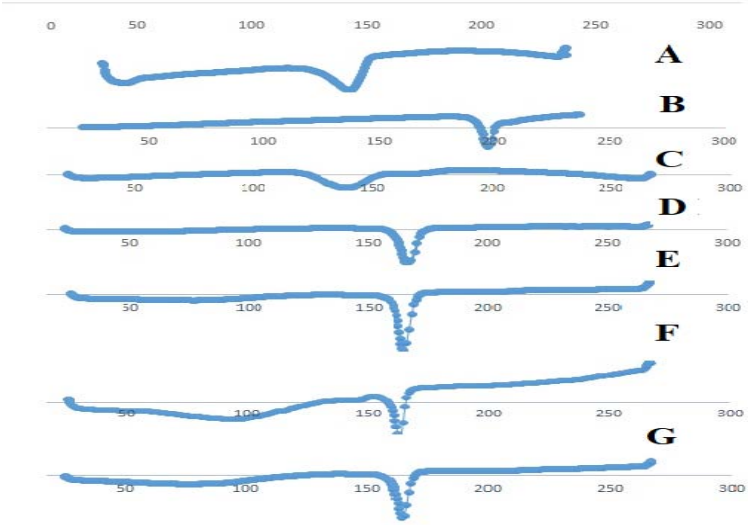

Fig. 1: DSC thermograms (A: Cloperastine HCl, B: Rupatadine fumarate, C: mixture of cloperastine HCl and rupatadine fumarate (1:1), D: F1ingredients of, E: F4 ingredients, F: F9 ingredients, G: F11 ingredients)

FTIR

FTIR spectra (fig. 2); for Cloperastine HCl in spectrum A has C-H stretching vibrations for the O-CH3 group in methoxyethane occur at wavenumbers 2830 to 2815 cm-1. From the ether linkage (C-O-C) was found around wavenumbers 1150 to 1060 cm-1. More specifically, the C-O stretching vibrations for a O-CH3 group occur at wavenumbers ~1250 cm-1. The spectrum B for rupatadine fumarate IR Spectrum had transmittance at wave no. 2987 cm-1 due to C-H stretching of alkanes and aromatic rings. Characteristic transmittance appeared at wave number 1420 cm-1 due to O-H splitting of carboxylic acids. Transmittance appeared at 1698 cm-1 due to C=O stretching. Transmittance appeared at 1327 due to C-N stretching of aromatic amine. IR spectra no. C, D,E and F of active constituents with excipients, it is noted that there is no absence of any characteristic peaks of each active constituent appeared in A and B spectra, this concluded that there is no physicochemical interactions among them.

Pre-compression evaluation

As per results recorded in table 4; angle of repose determination for F1, F2, F3, F4, F5, F7, F8, F9, F10, F11, F12, and F13 show excellent flowability behavior ranging from 27.51 to 29.84 while F6, F14, F17, F19, F20, F21 showed good flowability ranged from 31.41 to 35.91 while the rest formulae showed fair flowability ranged from 36.37 to 37.73. Hausner's ratio for F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F26, and F27 shows possible flowability results ranged from 1.208 to 1.305 as F1 has the best result of flowability in the absence of disintegrants and maximum allowed amount of Mannitol while the rest formulae show poor flowability results ranged from 1.374 to 1.532. Carr's index for F1, F2, F3, F4, F5, F9, F11, F12, and F26 have possible flowability results ranging from 20.81 to 24.95 while the rest formulae have poor flowability ranging from 28.96 to 53.26. It concluded that the best-powdered formulae have free flowable characters are F1, F2, F3, F4, F5, F9, F11, F12.

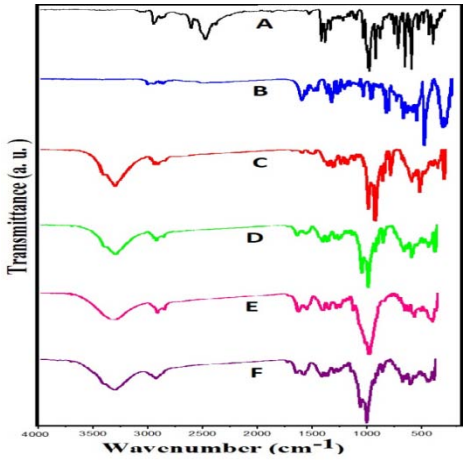

Fig. 2: FTIR spectra (A: Cloperastine HCl, B: Rupatadine Fumararate, C: F1 ingredients, D: F4 ingredients, E: F9 ingredients, F: F11 ingredients)

Physicochemical and mechanical characterization of ODTs

Weight evaluation

The weight of different conventional ODTs ranged from 152.5±0.08 mg to 156.67±0.53 as shown in table 5. All formulae were within the British Pharmacopeia specification for drug content and for weight variation, and none of the tablets deviated from the average weight by more than 7.5%.

Friability and hardness tests

As shown in table 5; the friability results are ≥ 1.0% except in F1 only with the result (0.10%±0.59) that has no super disintegrants as

well as in the Hardness test where all formulae had low hardness. However, since ODT formulations should have a lower hardness in order to be disintegrated quickly within the buccal cavity, they would be expected to have a higher friability than conventional tablets. Accordingly, the characteristics of hardness and friability corroborate with special packaging.

Table 4: Results of pre-compression evaluation tests

Formula no.	Characterization of powdered mixtures results*				
	Bulk density±SD	**Tapped density±SD**	**Angle of repose±SD**	**Carr's index±SD**	**Hausner's ratio±SD**
F1	0.514±0.21	0.621±0.56	29.84±0.72	20.81±0.48	1.21±0.83
F 2	0.524±0.80	0.638±0.84	29.91±0.15	21.75±0.71	1.22±0.55
F 3	0.501±1.20	0.626±0.17	27.75±0.12	24.95±0.57	1.25±0.19
F 4	0.451±0.74	0.562±0.89	27.47±0.48	24.61±0.91	1.25±0.95
F 5	0.481±0.59	0.597±0.85	27.51±0.19	24.11±0.90	1.24±0.08
F 6	0.440±0.11	0.577±1.12	31.41±0.71	31.13±0.24	1.31±0.31
F 7	0.468±0.95	0.623±0.39	26.88±0.43	33.71±0.97	1.33±0.74
F 8	0.472±0.74	0.594±0.84	28.83±0.20	25.84±0.39	1.26±0.29
F 9	0.498±0.22	0.614±1.00	29.57±0.18	23.29±0.74	1.23±0.63
F 10	0.459±0.27	0.599±0.71	28.34±0.55	30.50±0.81	1.305±0.28
F 11	0.518±1.10	0.630±0.69	29.10±0.76	21.62±0.19	1.22±0.27
F 12	0.497±0.95	0.626±0.71	29.43±1.01	23.29±0.77	1.26±0.81
F 13	0.460±0.49	0.589±0.74	28.81±0.16	30.50±0.44	1.28±0.12
F 14	0.413±0.50	0.633±0.76	34.37±0.39	53.26±0.93	1.53±0.36
F 15	0.428±0.91	0.617±0.78	37.16±0.74	44.15±0.20	1.44±0.33
F 16	0.464±0.15	0.647±0.65	37.73±0.98	28.28±0.29	1.39±0.17
F 17	0.451±0.11	0.635±0.85	34.41±0.48	40.79±0.09	1.41±0.32
F 18	0.428±0.89	0.618±0.66	38.24±0.17	44.39±0.31	1.44±0.75
F 19	0.432±0.85	0.606±0.29	34.05±0.78	40.27±0.17	1.40±0.66
F 20	0.413±0.76	0.618±0.58	32.57±0.94	49.63±0.29	1.50±0.18
F 21	0.403±0.28	0.588±0.51	34.76±0.22	45.90±0.19	1.46±1.02
F 22	0.449±1.01	0.643±0.54	37.01±0.27	43.20±0.9	1.43±0.82
F 23	0.433±0.59	0.651±0.94	35.38±0.83	50.34±0.55	1.50±0.91
F 24	0.454±0.74	0.664±0.32	36.37±0.81	46.25±0.67	1.46±0.14
F 25	0.422±0.85	0.580±0.61	35.79±0.98	37.44±0.09	1.37±0.56
F 26	0.467±0.66	0.529±0.54	35.91±0.21	24.47±0.92	1.24±1.01
F 27	0.435±0.41	0.561±0.19	35.53±1.03	28.96±1.01	1.29±0.09

All values are mean±SD values (Number of experiments, n= 3)

Wetting time (WT)

All tested formulae have acceptable wetting time (<180 secs) as shown in table 5. L1 prepared by lyophilization has WT 22.33 seconds±0.57 which is shorter than the other formulae prepared by direct compression. Data revealed that F1 has the longest WT than other formulae ($p<0.05$). These results were attributed to the absence of super disintegrants croscarmellose, Crospovidone, and Sodium starch glycolate. F4 included 10 mg of crospovidone and 10 mg of Sodium starch glycolate has longer WT than L1 ($p<0.05$) but better mean results compared to F1. While F9 has a relatively shorter time compared with the other formulae prepared by direct compression and with no significant difference with L1 ($p>0.05$) as it included 20 mg of each super disintegrant croscarmellose, Crospovidone, and sodium starch glycolate. F11 included 10 mg of croscarmellose, 10 of mg crospovidone, and of 20 mg Sodium starch glycol late has a relatively long time of WT compared with L1 ($p<0.05$). The results concluded that the formula F9 included maximum amounts of super disintegrants and has the shortest WT in direct compression formulae with no significant difference with L1 prepared by lyophilization which has the shortest WT in all formulae. L1 resulted in the best WT due to its high porosity that physically characterized the lyophilized tablets [29].

***In vitro* disintegration time (DT)**

F9 has a shorter DT than other formulae as shown in table 5. This could be explained by the presence of all super disintegrants croscarmellose, crospovidone and sodium starch glycolate in their maximum concentrations 20 mg for each. Croscarmellose sodium facilitates the disintegration process through the mechanism of swelling, recovery of elastic energy, and capillary action (wicking). It is a fiber-like polymer with a rather short size and adequate flow characteristics. Its long fiber-shaped structure can widen the distance between the constitutive particles of the matrix tablet, which accelerates the disintegration process [30, 31].

Furthermore, sodium starch glycolate presence that can make ODTs swell 7-12 folds in less than 30 seconds in three dimensions and high level serves as sustain release matrix. It can take up more than 20 times its weight in water resulting in high swelling capacity combined with the rapid uptake of water accounts for its high disintegration rate and efficiency. ODTs containing croscarmellose and sodium starch glycolate disintegrate almost instantaneously when they will come in contact with even a slight amount of saliva or water [32]. While crospovidone and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling impact [33]. Accordingly, F9 has the best disintegration results among the other formulae.

On the other hand, F4 with no croscarmellose shows non-significant difference compared with F9 ($p>0.05$). F11 with maximum concentration of sodium starch glycolate 20 mg and 10 mg of each crospovidone and croscarmellose showed non-significant difference compared with F9 ($p>0.05$). L1 showed significant difference compared with F9 as the lyophilized tablet has no super disintegrants in its composition while its disintegrating depends on high porosity. Thus, the results suggest that the disintegration time can be decreased by using wicking type of disintegrants. Hence the formulation F9 has less disintegration time compared to the other formula.

Lyophilized ODTs have marginally different physical characteristics compared to conventional ODTs as shown in table 5, the lyophilized ODT has diameter measure 2.23 folds the conventional ODT diameter, also the lyophilized ODT has thickness measure 1.8 folds the conventional ODT as shown in table 6.

Table 5: Physical evaluation of the ODTs

Formula no.	Physical evaluation tests				
	Weight (mg)±(SD)	Friability (%)±(SD)	Hardness (kg)±(SD)	WT (seconds)±(SD)	DT (seconds)±(SD)
F1	152.5±0.87	0.10±0.59	2.44±0.51	32.00±1.00	44.67±0.58
F4	155.5±0.50	1.27±0.61	3.6±0.60	26.33±0.57	6.33±1.15
F9	156.67±0.53	2.48±0.78	2.24±0.52	23.33±1.16	4.67±0.58
F11	155.83±0.47	2.10±0.72	0.61±0.88	24.33±1.30	5.33±0.58
L1	150.02±1.00	2.05±0.33	1.12±0.48	22.33±0.57	20.00±1.00

Abbreviations: F: formulae; WT, wetting time; DT, disintegration time, L1 lyophilized tablet, All values are mean±SD values (Number of experiments, n= 3)

Table 6: **Appearance and sizes of conventional and lyophilized ODT**

	Lyophilized ODT	Conventional ODT
		
Diameter (mm)	19±0.02 mm	8.5±0.25 mm
Thickness (mm)	6.5±0.15 gm	3.5±0.03 gm

***In vivo* taste masking evaluation**

All tablets prepared by direct compression F1, F4, F9, and F11 have the same bitter taste due to the presence of Cloperastine HCl in 10 mg per tablet. 1 volunteer rated taste as 1 (least unpleasant), 3 volunteers rated taste as 2 (less unpleasant), 6 volunteers rated taste as 3 (more unpleasant), and 2 volunteers rated taste as 5 (most unpleasant). While L1 the lyophilized tablet was prepared by using Eudragit® E PO as the carrier for the taste-masked formula. 5 volunteers rated taste as 1(least unpleasant), 6 volunteers rated taste as 2 (less unpleasant), 1 volunteer rated taste as 3 (more unpleasant). It is concluded that the lyophilized tablet prepared by Eudragit E PO® has more acceptable taste than tablets prepared by direct compression as shown in fig. 3

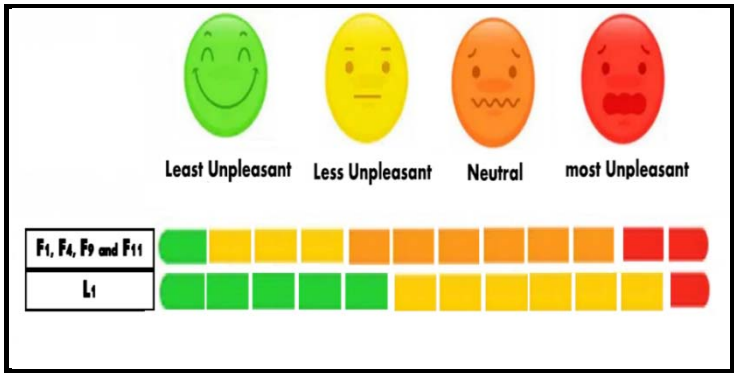

Fig. 3: Bitterness intensity scale

Table 7: Assay of cloperastine HCl and rupatadine

Formula no.	HPLC assay	
	Assay of cloperastine HCl (%)±(SD)	Assay of rupatadine (%)±(SD)
F1	97.82±0.67	97.50±0.23
F4	98.24±1.50	97.10±1.33
F9	98.12±1.04	96.33±1.17
F11	98.16±0.73	96.27±0.98
L1	98.45±0.57	97.45±1.01

All values are mean±SD values (Number of experiments, n= 3)

According to QbD approach; only the formulae showed acceptable results should be developed either as powdered mixtures before compression in characterization by Hausner's ratio and angle of repose to undergo ODTs formulation. Thus, ODTs were assessed through characterization relevant to the quality quantitative tests as DT, WT and HPLC assay to obtain a final elected formula with the most appropriate quality attributes. Thus, F9 was elected to undergo formula development by lyophilization technique.

Assay of cloperastine HCl and rupatadine

HPLC assay results for each active constituents and standard deviation for 3 results were determined as shown in table 7. thus, the results of all formulae were acceptable with no failure.

***In vitro* dissolution study**

As shown in fig. 4, 5 *in vitro* dissolution profiles of cloperastine HCl and rupatadine consecutively; the release of both active constituents

was apparently noticed from 3 min. The results showed the fastest release for L1 in the two active constituent's accumulative release due to its optimized formula by lyophilization that has more porosity and enhanced dissolution characteristics. L1 showed good release pattern at 30 min 81.25% of Cloperastine, L1 showed early good release pattern at 5 min 83.9% of Rupatadine. L1 has fastest dissolution release compared to the tablets prepared by the direct compression. Using Minitab® 18 Software basic statistical paired t program to compare each formula prepared by direct compression against lyophilized tablet for cloperastine HCl dissolution release; F1, F4, F9, F11 resulted in *p*-Values 0.008, 0.032, 0.702, 0.445 consecutively, it concluded that F1 and F4 had significant differences ($p<0.05$) from L1 while F9 and F11 had no significant difference ($p>0.05$). While rupatadine dissolution release; F1, F4, F9, F11 resulted in *p*-Values 0.008, 0.0, 0.15, 0.01 consecutively, it concluded that F1, F4, F11 had significant differences from L1<0.05 while F9 had no significant difference ($p<0.05$). F9 shows faster dissolution release compared to the other tablets prepared by direct compression. It corroborated that the presence of superdisintegrants croscarmellose, Sodium starch glycolate and crospovidone in maximum amount (20 mg for each) enhanced release of active constituents.

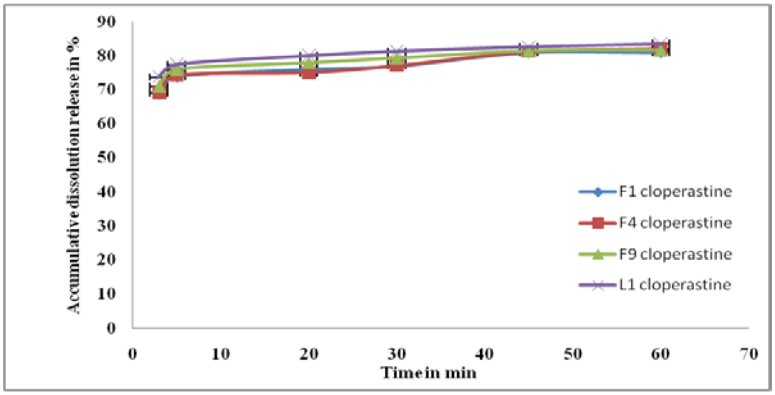

Fig. 4: Dissolution profile of cloperastine HCl for F1, F4, F9, F11, L1

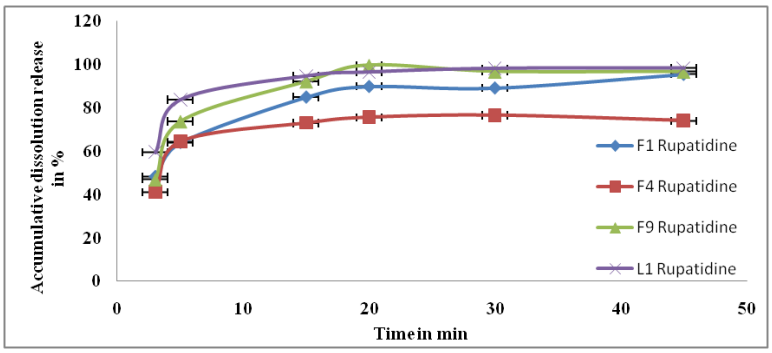

Fig. 5: Dissolution profile of rupatadine for F1, F4, F9, F11, L1

***In vivo* pharmacokinetics study**

Results of cloperastine HCl pharmacokinetics study as shown in table 8; group 1 of wistar rats commercial product taken has Cmax 10.45 mcg/ml and Tmax 1 h, group 2 of wistar rats lyophilized tablet taken has Cmax 16.561 mcg/ml and Tmax 0.75 h, group 3 of Wistar rats F9 direct compression formula taken resulted in Cmax 14.749 mcg/ml and Tmax 0.75 h. Results of rupatadine pharmacokinetics study as shown in table 9; group 1 of wistar rats commercial product taken resulted in Cmax 34.61 mcg/ml and Tmax 1 h, group 2 of wistar rats Lyophilized tablet taken resulted in Cmax 78.88 mcg/ml and Tmax 0.75 h, group 3 of wistar rats F9 direct compression formula taken resulted in Cmax 54.91 mcg/ml and Tmax 0.75 h. It concluded that Lyophilized tablet L1 had the greatest Cmax in plasma which reflected the fastest absorption for both cloperastine HCl and rupatadine. While both L1 group and F9 group had the same Tmax less than commercial group which reflected that they had the same rate of drug elimination for both active substances. Mean cloperastine HCl AUC_{last} value of group treated by Lyophilized tablet was 2.17 folds the mean of AUC_{last} value of group treated by market products. Mean rupatadine AUC_{last} value of group treated by Lyophilized tablet was 2.06 folds the mean of AUC_{last} value of group treated by market products

It concluded that lyophilized tablet owned the best bioavailability characters for both cloperastine HCl and rupatadine having higher results compared to commercial product and ODTs prepared by direct compression.

Table 8: Cloperastine HCl pharmacokinetics analysis

Measured pharmacokinetics item	Group 1 (Treated by market products)	Group 2 (Treated by lyophilized ODTs)	Group 3 (Treated by conventional ODTs)
Cmax (mcg/ml) mean±SD	10.45±0.68	17.25±0.42	14.75±1.75
AUC_{last} (h*{mcg/ml}) mean±SD	23.37±3.47	50.85±1.25	31.38±1.67
Tmax (h) mean±SD	1.0±0	0.75±0	0.75±0

All values are mean±SD values (Number of experiments, n= 2)

Table 9: Rupatadine pharmacokinetics analysis

Measured pharmacokinetics item	Group 1 (Treated by market products)	Group 2 (Treated by lyophilized ODTs)	Group 3 (Treated by conventional ODTs)
Cmax (mcg/ml) mean±SD	34.61±3.35	82.39±7.13	54.72±3.05
AUC_{last} (h*{mcg/ml}) mean±SD	57.05±5.64	118.03±10.22	81.79±9.40
Tmax (h) mean±SD	1.0±0	0.75±0	0.75±0

All values are mean±SD values (Number of experiments, n= 2)

For other literatures included studying of rupatadine taste masked ODTs; one of them investigated about development of rupatadine by formulating into oral dispersible film tablets, in order that rupatadine enclosed in Ethyl cellulose microparticles, the disintegration evaluation test was performed by using multiple methods of disintegration, results were ranged from 18.00±0.82 sec to 25.00±0.82 sec [34]. Moreover, another literature also developed rupatadine into oral dispersible film tablets by using pullulan and hydroxypropyl methyl cellulose as film former, the disintegration evaluation results ranged from 28.78±1.36 sec to 36.79±0.90 sec [5], while the disintegration results for cloperastine HCl and rupatadine taste masked ODTs in our study ranged from 4.67±0.58 sec to20.0±1.0 sec. Accordingly, the developed ODTs in our study has better results in disintegration evaluation that marginally represents a very important attribute for oral dispersible system.

CONCLUSION

The bitter taste of cloperastine Hcl and rupatadine were successfully masked using Eudragit E PO® and hence could be considered as a promising ODT formulation. The lyophilized ODTs showed efficient delivery and apparently fast onset in the comparative pharmacokinetic study carried out by Wistar rats as cloperastine HCl and rupatadine had AUC_{last} value more than 2 folds the AUC_{last} value of market products. Such a formulation could be found as a practical technology for adaptation in the pharmaceutical industry to be used in cough treatment for pediatric and adult. This formula could need further investigations as clinical experiment to discover more promising bioavailability behaviors in human bodies.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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