IJPSR (2022), Volume 13, Issue 12 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 April 2022; received in revised form, 21 May 2022; accepted, 03 June 2022; published 01 December 2022

DEVELOPMENT AND EVALUATION OF TASTE-MASKED ORALLY DISINTEGRATING TABLETS OF LEVOCETIRIZINE DIHYDROCHLORIDE

P. Thakker [1], T. Mehta [2], A. Kuchekar [3], V. Shetty [4], R. Aware [4] and J. Shah [* 5]

Institute of Pharmacy [1], Nirma University, Ahmedabad - 382481, Gujarat, India.
Department of Pharmaceutics [2], Institute of Pharmacy, Nirma University, Ahmedabad - 382481, Gujarat, India.
Department of Pharmaceutics [3], School of Pharmacy, Dr. Vishwanath Karad, MIT World Peace University, Pune - 411038, Maharashtra, India.
ACG Pharma Technologies Pvt Ltd. [4], Shirwal - 412801, Maharashtra, India.
Department of Pharmacology [5], Institute of Pharmacy, Nirma University, Ahmedabad - 382481, Gujarat, India.

Keywords:

Taste masking, Orally disintegrating tablets, Coating, Polymeric dispersion, Direct compression

Correspondence to Author:
Dr. Jigna Shah

Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad - 382481, India.

E-mail: jigna.shah@nirmauni.ac.in

ABSTRACT: Purpose: The goal of this study was to develop taste-masked orally disintegrating tablets of the bitter-tasting levocetirizine dihydrochloride (LCDH) to improve the accessibility and adherence of pediatric, elderly, non-cooperative and paraplegic patients. **Methods:** In the present study, orally disintegrating Levocetirizine dihydrochloride tablets were formulated by direct compression. Taste masking was achieved using a pH-independent polymeric dispersion of Surelease E-7-19040 in combination with Opadry YS-1-19025-A in different ratios. *In-vivo* taste evaluation was done to see if the tablets produced utilizing the direct compression approach were successfully disguised. **Results:** The present study investigated uncoated and coated drug substances and prepared tablets of coated LCDH for flow as well as compression behaviour, Fourier Transform Infrared absorption spectra, Differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy and *in-vitro* dissolution and disintegration properties. **Conclusion:** Using a combination of two polymeric dispersions "Sure lease E-1-19040" and "Opadry" coating for the delivery of LCDH, it was shown that a taste-masking evaluation could be performed to identify effective polymer-carriers for the LCDH.

INTRODUCTION: Taste is one of the important quality attributes that govern the palatability of the formulation and, in turn acceptability by the patient. The bitter taste is one of the foremost challenges that formulators encounter while working with bitter-taste drug molecules.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(12).5090-07

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(12).5090-07

Therefore, designing a formulation of the bitter-tasting drug for oral administration, especially for the pediatric population, is very challenging [1]. Most of the pharmaceutical products administered orally have undesired taste; masking the bitterness of such unpleasant drugs and designing a formulation would result in improved acceptability by the patient.

Designing a formulation with improved patient compliance also results in increased market share and profitability for the company. One approach to reducing unpleasant tastes is to identify universal

inhibitors of all bitter-tasting substances that do not affect other taste sensations like sweetness & saltiness [1]. Human beings can sense taste by receptor proteins located in the oral cavity. In-depth work has been done to improve the palatability of unpleasant drugs and design a formulation of that taste-masked drug. Different techniques for masking the unpleasant taste of the drug-like use of ingredients such as flavors [2], sweeteners and amino acids, coating of unpleasant drug-using polymeric dispersion, use of traditional granulation technique [3], forming a complex of unpleasant drug with Ion exchange resins [4] and using that complex or resinate to formulate pharmaceutical dosage form, use of spray congealing technique with lipids [5], forming a complex of unpleasant drug with β-cyclodextrin [6] and using that complex to formulate pharmaceutical dosage form, use of Freeze-drying technique [7], palatability of the drug is improved by preparing emulsions of different types and use of other excipients for masking unpleasant taste such as starch [8], gelatin, lecithin, liposomes [9], surfactants [10], salts or polymeric membrane and many more [11].

The unpleasant taste of the drug is disguised by either of the techniques described above and then the development of a solid oral dosage form [12, 13]. LCDH is a racemic compound with antihistaminic properties that is the R-enantiomer of cetirizine hydrochloride [14]. It is white, crystalline powder, and freely soluble in water. The drug is not hygroscopic, and it does not exist as a polymorph [15]. The study aimed to develop a patient compliant orally disintegrating tablet of LCDH considering safety-by-design principles outlined by the US FDA [16].

The study also highlights the unique technique for masking the bitterness of the LCDH which can be easily adopted across the pharmaceutical industry without much need for specialized equipment and at a reasonable and affordable cost. The majority of the taste-masking techniques are based on either forming a complex using ion exchange resins or β-cyclodextrin or applying of pH-dependent polymeric layer over the bitter-tasting substrate to mask the bitter taste of the drug; however, the current study has adopted the unique technique of applying a combination of pH-independent water-insoluble and water-soluble polymeric layer over bitter drug particles; thereby retarding the drug release at initial time points of 1 minute followed by complete drug release at later time points to retain immediate drug release characteristic of the formulation. The goal of the present work was to formulate taste-masked ODTs of LCDH by employing the physical barrier technique for taste masking using a combination of pH-independent, water-insoluble polymeric dispersion with a combination of pH-independent, water-insoluble polymeric dispersion pH-independent, a water-soluble polymer as a pore former [17].

Three different water-insoluble to water-soluble polymer ratios were optimized using a 3^2 full factorial design approach [18]. Coated LCDH granules were evaluated for powder properties such as bulk density, tapped density, Carr's index, Hausner's ratio and *in-vitro* disintegration time, *in-vitro* drug release studies, and *in-vivo* taste evaluation. The optimized formulation was also evaluated for DSC, FTIR, PXRD, and SEM for solid-state study, and surface properties. These coated LCDH granules were then used to develop orally disintegrating tablets. Formulations were evaluated for pre-compression properties like bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, and post-compression properties such as thickness, hardness, friability, *in-vitro* disintegration time, drug content, *in-vitro* drug release studies, and *in-vivo* taste evaluation.

MATERIALS AND METHODS:

Materials: LCDH was obtained from Perrigo Ltd, Mumbai, India; Surelease E-7-19040 and Opadry YS-1-19025-A Clear were provided by Colorcon Asia Pvt Ltd, Goa, India; Avicel pH 102 was obtained from DuPont, Mumbai, India; Pearlitol 25C was provided by Roquette, Mumbai, India; Pharmatose 200M was obtained from DFE Pharma, Bangalore, India; Kollidone CL was obtained from BASF, Mumbai, India; Citric acid, Talc, and Magnesium stearate were obtained from Colorcon Asia Pvt Ltd., Goa, India; Aspartame and Peppermint flavor were obtained from Cipla Ltd, Mumbai, India; All other ingredients and reagents used in the study were of analytical grade.

Methods:

Preparation of Polymeric Dispersion for Taste Masking: For enhancing the palatability of the LCDH, a combination of pH-independent

polymeric dispersion (water-insoluble polymer & water-soluble polymer) was used. Surelease E-7-19040, an aqueous dispersion of Ethylcellulose, which is a pH-independent water-insoluble polymeric system serving as a continuous phase, and HPMC-based Opadry YS-1-19025-A clear, ready-to-coat film coating system, which is a pH-independent water-soluble polymeric system serving as a pore former was used [19]. In the present study, different ratios of polymer to pore former (90:10, 85:15 & 80:20) and weight gain upon coating (20%, 35% & 50%) were optimized. Opadry YS-1-19025-A Clear was added to purified water under vigorous stirring. Post addition, it was stirred continuously for at least 45 min. This aqueous dispersion of Opadry YS-1-19025-A was added to Surelease E-7-19040 and stirred for 20 minutes [20].

Preparation of Taste masked LCDH Granules: To retain powder material and allow the air to pass through the container, the fluid bed granulator MiniQuest-F was used with a cylindrical container and a cylindrical top section, fitted with a fine mesh retention screen at the bottom [21]. To prevent particle elutriation, the container lid had three socks. The air for fluidization was generated by a suction created by a blower which sucks the air through the coil of the heater, fine mesh retention screen, and the product container. The air was measured for its flow rate, humidity, and temperature before entering the process chamber. The polymeric dispersion was sprayed through the nozzle inserted vertically inside the column at about 5 to 6 centimeters above the powder bed so that the powder particle gets uniformly wetted [22].

A peristaltic pump was used to draw the polymeric dispersion into the nozzle, where it was atomized by compressed air. Inlet air temperature and product bed temperature were measured with two thermocouples, one underneath the distributor plate and one in the bed. The bed was loaded with 50 grams of powder and was fluidized with hot air at a velocity of 0.8 to 1.0 cubic feet/minute (cfm) to remove the initial moisture present in the powder [23]. Once desired product bed temperature was achieved, polymeric dispersion was pumped through the spray nozzle at 0.5 to 1.2 g/minute. The collision of powder particles with one another during spray application resulted in the formation of liquid bridges between the particles, leading to the formation of granules. This process is commonly referred to as agglomeration [24]. This formation of a liquid bridge between the particles resulted in the bonding of particles *via* two mechanisms: Surface tension at the interface & Hydrostatic suction [25]. As the water evaporates, these liquid bridges get converted into solid bridges and the process is repeated eventually to form a bigger agglomerate **Fig. 1.**

A peristaltic pump was switched off once the desired quantity of polymeric dispersion was applied, and the fluidization rate was reduced to allow particles to dry until the desired moisture level was achieved [26]. As a part of the granulation process, the bed temperature and pressure differential were also recorded [27]. Since sieving was less labor-intensive [28] and reduced attrition, coated LCDH granules were manually sieved through 20, 40, 60, 80 and 100 mesh sizes.

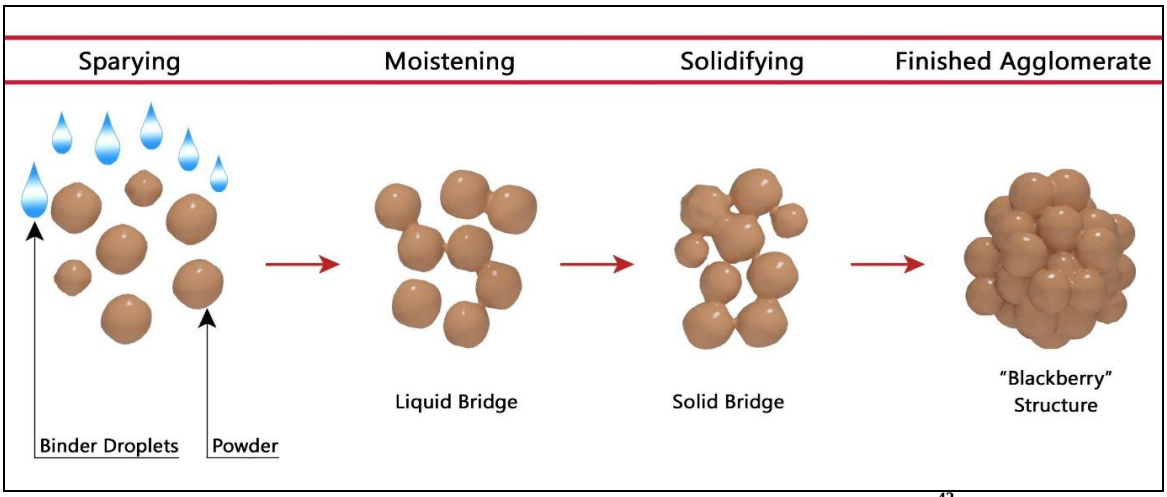

FIG. 1: STEPS INVOLVED IN FLUID BED GRANULATION [42]

Preparation of LCDH ODT: The coated LCDH granules from the optimized batch were used for designing orally disintegrating tablet formulation by direct compression method [29].

LCDH granules were mixed with other formulation components and compressed into ODT's [30].

Tablets were compressed at 50 mg core weight in 8 station Tablet press (Remik) using 5 mm round, standard concave, D type tooling [31].

Use of 3^2 full factorial designs for identification of formulation variable and its impact on product quality: A 3^2 full factorial design was employed to study the effect of formulation variables A (pore former concentration) and B (percent weight gain) on the dependent variable (taste evaluation score by human volunteers) [32]. In this design, two factors were evaluated at three levels, and experimental trials were performed at all nine possible combinations. Details are provided in **Table 1**.

To study the effect of pore former concentration: Optimization of the pore former concentration was determined on the prepared LCDH granules.

The effect of the pore former on taste evaluation was studied at 10, 15 and 20% concentration, as shown in **Table 1.** Detailed formulation composition is given in **Table 2.** To study the effect of percent weight gain:

Optimization of percent weight gain was determined on the prepared LCDH granules. The effect of percent weight gain on taste evaluation was studied at 20, 35 and 50% as shown in **Table 1**. Detailed formulation composition is given in **Table 2.**

TABLE 1: 3^2 FULL FACTORIAL DESIGN STUDY FOR COATED LCDH GRANULES

Batch no.	Coated values		Actual values	
	X_1 (Pore former percentage)	X_2 (Percent weight gain)	X_1 (Pore former percentage)	X_2 (Percent weight gain)
-	Control Sample		Uncoated API	
F1	-1	-1	10% (90:10)	20%
F2	-1	0	10% (90:10)	35%
F3	-1	+1	10% (90:10)	50%
F4	0	-1	15% (85:15)	20%
F5	0	0	15% (85:15)	35%
F6	0	+1	15% (85:15)	50%
F7	+1	-1	20% (80:20)	20%
F8	+1	0	20% (80:20)	35%
F9	+1	+1	20% (80:20)	50%

TABLE 2: FORMULATION COMPOSITION – COATED LCDH GRANULES

Exp. no.	Batch size (g)	LCDH Qty (g)	Surelease Qty (g)	Opadry Qty (g)	Pore former (%)	Weight gain (%)	Total load (g)
F1	50.00	50.00	46.80	1.30	10.00	20.00	60.00
F2	50.00	50.00	81.90	2.275	10.00	35.00	67.50
F3	50.00	50.00	117.00	3.27	10.00	50.00	75.00
F4	50.00	50.00	44.20	1.95	15.00	20.00	60.00
F5	50.00	50.00	77.36	3.41	15.00	35.00	67.50
F6	50.00	50.00	110.50	4.875	15.00	50.00	75.00
F7	50.00	50.00	41.60	2.60	20.00	20.00	60.00
F8	50.00	50.00	72.80	4.55	20.00	35.00	67.50
F9	50.00	50.00	104.00	6.50	20.00	50.00	75.00

Evaluation Parameters of uncoated LCDH powder coated LCDH granules and LCDH ODTs:

The Angle of Repose: The angle of repose was determined for a lubricated blend of LCDH ODT formulations using a stationary funnel or sample holder. The lubricated blend or powder sample was poured through this funnel or sample holder which was raised vertically until a maximum cone height (h) was obtained (Physical Pharmacy by Martin). The radius of the heap (r) and the angle of repose (Θ) were calculated using the formula;

$$\Theta = \tan^{-1}(h/r) \ldots\ldots (1)$$

Flow Properties:

Bulk Density and Tapped Density: The measuring cylinder was filled with coated samples to measure the density. Weight-to-volume density measures the weight of a sample per unit volume. After tapping a measuring cylinder 500 times from a height of 1.5 inches, the tapped density has been determined.

Bulk density = Weight of the blend/ Bulk Volume.... (2)

Tapped density = Weight of blend/ Volume occupied in the cylinder..... (3)

Hausner's Ratio and Carr's Index: The Hausner's ratio was determined using the following equation:

Hausner's ratio = Tapped Density/Bulk Density ..... (4)

A Carr's index is a ratio of the differences between tapped density and bulk density to tapped density, multiplied by 100:

Carr's index = (Tapped Density − Bulk Density) Tapped Density × 100 ..... (5)

Thickness and Weight Variation: The thickness measurements were performed on 10 tablets of each LCDH orally disintegrated tablet formulation using Digital Vernier Calliper. The average thickness, the standard deviation was determined.

Weight Variation was determined by using 20 randomly selected tablets from each formulation and weighing it on electronic balance (Shimadzu Corp. Japan Type AX200).

Hardness: The hardness of LCDH orally disintegrated tablet formulation was determined using Erweka GmbH hardness tester for 10 tablets of each formula with known weight and thickness. The average hardness and standard deviation were calculated.

Friability: A weighed sample of 10 tablets is subjected in the apparatus to a tumbling action and the shock resulting from a free-fall of six inches. The standard Roche operates at a constant speed of 25 RPM ±1. The loss of weight suffered is a measure of the friability of the tablets. The acceptance criteria for coated tablets are 0.5 to 1%.

Friability = Initial weight – Final Weight/ Initial weight x 100..... (6)

***In-vitro* Disintegration time:** A tablet disintegration experiment was carried out using a tablet disintegration test apparatus (Electro Lab, ED-21, Mumbai, India) on 6 tablets each of LCDH orally disintegrated tablet formulation according to the pharmacopoeial guidelines (USP 30-NF 25) for immediate release ODTs. One tablet was placed in each of six tubes of the basket containing water maintained at 37°C ± 1°C. The tablet was considered to disintegrate completely when all the particles passed through the screen. The disintegration time and standard deviation of six individual tablets were recorded.

***In-vitro* Dissolution Studies:** Drug release of coated LCDH granules was determined using the basket method, *i.e.*, the USP I Apparatus; *in-vitro* dissolutions were conducted at pH 6.8 as the dissolution media in 500 mL of phosphate buffer rotating speed at 100 rpm at a temperature of 37 ± 0.5°C. At various time intervals of 1, 3, 5, 10, 15 & 30 min, 10 mL of the dissolving medium was removed and replaced with the same medium quantity to ensure sink conditions. The contents of the removed samples were evaluated spectrophotometrically at 226 nm after they were filtered. A standard calibration curve of LCDH produced in a pH 6.8 medium was used to quantify the percent cumulative drug release [33].

Drug release of LCDH orally disintegrated tablets was determined using the paddle method, *i.e.*, the USP II Apparatus, *in-vitro* dissolutions were conducted at pH 6.8 as the dissolution media in 500 mL of phosphate buffer rotating speed at 50 rpm at a temperature of 37 ± 0.5°C. At various time intervals of 2, 4, 6, 8, 10, 15, 20, 25 & 30 minutes, 10 mL serial dilutions were extracted. Every time, an equivalent amount of fresh dissolving media was introduced to the bulk that was kept at about the same temperature. Using Whatman filter paper, samples were filtered, the dilutions were performed according to the calibration curve, and the absorbance was measured at 226 nm. The percentage of the labelled amount of medication released was computed, and a graph was drawn at each time interval [34].

Determination of Drug Content (Percent Assay): Methanol was utilized to prepare the standard stock solution. In methanol, 1.00 mg mL^{-1} of LCDH was

combined to prepare the stock solution. The standard stock solution was kept at 2–8°C and stored in the dark. For LCDH, test solutions for HPLC were made *via* dilution of the aforesaid stock solution in the phase of mobility to achieve several different concentrations of 1–10g mL^{-1}. The UV spectrum of a drug substance with a concentration of 10 g mL^{-1} was obtained. Maximum absorbance of 226 nm was observed for LCDH [35]. The drug content was determined using an equation generated in the standard curve.

In-vivo Taste Evaluation:

Taste Evaluation of Coated LCDH granules: *In-vivo* Taste Evaluation protocol was approved by Institutional Ethics Committee entitled IEC/NU/19/IP/01. The study was divided into three phases for *in-vivo* taste evaluation [36]. Each phase consisted of 4 samples. Details of each phase and procedure are explained below:

In the Phase 1 study, individual volunteers were subjected to 4 different samples, one sample of uncoated LCDH powder and three samples of coated LCDH granules, coated with a polymeric dispersion comprising 10% pore former and three different weight gains 20%, 35% & 50% respectively. In the Phase 2 study, individual volunteers were subjected to 4 different samples, one sample of uncoated LCDH powder and three samples of coated LCDH granules, coated with a polymeric dispersion comprising 15% pore former and three different weight gains 20%, 35% & 50% respectively. In Phase 3 study, individual volunteers were subjected to 4 different samples, one sample of uncoated LCDH powder and three samples of coated LCDH granules, coated with a polymeric dispersion comprising 20% pore former and three different weight gains 20%, 35% & 50% respectively.

Procedure: The study was divided into 3 phases with 3 hours gap between each phase. Three formulations and uncoated LCDH powder (control sample) were given to individual volunteers for tasting purposes with a minimum 20-minute gap between each formulation tasting. About 13.5 mg of sample was placed at the rear end of the tongue for about 10 seconds. After 10 seconds, the sample was spitted and gargled with plain water, if needed; volunteers were allowed to consume additional water. To overcome bitter sensation, 2 to 3 salty biscuits and a few salted peanuts were consumed to neutralize taste buds. Half a glass of water was given to individual volunteers, and they were asked to wait for 20 minutes before proceeding for the next sample taste evaluation. The bitterness of the sample was evaluated on ascale of 0 to 10 (0 being the highly bitter). A minimum 3-hour gap was maintained after completion of each phase and before starting the next phase.

Taste Evaluation of LCDH ODT: The format of the *in-vivo* taste evaluation study for LCDH ODT was the same as that of coated LCDH granules. The study was divided into three phases, each phase consisted of 3 samples. Details of each phase and procedure are explained as follows-

In the Phase 1 study, individual volunteers were subjected to 3 different samples of LCDHODT containing Microcrystalline cellulose as a diluent and three different concentrations of Crospovidone as super-disintegrants *i.e.* 2%, 4%, and 6%, respectively. In the Phase 2 study, individual volunteers were subjected to 3 different samples of LCDHODT containing Mannitol as a diluent and three different concentrations of Crospovidone as super-disintegrants *i.e.* 2%, 4% and 6%, respectively. In the Phase 3 study, individual volunteers were subjected to 3 different samples of LCDHODT containing Lactose monohydrate as a diluent and three different concentrations of Crospovidone as super-disintegrants *i.e.* 2%, 4%, and 6%, respectively.

Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetry of uncoated LCDH powder and coated LCDH granules obtained from optimized formulations F2 were performed as per the procedure outlined in this section. To study the effect of processing condition on change in melting point, crystallization behaviour, and chemical reaction of LCDH as a function of temperature or time, Optimized formulation F2 was subjected to DSC studies. The DSC thermograms of uncoated LCDH powder and coated LCDH granules were recorded using a differential scanning calorimeter (DSC 823 Mettler Toledo, Japan). Samples were precisely weighed on the aluminium pans and then tightly packed with aluminium lids. Thermo grams were collected in a

liquid nitrogen atmosphere at a frequency in the range of 10°C/min above temperature ranging between 30-250° C [37].

Fourier Transform Infrared Absorption Spectra (FTIR): Fourier Transform Infrared absorption of uncoated LCDH powder, coated LCDH granules obtained from optimized formulations F2 and LCDH orally disintegrated tablet formulation ODT6 were performed as per the procedure outlined in this section.

To study the effect of processing condition on change in LCDH powder at molecular level, Optimized formulation was subjected to FTIR studies. FTIR spectroscopy was performed using FT/IR 4100 Jasco (Japan). By hydraulic press, the uncoated and coated LCDH granules were combined with KBr and transformed in the form of pellets at 100 kg pressure. Recorded spectra ranged between 4000–400 cm^{-1} ranges.

Powder X-Ray Diffraction analysis (P-XRD): Powder X-Ray Diffraction analysis of uncoated LCDH powder and coated LCDH granules obtained from optimized formulations F2 was performed as per the procedure outlined in this section.

To study the effect of processing condition on change in LCDH powder at molecular level, Optimized formulation was subjected to P-XRD studies. P-XRD of both uncoated and coated LCDH granules were examined using Phillips-X′Pert MPD System, Netherland. At a speed of scanning of 0.3 deg/s, P-XRD was observed from 2° to 60 ° [2].

The X-ray supply was PW3123/00 curved Ni-filtered Cu-K (=1.54056) radiation.

Scanning Electron Microscopy (SEM): Scanning Electron Microscopic study of uncoated LCDH powder and coated LCDH granules of optimized formulations F2 was performed as Surface morphology of uncoated LCDH powder and coated LCDH granules of optimized formulation F2 was investigated using SEM (Zeiss Ultra Plus-FESEM). These particles were earlier sputter-coated using gold.

Stability Studies: For stability studies, the optimized formulation of LCDH ODT ODT6 was packed in two different packaging conditions: Aluminum pouch manually filled with 100 tablets and sealed with sealing machine and HDPE container manually filled with 100 tablets with one silica bag and sealed with aluminum seal. All these samples were subjected to accelerated stability conditions (40°C / 75% RH) and evaluated for 1, 3, and 6 months [38]. They were packaged in Alu-Alu pouches and kept in stability chamber for the time specified by the ICH recommendations for expedited research.

RESULTS:

Evaluation of Coated LCDH Granules:

Development of Taste Masked LCDH Granules using 3^2 Full Factorial Design: To evaluate taste masking efficiency of coated LCDH granules, two formulation variables *i.e.*, pore former concentration and percent weight gain, were studied using 3^2 full factorial designs as shown in **Table 1**. All the additives were chosen based on the results of the preformulation research and a thorough review of the literature. Results of LCDH formulations –Human volunteers rating and Percent drug release are given in **Table 3.**

TABLE 3: LCDH FORMULATIONS– HUMAN VOLUNTEERS TASTE RATING AND PERCENT DRUG RELEASE

Formulations	Taste evaluation rating by human volunteers (*)	Percent drug release in 30 min (%)
F1	5.80±1.43	57.65±0.76
F2	6.30±1.64	44.53±0.89
F3	6.29±1.64	45.42± 0.65
F4	3.79±1.03	67.15± 1.75
F5	4.63±1.38	56.50± 0.96
F6	6.15±1.42	52.89± 0.84
F7	3.00±1.25	89.27± 1.15
F8	3.90±1.20	73.22± 0.53
F9	5.42±1.15	68.66± 0.98

(*)The bitterness of the sample was evaluated on a scale of 0 to 10 (0 being the highly bitter)

Multiple regression analysis was performed between selected variables and taste efficiency and equation 7 was generated.

$$\text{Human Volunteer score} = 5.03 - 1.01A + 0.8783B + 0.4835AB \ldots\ldots (7)$$

The correlation coefficient values (R^2= 0.9513) indicate a good fit. Taste evaluation rating by human volunteers and percent drug release in 1 min given in **Table 3.**

Influence of Poreformerontaste and Drug Release: The model equation significantly reflects both the factors with less than 0.05 vales. The negative sign of pore former (A) signifies that the higher the pore former concentration, the higher the drug release. Therefore, a more bitter sensation leads to a lower rating of inhuman volunteers. As shown in **Table 3**, at a constant 20% of weight gain and varying concentrations of pore former *i.e.* 20, 15, and 10%, the taste evaluation rating by human volunteers was found to be 3.0,3.79 and 5.8, respectively. While at 35% weight gain, it was 3.9, 4.63, and 6.3. At the same time, a t50% weight gain was 5.42, 6.15, and 6.29. The results indicated palatability of coated LCDH granules improved with increased percent weight gain and reduced performer concentration. This reflected the polymer to pore former ratio of 90:10 out of the three ratios (90:10, 85:15, and 80:20) used, along with the 35% target weight gain (Formulation F2) an optimum balance for the taste evaluation and percent drug release at 1-minute time point. According to the results, the produced granules have a good flow property. Percent weight gain (B) confirms that the higher the weight gain, the slower the drug release is; therefore, less is the bitter sensation, and higher is the acceptance in the human volunteers.

As shown in **Table 3**, at a constant 10% of performer concentration and varying percent of target weight gain, the taste evaluation rating by human volunteers was found to be in the range of 5.8 –6.3, which portrayed high acceptability. At a constant 15% of pore former concentration and varying percent of target weight gain, the taste evaluation rating by human volunteers was found to be in the range of 3.79 – 6.15, which depicted a reasonable impact of the pore former on masking the bitterness of LCDH. While at a constant 20% of pore former concentration and varying percent of weight gain the taste evaluation rating by human volunteers was found to be in the range of 3.0 – 5.42, which resulted in the low acceptability. The former pore concentration of 10 % with a weight gain at 35% (formulation F2) showed masking the unpleasant taste of LCDH and exhibited good palatability. Although the individual terms A and B showed different impacts, the combined effect of AB positively impacted the response. The same has been reflected in equation 7.

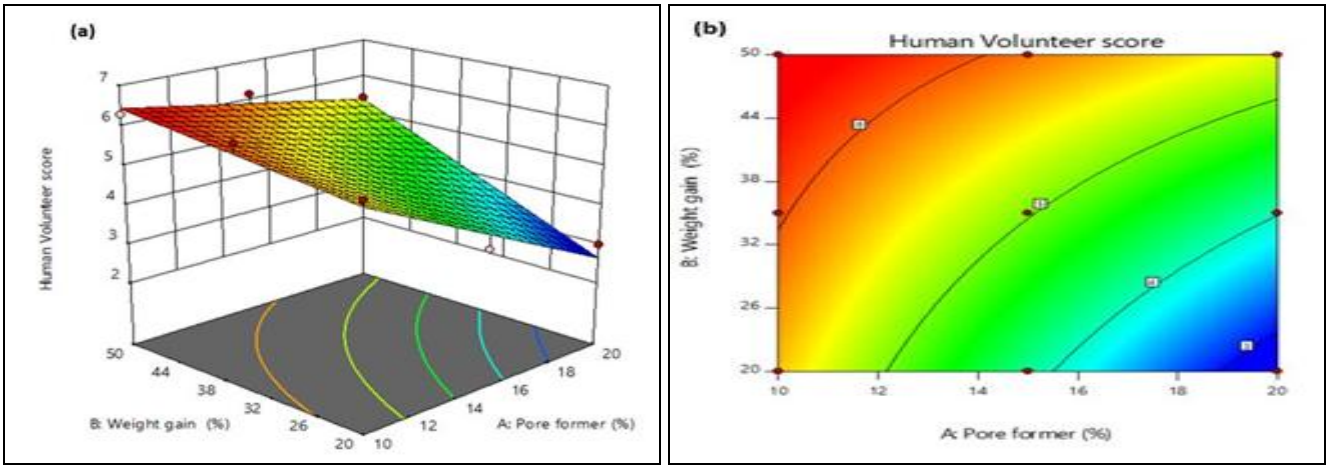

FIG. 2: (A) SURFACE PLOTS SHOWING THE EFFECT OF LCDH FORMULATION VARIABLES ON HUMAN VOLUNTEERS SCORES AND (B) COUNTER PLOTS SHOWING THE EFFECT OF LCDH FORMULATION VARIABLES ON HUMAN VOLUNTEER'S SCORE

In-vivo **Taste Evaluation:** As indicated in the graph below **Fig. 3**, Phase 1 / sample 3 (F2), & Phase 1 / sample 4 (F3), and Phase 2 / sample 4 (F6) had the highest preference, which depicted that these samples were more acceptable by human volunteers with regards to palatability. However,

Phase 1 / Sample 3 (F2) showed the excellent taste masking based on the rating provided and hence was considered for further development of ODT formulation.

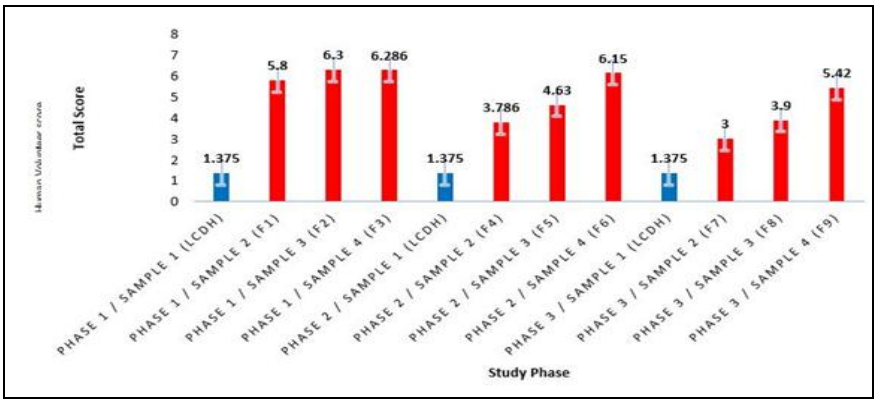

FIG. 3: TASTE EVALUATION OF UNCOATED LCDH POWDER AND COATED LCDH GRANULES

Powder Properties: Powder properties of coated LCDH granules obtained for formulations were found to be satisfactory with desired flow characteristics. The bulk density of uncoated LCDH powder was 0.36 g/cc, however, for coated LCDH granules, it was found to be in the range of 0.30 g/cc to 0.48 g/cc. Tapped density of uncoated LCDH powder was 0.56 g/cc, however, for coated LCDH granules, it was found to be in the range of 0.40 g/cc to 0.60 g/cc. Hausner's ratio of uncoated LCDH powder was 1.555, however for coated LCDH granules, it was found to be in the range of 1.22 to 1.34. Carr's index of uncoated LCDH powder was 35.71, however for coated LCDH granules, it was found to be in the range of 18.52 to 25.58.

Determination of Drug Content: An assay of coated LCDH granules by the proposed chromatographic method was carried out, and results were found to be satisfactory in an excellent match with the label claims in a good agreement followed by method suitability ranging from 96.9% to 109.4 %.

TABLE 4: FORMULATION COMPOSITION OF CUMULATIVE % DRUG RELEASE OF LCDH COATED GRANULES

Formulation Code	Drug Content (%)
F1	98.1 ± 0.78
F2	102 ± 0.87
F3	105.1 ± 0.94
F4	107.4 ± 0.67
F5	109.4 ± 1.08
F6	105.3 ± 0.88
F7	96.9 ± 0.56
F8	107 ± 0.74
F9	103.4± 1.12

***In-vitro* Dissolution Studies:** Impact of formulation variable on drug release profile: Two formulation variables evaluated to study the effect of taste masking efficiency of LCDH coated granules are "ratio of polymer to pore former" (also referred as pore former concentration) and "target weight gain" of polymeric dispersion to achieve desired retardation in drug release at 1-minute time point followed by complete drug release at later time points. At the lowest concentration of pore former (10%), all the formulations resulted in relatively slower drug release at the first time point of 1 minute ranging from 45.75%, 77.67% & 86.42%, and at the highest level of pore former (20%), all the formulations resulted in relatively faster drug release. The dissolution profiles for each of the nine formulations are displayed in **Fig. 4.**

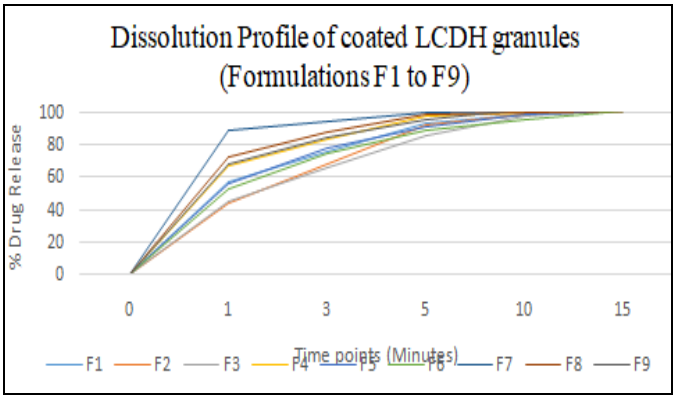

FIG. 4: DISSOLUTION PROFILE OF LCDH COATED GRANULES IN PH 6.8 PHOSPHATE BUFFER (USP TYPE 1 APPARATUS)

Differential Scanning Calorimetry Analysis: The thermal behavior of the LCDH reveals a strong endothermic peak at 221.9°C, which corresponds to

the loss of fluid during crystallization and the melting. The height and sharpness of the endothermic peak show the crystalline nature of LCDH. Similarly, the LCDH coated with polymeric dispersion shows a sharp endothermic peak at 214.9°C. The endotherms equivalent to the coated LCDH granules are slightly decreased *i.e.*, by ~7°C which is due to the presence of coating material and uniformity of coating, which is further supported by the decrease in enthalpy change from 106mJ/mg to 41.4mJ/mg. The height and sharpness of the endothermic peak in coated LCDH granules show the crystalline state/nature of LCDH, an integral part, and the polymorph of LCDH after the coating is thermodynamically stable. The application of polymeric dispersion and the processing condition is not affecting the characteristics of LCDH.

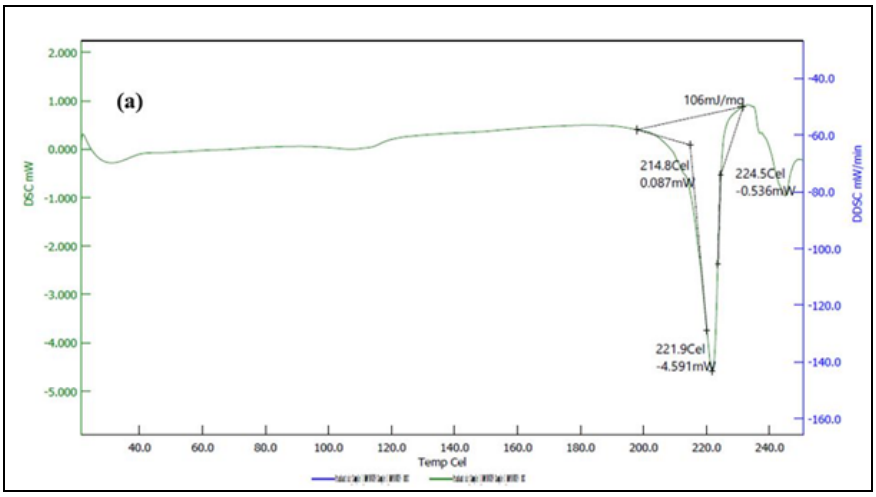

FIG. 5A: DIFFERENTIAL SCANNING CALORIMETRY CURVES OF UNCOATED LCDH POWDER

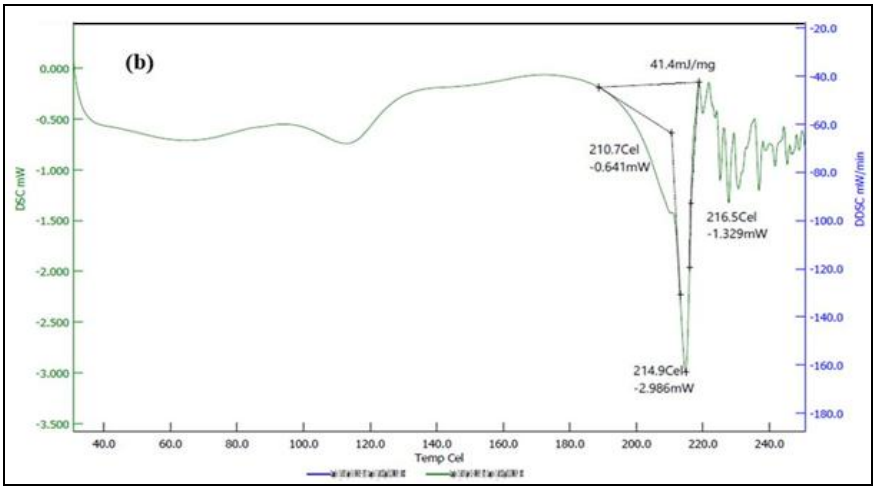

FIG. 5(B): DIFFERENTIAL SCANNING CALORIMETRY CURVES OF COATED LCDH GRANULES

Fourier-transform Infrared Spectroscopy (FTIR): The observed absorbance bands in IR spectrum indicated the characteristic functional groups that matched with LCDH; these similar absorbance bands were also seen in case of the spectrum obtained for coated LCDH granules (40).

This suggested that identity of the molecule is not changed during the manufacturing of coated LCDH granules. A stretching vibration at 3439 cm^{-1} in the uncoated LCDH powder spectrum is assigned to the drug's -N-H asymmetric stretching. The band at 1716 cm^{-1} LCDH spectrum is assign to carbonyl group (-COOH group).

Also, the band is assignable to -C-N asymmetric stretching at 1276 cm^{-1}. The -Cl bands are significant at 759.9 cm^{-1} and 806.2 cm^{-1}. The stretching vibrations of C-O is assigned at 1126.4 cm^{-1}. The stretching at 759.9 cm^{-1} is allotted to CH mono substituted.

The mono substituted strong -C-C stretching vibrations are significant at 1610.5 cm^{-1} and 1492.9 cm^{-1}.

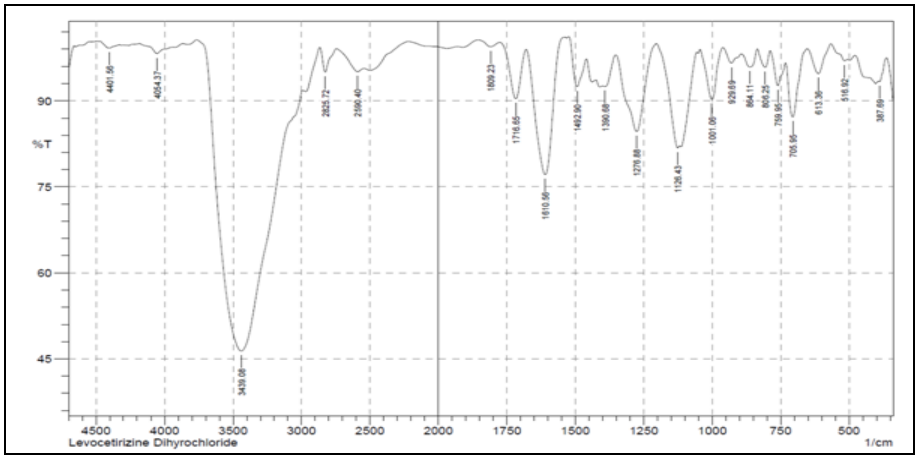

FIG. 6 (A): FT-IR SPECTRA OF UNCOATED LCDH POWDER

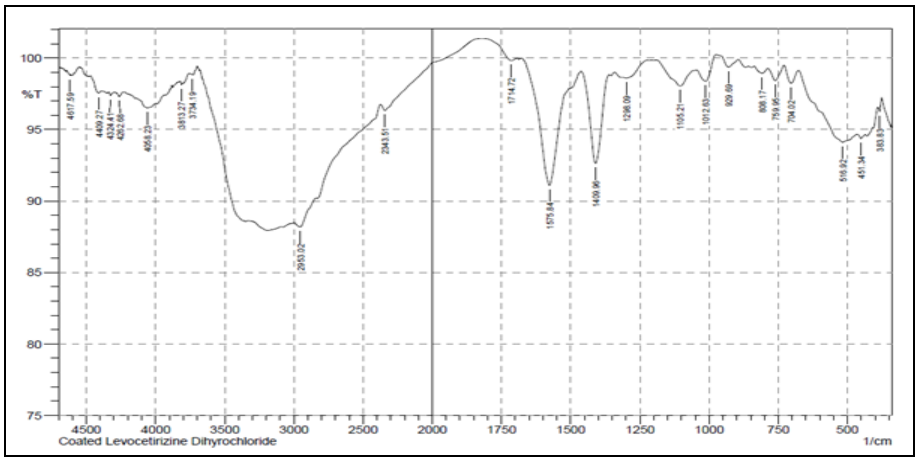

FIG. 6(B): FT-IR SPECTRA OF COATED LCDH GRANULES

Powder X-Ray Diffraction Analysis: The overlay of diffract grams for uncoated LCDH powder and coated LCDH granules with polymeric dispersion has shown a specific behaviour. The LCDH shows several sharp peaks in P-XRD diffract grams, which represents the crystalline nature of LCDH. After coating LCDH with polymeric dispersion, the characteristic 2θ peaks are exactly overlaid with the pure LCDH, suggesting that polymorphism is not changed after coating and the polymorph is thermodynamically stable.

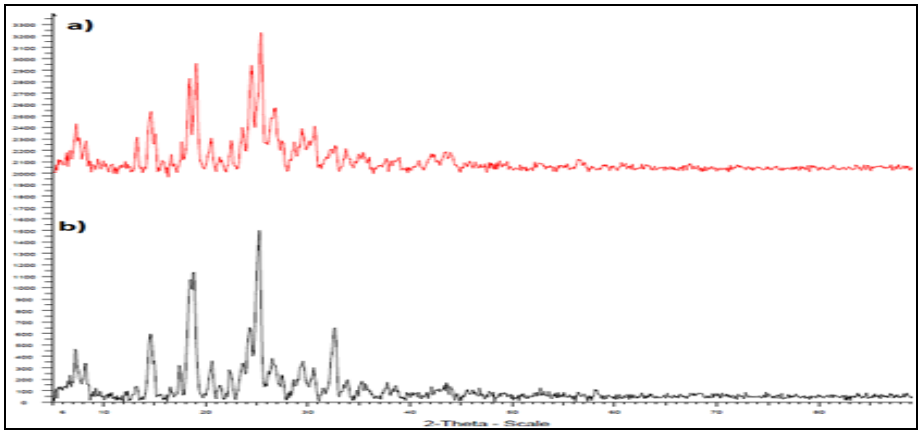

FIG. 7: P-XRD IMAGES OF (A)-UNCOATED LCDH POWDER AND (B)-COATED LCDH GRANULES

Scanning Electron Microscopy (SEM): Uncoated LCDH powder had a particle size of 20 to 50 microns however coating process employed resulted in significant particle growth or agglomeration, as seen in **Fig. 8**. Additionally, image of scanning electron microscope of coated

LCDH granules indicates deposition of polymeric particles over the surface of agglomerates, resulting in a homogeneous polymeric covering to achieve desired masking of unpleasant taste of LCDH and to achieve desired retardation of drug release at initial time point followed by complete drug release at latter time points.

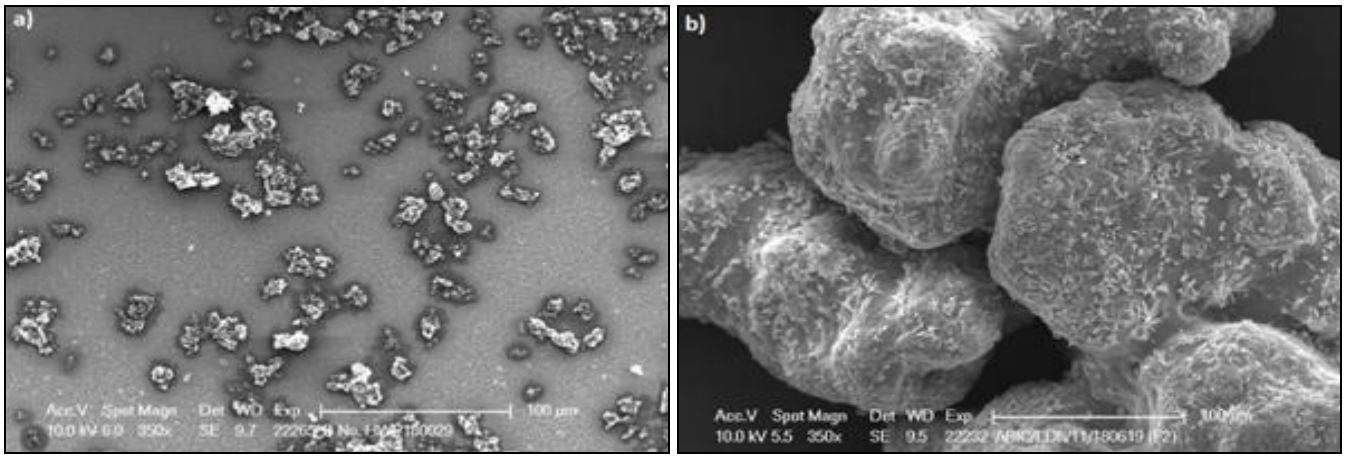

FIG. 8: MICROSCOPIC IMAGES OF UNCOATED LCDH POWDER AND COATED LCDH GRANULES

Evaluation of LCDH ODT: Formulation F2 from polymeric dispersion optimized batches was selected for further preparation of ODT. The formulation was chosen because of its desired masking of unpleasant taste, had the required drug content, and had a superior dissolving profile. The pre-compression and post-compression characteristics of the LCDH ODT's were tested on the produced batches. Using direct compression technique, LCDH ODT was formulated.

Pre-compression Properties of Lubricated Blend of LCDH ODT: Pre-compression properties of lubricated blend of all the formulations were found to be satisfactory. Angle of repose, bulk density, tapped density, Percentage compressibility and Hausner's ratio for LCDH ODT was found to be in the range of 18.26 to 23.63, 0.45 to 0.59, 0.51 to 0.69, 11.43 to 15.68 and 1.103 to 1.192 respectively.

Evaluation of LCDHODT: The parameters of all the formulations were assessed as hardness, thickness, weight variation, *in-vitro* disintegrating time, *in-vitro* dissolution rate, and *in-vivo* taste evaluation.

Evaluation of Tablet properties (Hardness, Friability, Thickness and Weight Variation): The evaluated properties of LCDH ODT formulations were shown in Table 3. All the LCDH ODT showed values for hardness (3.5 ± 0.12 to 4.6 ± 0.15 Kg/cm^2) and friability (0.51 to 0.82%). In addition, manufactured tablet exhibited uniform weight range (99.15 ± 1.011 to 104.25 ± 1.5%) and thickness from 2.25 ± 0.01 to 2.27 ± 0.03mm.

***In-vitro* Disintegration Time:** In the development of ODT, the disintegration time of tablets is the most important parameter that should be optimized. The effect of different fillers (Microcrystalline cellulose, Mannitol, Lactose monohydrate) and three different concentrations of Crospovidone (2, 4 & 6%) on the *in-vitro* disintegration of LCDH ODT formulations are displayed in Table 6. The disintegration time of formulations with Microcrystalline cellulose as a filler and different concentration of Crospovidone (2, 4 & 6%) was in the range of 11 ± 1 to 19 ± 1 seconds. Disintegration time of formulations with Mannitol as a filler and different concentration of Crospovidone (2, 4 & 6%) was in the range of 4 ± 1 to 14 ± 1 seconds and disintegration time of formulations with Lactose monohydrate as a filler and different concentration of Crospovidone (2, 4 & 6%) was in the range of 10 ± 1 to 26 ± 1 seconds. Formulation with Mannitol as a filler and concentration of Crospovidone at 6% (ODT6) resulted in the lowest disintegration time of 4 ± 1 seconds and was considered as an optimized formulation for stability studies.

Determination of Drug Content: The drug content of LCDH ODT's was in the range of 97.69 ± 0.63 to 99.63 ± 0.54% as shown in **Table 5**

which was in accordance with Pharmacopeial requirement.

***In-vitro* Dissolution Studies:** *In-vitro* drug release of LCDH ODT's was found to be ranging between 95.15 ± 0.35 and 99.92 ± 0.31% as shown in **Fig. 9**. The use of different fillers and different concentrations of Crospovidone showed slight differences in disintegration time, which had marginal difference at the initial time however, all the 9 formulations resulted in more than 90% drug release in 15 min. Based on the evaluation criteria's, formulation ODT 6 was selected as an optimized formulation for further evaluation at accelerated storage conditions.

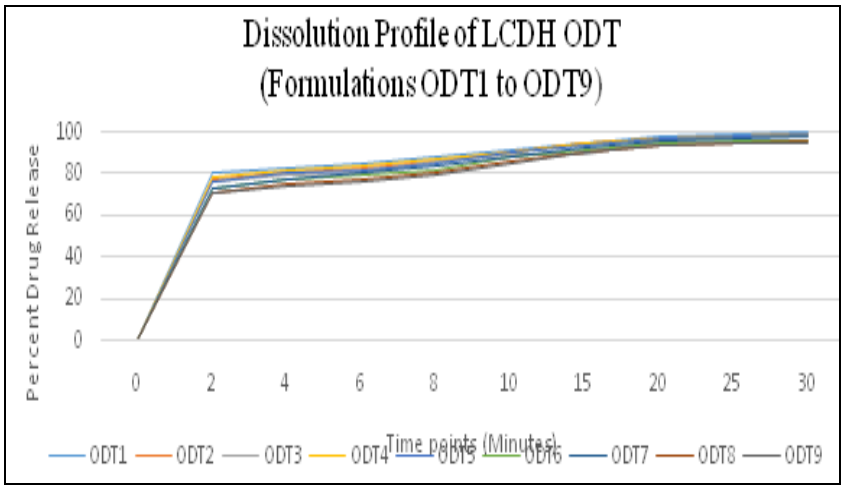

FIG. 9: CUMULATIVE % DRUG RELEASE OF LCDH ODT

TABLE 5: DRUG CONTENT AND CUMULATIVE % DRUG RELEASE OF LCDH ODT

Formulation code	Drug Content (%)	Cumulative drug release in 30 min
ODT1	99.63 ± 0.54	99.92±0.31
ODT2	98.54 ± 0.80	99.22±0.26
ODT3	98.29 ± 0.76	98.35±0.33
ODT4	98.42 ± 1.13	99.14±0.60
ODT5	99.26 ± 0.85	98.77±0.28
ODT6	97.69 ± 0.63	96.04±0.49
ODT7	98.80 ± 0.92	97.82±0.64
ODT8	98.84 ± 0.66	95.74±0.27
ODT9	97.98 ± 1.55	95.15±0.35

***In-vivo* Taste Evaluation:** The format of the *in-vivo* taste evaluation study for LCDH ODT was the same as that of coated LCDH granules. The study was divided into three phases; each phase consisted of 3 samples. Details of each phase and procedure are explained as follows-In In Phase 1 study; individual volunteers were subjected to 3 different samples of LCDH ODT containing Microcrystalline cellulose as a diluent and three different concentrations of Crospovidone as a super-disintegrants *i.e.* 2%, 4%, and 6% respectively. In the Phase 2 study, individual volunteers were subjected to 3 different samples of LCDH ODT containing Mannitol as a diluent and three different concentrations of Crospovidone as a super-disintegrants *i.e.* 2%, 4% and 6% respectively. In Phase 3 study, individual volunteers were subjected to 3 different samples of LCDH ODT containing Lactose monohydrate as a diluent and three concentrations of Crospovidone as a super-disintegrants, *i.e.,* 2%, 4%, and 6%, respectively. The study was conducted in three phases with a minimum of 3 hours gap between each phase. Three formulations were given to individual volunteers for tasting purposes, with a minimum 20-minute gap between each formulation tasting. Volunteers were asked to place one sample of ODT on the tongue for about 30 seconds and then spit the sample and gargle with plain water if required; volunteers were allowed to consume additional water. To neutralize bitter sensation between consequent sample testing, 2 to 3 salty biscuits and few pieces of salted peanuts were given to volunteers followed by half a glass of

water and they were asked to rate their mouth feel experience on a scale of 0 to 10 (0 being extremely bitter and non-palatable). Post 20 minutes of gap, volunteers were asked to evaluate the second sample. Minimum 3 h gap was maintained after completion of Phase 1 taste evaluation and before starting Phase 2. A similar procedure was followed for Phase 2 and Phase 3 studies.

TABLE 6: RESULTS OF POST-COMPRESSION PARAMETERS

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	*In-vitro* Disintegration Time (Sec)	Drug Content (%)	Taste Evaluation Score
ODT1	2.26 ±0.01	4.2 ± 0.11	0.55	99.15 ± 1.011	19 ± 1	99.63 ± 0.54	3.2±0.89
ODT2	2.25 ± 0.02	4.3 ± 0.14	0.64	99.65 ± 1.120	15 ± 1	98.54 ± 0.80	3.3±1.75
ODT3	2.27± 0.01	4.1 ± 1.56	051	99.30 ± 1.123	11 ± 1	98.29 ± 0.76	2.8±1.40
ODT4	2.26 ±0.01	3.5 ± 0.12	0.59	101.0 ± 1.775	14 ± 1	98.42 ± 1.13	7.3±1.25
ODT5	2.27± 0.02	3.7 ± 0.13	0.68	102.05 ± 1.00	8 ± 1	99.26 ± 0.85	8.4±1.10
ODT6	2.25 ± 0.11	3.6 ± 0.14	0.82	103.55 ± 1.11	4 ± 1	97.69 ± 0.63	9.4±0.70
ODT7	2.27± 0.03	4.4 ± 0.10	0.53	100.55 ± 1.15	26 ± 1	98.80 ± 0.92	6.2±1.39
ODT8	2.25 ± 0.01	4.5 ± 0.16	0.77	104.25 ± 1.5	18 ± 1	98.84 ± 0.66	6.6±1.39
ODT9	2.25± 0.01	4.6 ± 0.15	0.62	104.00 ± 1.80	10 ± 1	97.98 ± 1.55	6.5±1.00

Fourier Transform Infrared Spectroscopy (FTIR): To understand the impact of processing conditions, samples of uncoated LCDH powder and LCDH ODT were subjected for Fourier Transform Infrared Spectroscopic analysis.

The characteristics function group matches for both uncoated LCDH powder as well as LCDH ODT. This suggests that molecule identity is not changing during the process of manufacturing.

Some bands are seen with low intensity in the sample of formulation which is because of the presence of excipients at relatively higher concentrations in tablet formulation resulting in low intensities bands of LCDH. A stretching vibration at 3439 cm^{-1} in the API spectrum is assigned to the drug's -N-H asymmetric stretching.

The band at 1716 cm^{-1} API spectrum is assigned to carbonyl group (-COOH group). Also, the band is assignable to -C-N asymmetric stretching at 1276 cm^{-1}. The –Cl bands are significant at 759.9 cm^{-1} and 806.2 cm^{-1}. The stretching vibrations of –C-O is assigned at 1126.4 cm^{-1}.

The stretching at 759.9 cm^{-1} is assigned to–CH mono substituted. The mono substituted strong -C=C stretching vibrations are significant at 1610.5 cm^{-1} and 1492.9cm^{-1}.

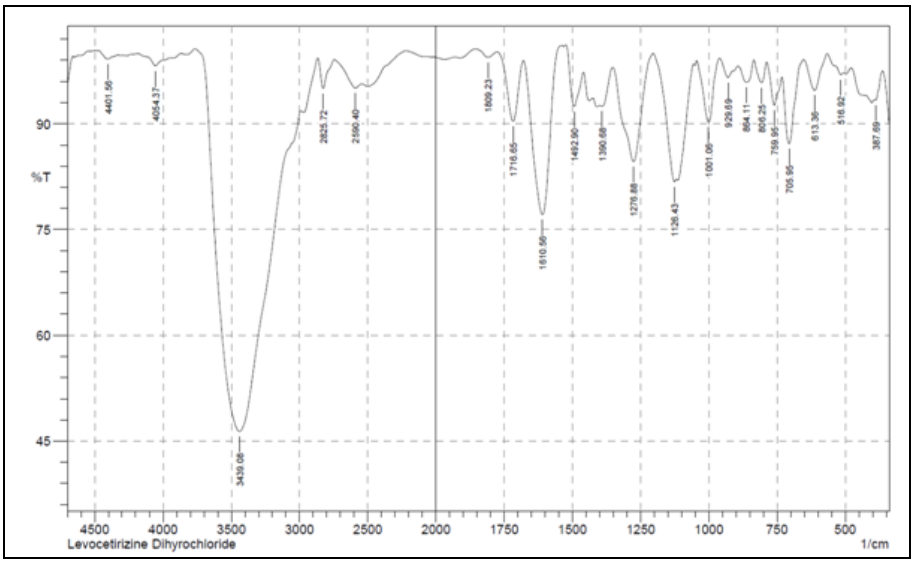

FIG. 10(A): FT-IR SPECTRA OF UNCOATED LCDH POWDER

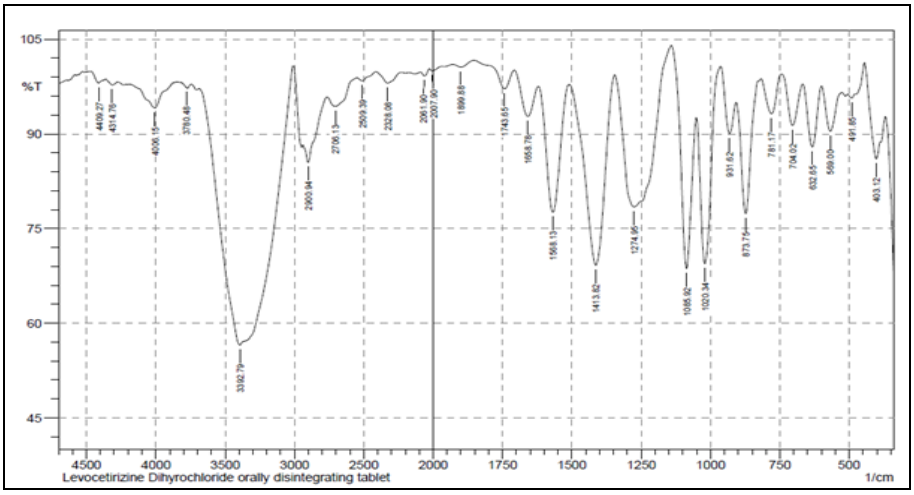

FIG. 10(B): FT-IR SPECTRA OF LCDH ODT

***In-vivo* Taste Evaluation of LCDH ODTs:** For human volunteer tasting study of LCDH ODT's, optimized taste-masked formulation of coated LCDH granules was selected to produce an ODT.

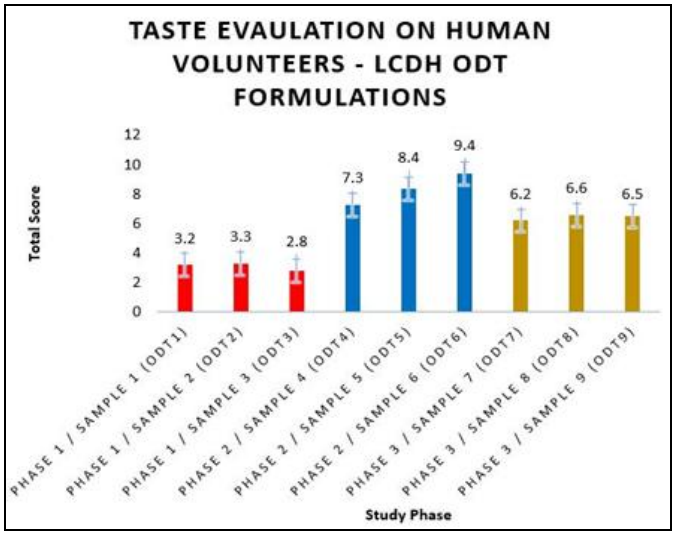

FIG. 11: TASTE EVALUATION ON HUMAN VOLUNTEERS

In addition to other formulation components, three different Diluents (Microcrystalline cellulose, Mannitol and Lactose monohydrate) and three different concentrations of Crospovidone (2%, 4% & 6%) were evaluated and all these formulations were evaluated for palatability and taste masking ability on healthy human volunteers.

As indicated in **Fig. 11** - Phase 2 / sample 6 (Formulation No: ODT6) had the highest preference which means these samples were more acceptable by human volunteers with regards to overall palatability & taste.

Stability Studies: The optimized formulation of LCDH ODT (ODT6) packed in two different packaging conditions were allowed for accelerated stability conditions (40°C / 75% RH) and evaluated for 1, 3 and 6 months for disintegration, drug content and cumulative drug release **Table 7, 8** & **9.**

TABLE 7: DISINTEGRATION TIME OF LCDH ODT

Stability study at 40°C and 75 % RH (For Optimized Formulation ODT6)		
Test after time (Months)	**Disintegration time (Sec.) Pack: Aluminium pouch**	**Disintegration time (Sec.) Pack: HDPE container**
Initial	4± 1	4± 1
1	7± 1	6± 2
3	9± 2	8± 1
6	13± 1	10± 1

TABLE 8: DRUG CONTENT OF LCDH ODT

Stability study at 40°C and 75 % RH (For Optimized Formulation ODT6)		
Test after time (Months)	**% Drug content Pack: Aluminium pouch**	**% Drug content Pack: HDPE container**
Initial	97.69± 0.63	97.69± 0.63
1	96.99± 0.99	97.02± 0.78
3	96.04± 1.06	96.45± 0.85
6	95.53± 0.87	95.98± 0.94

TABLE 9: CUMULATIVE % DRUG RELEASE AFTER 30 MINUTES

Stability study at 40°C and 75 % RH (For Optimized Formulation ODT6)		
Test after time (months)	**% Cumulative drug release after 30 min. time point Pack: Aluminium Pouch**	**% Cumulative drug release after 30 min. time point Pack: HDPE container**
At initial time	96.04± 0.49	96.04± 0.49
1	97.23± 0.68	97.21± 0.35
3	96.00± 0.79	96.00± 0.56
6	97.69± 0.95	97.54± 0.85

DISCUSSION: In this study, the author has developed a taste-masked orally disintegration tablet of LCDH and evaluates the application of physical barrier using insoluble polymeric layer over bitter-tasting drug substrate as a taste masking technique. Using this approach, the primary aims to determine the product's quality is to retard drug release at the initial time point of 1 min, followed by complete drug release at later time points from polymeric coated drug substance in aqueous media. The need to control drug release at the first time point of 1 minute is crucial to achieve desired taste masking and still retain the immediate drug release criteria of the formulation. Polymeric dispersion used for masking the bitterness of LCDH comprises of pH-independent polymeric dispersion "Surelease E-7-19040" an aqueous dispersion of Ethyl cellulose and "Opadry YS-1-19025-A" an Hypromellose based polymeric system as a water-soluble pore former.

The drug release mechanism from such coated particles is supposed to be by "Molecular Hindered Diffusion" as well as by "Convection [39]. The mechanism of drug release from such coated particles is governed by Fick's first law of diffusion i.e. extent of a polymeric material deposited is directly proportional to the diffusional path length and inversely proportional to drug release. The presence of water-soluble pore former in a continuous water-insoluble polymeric phase would facilitate drug release or diffusion of relatively insoluble drugs. To understand the impact of formulation variable on taste masking efficiency of coated LCDH granules, two formulation variables such as "poreformer concentration" and "percent weight gain" were studied using 3^2 full factorial designs as shown in **Table 1**. The study indicated, higher the concentration of pore former, relatively faster is the drug release, probably because pore former impacts diffusivity of the barrier membrane, whereas higher the percent weight gain, slower is the drug release, because higher percent weight gain results in longer diffusional path length and hence slower drug release [41]. A higher rating given by human volunteers further confirmed these findings, indicating better acceptance for all the formulations with lower pore former concentration. The current study also evaluated the impact of formulation variables such as "diluent type" and "super disintegrant concentration" on desired product quality of LCDH ODT such as disintegration time, percent drug release and mouth feel.

The study indicated that the higher the super disintegrant concentration, the shorter the disintegration time. In contrast, the presence of mannitol as a diluent in ODT helped achieve the desired mouth feel. The use of other formulation components, mainly sweetener and flavor helped further improve the overall palatability of the formulation as indicated by the higher score given by human volunteers during taste evaluation studies.

The approach of masking the bitterness of the unpleasant drug using the technique outlined in the study offers great simplicity and cost benefits for pharmaceutical manufacturers and can successfully be implemented for other bitter-tasting drug molecules.

CONCLUSION: In comparison to traditional oral dosage forms, ODTs have higher patient acceptability and compliance and may have better biopharmaceutical characteristics, effectiveness, and safety. To fulfill the demand of patients, healthcare professionals, novel and simple LCDHODTs were formulated to release the drug in the buccal cavity.

In addition, this formulation also provided a desirable taste and after taste within the buccal cavity and hence could be considered as an appropriate ODT formulation for LCDH. The optimized ODT formulation (ODT6) showed a

disintegration time of 4 seconds and complete drug dissolution in 30 min. with acceptable taste and other parameters as per standard limits. The study demonstrated that by using a combination of water insoluble and water soluble, pH independent polymeric dispersion as a physical barrier over bitter tasting particles, effective taste masking could be achieved, resulting in improved patient compliance.

ACKNOWLEDGEMENT: Authors are thankful to ACG and Dr. Vishwanath Karad MIT World Peace University, Pune, India, for letting permission to conduct practical work. Also, thankful to the Department of Pharmaceutics, Nirma University, Ahmedabad, India, and Vivekanand Education Society's College of Pharmacy, Chembur, Mumbai, India, for letting the permission to conduct analytical work.

CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

REFERENCES:

1. Aliasgar SF and AlAteibi NA: Taste Masking Approaches for Unpleasant Taste Drugs. Drug Des Dev Deliv J Tast 2019; 2(1): 1–3.
2. Suttee A, Sriram P, Arsham P and Thout RR: Formulation and Evaluation of Levocetirizine Dihydrochloride and Ambroxol Hydrochloride Lozenges. IJPQA 2020; 25 11(03):417-23.
3. de Freitas LAP: Pharmaceutical applications of spouted beds: A review on solid dosage forms. Particuology 2019; 42: 126-136.
4. Verma U, Mujumdar A and Naik J: Preparation of Efavirenz resinate by spray drying using response surface methodology and its physicochemical characterization for taste masking. Dry Technol 2020; 38(5-6): 93-805.
5. Sorita GD, Santamaria-Echart A, Gozzo AM, Gonçalves OH, Leimann FV and Bona E: Lipid composition optimization in spray congealing technique and testing with curcumin-loaded microparticles. Adv Powder Technology 2021; 32(5): 1710-1722.
6. Zheng X, Wu F, Hong Y, Shen L, Lin X and Feng Y: Developments in taste-masking techniques for traditional Chinese medicines. Pharmaceutics 2018; 10(3): 157.
7. Amelian A, Wasilewska K, Wesoły M, Ciosek-Skibińska P and Winnicka K: Taste-masking assessment of orally disintegrating tablets and lyophilisates with cetirizine dihydrochloride microparticles. Saudi Pharm J 2017; 25(8): 1144-1150.
8. Marzouk MA, Osman DA and Mohamed OS: *In-vitro* and *in-vivo* evaluation of taste-masked orodispersible tablets of fluoxetine hydrochloride for the treatment of depression. Drug Dev Ind Pharm 2021; 47(4): 645-653.
9. Ahire S: a Review : Taste Masking Techniques in Pharmaceuticals. An Int J Pharm Sci 2018; 33(3): 68-82.
10. Bajac JD, Nikolovski BG, Nesterović AG, Lončarević IS and Petrović JS: Determination of optimal ultrasound conditions for preparation of o/w emulsions with encapsulated juniper berry essential oil (*Juniperus communis* L.). Acta Period Technol 2019; (50): 23-32.
11. Prashant T, Jigna S, Tejal M and Gaurav A: Taste Masking of Pharmaceutical Formulations: Review on Technologies, Recent Trends and Patents. Int J Pharma Bio Sci 2020; 10(3): 88-96.
12. Kadota K, Terada H, Fujimoto A, Nogami S, Uchiyama H and Tozuka Y: Formulation and evaluation of bitter tastemasked orally disintegrating tablets of high memantine hydrochloride loaded granules coated with polymer via layering technique. Int J Pharm 2021; 604 :120725.
13. Meher A and Dighe NS: An Overview of Fast Dissolving Oral Film. J Drug Deliv Ther 2019; 9(4): 822-825.
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022064s038,022157s020lbl.pdf Highlights of Prescribing information for Levocetirizine Dihydrochloride from US FDA website.
15. Kaduk JA, Gindhart AM and Blanton TN: Crystal structure of levocetirizine dihydrochloride Form I, C21H27ClN2O3Cl2. Powder Diffr 2021; 36(3): 181-189.
16. Kathpalia H and Patil A: Formulation and evaluation of orally disintegrating films of levocetirizine dihydrochloride. Indian J Pharm Sci 2017; 79(2): 204-211.
17. Xiao Zheng, Fei Wu, Yanlong Hong, Lan Shen, Xiao Lin and Yi Feng: Develoment in taste masking techniques for traditional chinese medicines. Pharma 2018; 10: 157.
18. Jagan Mohan TSS, Varma DP, Bhavyasri K, Prasad K, Mukkanti K and Jogia HA: Development and validation of piribedil in tablet dosage form by HPLC: A QbD and OFAT approach. Asian J Chem 2017; 29(5): 1113-1118.
19. Wei C, Solanki NG, Vasoya JM, Shah AV and Serajuddin ATM: Development of 3D Printed Tablets by Fused Deposition Modeling Using Polyvinyl Alcohol as Polymeric Matrix for Rapid Drug Release. J Pharm Sci 2020; 109(4): 1558–1572.
20. Luo D, Kim JH, Park C, Oh E, Park JB and Cui JH: Design of fixed dose combination and physicochemical characterization of enteric-coated bilayer tablet with circadian rhythmic variations containing telmisartan and pravastatin sodium. Int J Pharm 2017; 523(1): 343–356.
21. Morin G and Briens L: A comparison of granules produced by high-shear and fluidized-bed granulation methods. AAPS Pharm Sci Tech 2014; 15(4): 1039–1048.
22. Loh ZH, ER DZL, Chan LW, Liew CV and Heng PWS: Spray granulation for drug formulation. Expert Opinion on Drug Delivery 2011; 8(12): 1645-1661.
23. Pawar N, Saha A, Nandan N and Parambil JV: Solution cocrystallization: A scalable approach for cocrystal production. Crystals 2021; 11: 303.
24. Haas K, Dohnal T, Andreu P, Zehetner E, Kiesslich A and Volkert M: Particle engineering for improved stability and handling properties of carrot concentrate powders using fluidized bed granulation and agglomeration. Powder Technol 2020; 6: 104-115.
25. Sanaei-Moghadam M, Jahangiri M and Hormozi F: An experimental study on the spray characteristics of pressure nozzle in a fluid bed granulation. Part Sci Technol 2019; 39-50.
26. Takahashi AI, Lourenço FR, Duque MD, Consiglieri VO and Ferraz HG: Using fluid bed granulation to improve the dissolution of poorly water-soluble drugs. Brazilian Arch Biol Technol 2012; 55(3): 477-484.
27. Stefan T, Markus H and Paul S: Experimental Investigation of the Heat Transfer between Finned Tubes

and a Bubbling Fluidized Bed with Horizontal Sand Mass Flow. Energies 2022: 15: 1316.
28. Karim S, Baie SH, Hay YK and Bukhari NI: Development and evaluation of omeprazole pellets fabricated by sieving-spheronization and extrusion - Spheronization process. Pak J Pharm Sci Pak J Pharm Sci. 2014; 27(3): 425-438.
29. Dawadi S, Bipindra Pandey, Nepal S, Gurau Y, Shahi R and Gautam B: Formulation and Evaluation of Orally Disintegrating Tablet of Metoclopramide Hydrochloride. World J Curr Med Pharm Res 2020; 2(6): 322–329
30. Akhtar S, Hussain S and Mandal SK: Formulation development and characterization of effervescent tablets along with levocetirizine dihydrochloride. Asian J Pharm Clin Res 2020; 13(8): 124-130.
31. Shah HG, Dugar RP, Li HH, Dave VS and Dave RH: Influence of punch geometry (head-flat diameter) and tooling type (‘B’ or ‘D’) on the physical–mechanical properties of formulation tablets. Drug Dev Ind Pharm 2019; 45(1): 117-123.
32. Sharma SS and Raval AG: Formulation and evaluation of controlled release osmotic tablet of carvedilol phosphate. Int J Pharm Biol Sci Arch 2019; 7(2): 117–160.
33. Dhahir RK and Al-Kotaji MYASAR: Formulation of orally disintegrating tablets of cinnarizine by using direct compression method. International Journal of Applied 2019; 11(1): 117-123.
34. Fan Y, Chen H, Huang Z, Zhu J, Wan F and Peng T: Taste-masking and colloidal-stable cubosomes loaded with Cefpodoxime proxetil for pediatric oral delivery. Int J Pharm 2020; 575.
35. Saeed AM, Hamzah MJ and Ahmed NQ: Quantitative assay of aspirin and (Salicylic acid and heavy metals as impurities) in Iraqi’s market aspirin tablets using different analytical methods. Int J Appl Pharm 2018; 10(5): 167-172.
36. Naqvi RF, Khan A, Umer MF, Malik O and Shahwani NA: Design and optimization of novel taste-masked medicated chocolates of dextromethorphan with in-vitro and *in-vivo* taste evaluation. J Pharm Innov 2020.https://doi.org/10.1007/s12247-020-09511-8.
37. Gajbhiye SV, Jalgaonkar SV, Dabba SG, Surve S and Lad MS: Assessing completion reports for compliance with institutional ethics committee-approved protocols: An observational study. Indian J Med Ethi 2020; (2): 119–123.
38. Annex 10 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Technical Report Series, No. 1010, 2018
39. Abo Dena AS and Abdel Gaber SA: *In-vitro* drug interaction of levocetirizine and diclofenac: Theoretical and spectroscopic studies. Spectrochim Acta - Part A Mol Biomol Spectrosc 2017; 181: 239 –248.
40. Chio CC and Tse YLS: Hindered Diffusion near Fluid-Solid Interfaces: Comparison of Molecular Dynamics to Continuum Hydrodynamics. Langmuir 2020; 36(32): 9412-9423.
41. Palmer D, Vuong H, Levina M and Rajabi-Siahboomi A. The influence of hydrophilic pore formers on dipyridamole release from aqueous ethylcellulose film-coated pellets. Poster Reprint AAPS Annual Meeting. November 2007.

How to cite this article:
Shah J, Mehta T, Thakker P, Kuchekar A, Shetty V and Aware R: Development and evaluation of taste masked orally disintegrating tablets of levocetirizine dihydrochloride. Int J Pharm Sci & Res 2022; 13(12): 5090-07. doi: 10.13040/IJPSR.0975-8232.13(12).5090-07.